15th & 17th BISOP

Serbian Pain Society

15th & 17th Belgrade International Symposium on Pain

PROCEEDINGS

October 22-25, 2020 & May 13-14, 2022

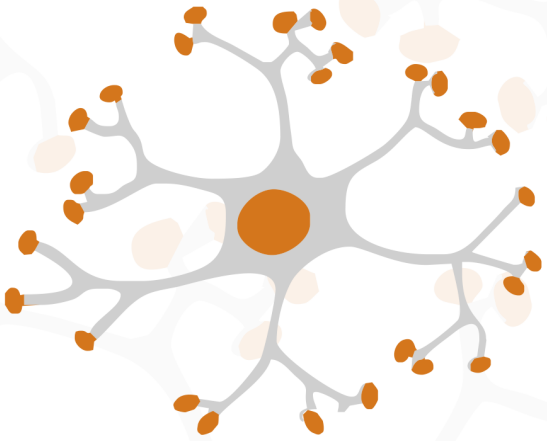
Belgrade, Serbia

15. i 17. beogradski internacionalni simpozijum o bolu

ZBORNIK PREDAVANJA

Oktobar 22-25, 2020. i maj 13-14, 2022.

Beograd, Srbija



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15th Belgrade International Symposium on Pain

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1 Science Behind Medical Marijuana and CBD Oil

Nebojsa Nick Knezevic, MD, PhD

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History

The first direct reference to a cannabis product use for medicinal purposes dates from 2900 B.C., described in a Chinese medical reference. In ancient China and Egypt, cannabis was used medicinally for soreness from gout, rheumatism and other problems. In ancient India, it was used to treat insomnia, gastrointestinal disorders and pains such as headache and childbirth. The ancient Greeks used cannabis to relieve inflammation. In 1545 the Spanish brought marijuana to the New World, and in the mid-19th century, marijuana was introduced to Western medicine as a substitute for opium, among other uses. Interest in marijuana use for both medicinal and recreational purposes has increased in recent years, especially following its legalization in 33 USA states, Canada and several European countries.

Cannabinoid receptors

Endocannabinoids are lipid-based retrograde neurotransmitters that bind to cannabinoid receptors, of which two are currently described: CB1 and CB2.[1] CB1 are present throughout CNS: particularly in the hippocampus (responsible for short-term memory), cortex, basal ganglia (motor activity), cerebellum (motor coordination), hypothalamus, limbic system, and spinal cord. In the brain, cannabinoids affect functions such as cognition, memory, motor movement and pain perception. This is due to the inhibitory-mediated action of CB1 receptor on ongoing release of a number of excitatory and inhibitory neurotransmitter systems at the terminals of central and peripheral neurons.[2] CB2 receptors are mostly expressed in immune cells: CB2A in B lymphocytes, NK cells, monocytes, testes; CB2B in spleen and gastrointestinal system. This suggests

that cannabinoids exert specific receptor-mediated actions on the immune system through the CB2 receptor.[3]

THC and Cannabidol

The two main components of cannabis are THC and cannabidiol (CBD). They have similar effects on certain domains while having almost opposite effects in others. Through its interaction with CB1 receptors, THC is attributed analgesic effects on central and neuropathic pain, as well as relief from pain associated with cancer, HIV and fibromyalgia. THC also produces, in a dose-dependent manner, hypoactivity, hypothermia, spatial and verbal short-term memory impairment. It was also found that THC causes transient psychotic symptoms and increased levels of anxiety, intoxication and sedation.

CBD was shown to be efficient in blocking most of the effects of THC, when both drugs were given together. CBD had no significant effect on behavior, and when administered together it prevented the transient psychotic symptoms induced by THC. CBD's anxiolytic effect is produced through its activity on limbic and paralimbic system.[4] CBD is also considered to have antipsychotic effects, being considered as a potential antipsychotic medicine, and also as a possible remedy for other conditions such as inflammation, diabetes, cancer and neurodegenerative diseases.[5] CBD is not associated with analgesia, in fact it has a negative correlation with relief from certain forms of pain.[6]

Due to these varied properties of THC and CBD, the therapeutic effect of marijuana is directly correlated with the THC content in a particular formulation, as well as the THC:CBD ratio. More research is needed to determine the safe therapeutic index in terms of dosing and THC:CBD ratio. For example, the majority of products available on the market are advertised as >15% THC, which may be unsuitable for the treatment of neuropathic pain.[7]

Since the legalization of marijuana under some USA state laws, markets have seen an expanse of marijuana-derived CBD products such as CBD oil in drops, capsules, food products, topical lotions and dietary supplements. Claims about the benefits of these products are often exaggerated and unfounded, varying from the treatment of anxiety and insomnia to the treatment of dementia and cancer. The addition of drug products to human and animal food products based on insufficient scientific evidence was condemned by the US Food and Drug Administration (FDA). The FDA has approved Epidiolex (cannabidiol), a cannabis-derived CBD drug product for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older. Three synthetic THC drug products have also been approved: Marinol (dronabinol), Syndros (dronabinol), and Cesamet (nabilone). These

are available with prescription for use in nausea associated with cancer chemotherapy and for the treatment of anorexia associated with weight loss in AIDS patients.

New Scientific Evidence: Pain Conditions

Medical marijuana is increasingly popular as an alternative to traditional pain-relieving medications. Evidence points to a small analgesic effect in the treatment of chronic neuropathic pain.[8,9] One randomized controlled trial has found that medical marijuana, THC in particular, causes a significant increase in pressure pain threshold.10 Alternatively, CBD may have synergistic pharmacokinetic interactions, by increasing THC plasma concentrations, but antagonistic pharmacodynamic interactions, by decreasing THC-induced analgesia.[10] A systematic review also investigating the specific mechanisms by which cannabinoids modulate pain has found that cannabinoids increase pain thresholds, increase pain tolerance and reduce the unpleasantness of ongoing experimental pain. However, cannabinoids didn't decrease experimental pain intensity or mechanical hyperalgesia.[11]

In the treatment of cancer pain, evidence from systematic reviews has been inconclusive, most likely due to the very low quality of evidence available. Most notably, studies carried design limitations, such as poor controls, and publication bias.

Challenges when it comes to legalizing marijuana include the risk of misuse, dependence and addiction which have been associated with long-term duration of use, and the potential for adverse effects. Marijuana has been associated with CNS-related adverse effects (psychosis, cognitive impairment) and GI-related adverse effects (dry mouth, nausea, cannabinoid hyperemesis syndrome). Long-term duration of use has been associated with dependence and addiction.8 Severe adverse effects, however, were found to be similar between cannabinoid and placebo treatment groups.9

New Scientific Evidence: Opioid Replacement

Finding an alternative to opioid in the treatment of chronic pain would constitute major progress in the fight against the opioid crisis. For instance, in the years after Colorado legalized marijuana, they witnessed a significant drop in opioid distribution, a larger decrease than seen in states without recreational marijuana policies.[12] Among chronic pain sufferers using opioids, daily marijuana use was associated with significantly lower odds of daily illicit opioid use.[13] A survey among people who used both opioids and marijuana in the past year showed that 41% reported a decrease or cessation of opioid use due to marijuana use.[14] There are several other new reports of marijuana consumption leading to a significant reduction in opioid consumption.[15,16] Promisingly, marijuana use was not associated with opioid dose or opioid misuse behavior.[17] In fact, emotional symptoms improved in patients taking medical marijuana.[18]

Methodology and Challenges in Research

There is much variability in marijuana research methodology which needs to be addressed in order to improve the quality of evidence and enable better informed conclusions to be drawn. A systematic review into the topic found that study conclusions were generally more positive in noncontrolled studies, and that 15 of 21 primary studies on marijuana were noncontrolled. Additionally, they found that studies using higher doses tended to conclude that marijuana was effective, which is an issue because drugs and protocols of administrations varied greatly across studies.[19]

A common inconsistency in research on medical marijuana revolves around the THC:CBD ratio and dosing. Overall, <10% THC has demonstrated the highest efficacy in the treatment of neuropathic pain, yet the great majority of cannabis products available are >15% THC, most likely to appeal to the recreational use realm.7 Currently, none of the states with legalized medical or recreational marijuana consider the THC:CBD ratio in regulations. Moreover, in published studies, the ratio is often not listed or trivialized based on availability.[20]

There is also a high need of more research into marijuana use in specific patient populations including pregnancy, geriatric and pediatric populations. Concerning the latter, for instance, there are currently only two published studies on medical marijuana on pediatric pain, of which one is a case report.[21] There is also a great need of more long-term studies to assess the risks and benefits associated with long-term use. To date, long-term chronic use in people younger than 25 years old was associated with memory loss, cognitive dysfunction, early onset psychosis or schizophrenia.[22]

Conclusions

Medical marijuana has many potential medical benefits, as well as possible health risks. Emerging guidelines from institutions such as the FDA, AMA, WMA and the American Cancer Society encourage more rigorous research. The evidence of cannabinoids' benefit in pain disorders is of low-to-moderate quality, but greatly promising in providing alternatives to opioids. Most studies were comprised of small populations, poor controls and short duration, and further research is necessary to examine marijuana safety and efficacy.

References:

1. Alger BE. Getting high on the endocannabinoid system. Cerebrum 2013;2013:14.
2. Howlett A, Barth F, Bonner T, et al. International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. Pharmacological reviews 2002;54:161-202.
3. Galiègue S, Mary S, Marchand J, et al. Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations. European journal of biochemistry 1995;232:54-61.
4. Crippa JAS, Derenusson GN, Ferrari TB, et al. Neural basis of anxiolytic effects of

cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report. Journal of Psychopharmacology 2011;25:121-30.
5. Atakan Z. Cannabis, a complex plant: different compounds and different effects on individuals. Therapeutic advances in psychopharmacology 2012;2:241-54.
6. Li X, Vigil JM, Stith SS, Brockelman F, Keeling K, Hall B. The effectiveness of self-directed medical cannabis treatment for pain. Complement Ther Med 2019;46:123-30.
7. Cash MC, Cunnane K, Fan C, Romero-Sandoval EA. Mapping cannabis potency in medical and recreational programs in the United States. PLoS One 2020;15:e0230167.
8. Maharajan MK, Yong YJ, Yip HY, et al. Medical cannabis for chronic pain: can it make a difference in pain management? J Anesth 2020;34:95-103.
9. Johal H, Devji T, Chang Y, Simone J, Vannabouathong C, Bhandari M. Cannabinoids in Chronic Non-Cancer Pain: A Systematic Review and Meta-Analysis. Clin Med Insights Arthritis Musculoskelet Disord 2020;13:1179544120906461.
10. van de Donk T, Niesters M, Kowal MA, Olofsen E, Dahan A, van Velzen M. An experimental randomized study on the analgesic effects of pharmaceutical-grade cannabis in chronic pain patients with fibromyalgia. Pain 2019;160:860-9.
11. De Vita MJ, Moskal D, Maisto SA, Ansell EB. Association of Cannabinoid Administration With Experimental Pain in Healthy Adults: A Systematic Review and Meta-analysis. JAMA Psychiatry 2018;75:1118-27.
12. Kropp Lopez AK, Nichols SD, Chung DY, Kaufman DE, McCall KL, Piper BJ. Prescription Opioid Distribution after the Legalization of Recreational Marijuana in Colorado. Int J Environ Res Public Health 2020;17.
13. Lake S, Walsh Z, Kerr T, et al. Frequency of cannabis and illicit opioid use among people who use drugs and report chronic pain: A longitudinal analysis. PLoS Med 2019;16:e1002967.
14. Ishida JH, Wong PO, Cohen BE, Vali M, Steigerwald S, Keyhani S. Substitution of marijuana for opioids in a national survey of US adults. PLoS One 2019;14:e0222577.
15. Schneider-Smith E, Salottolo K, Swartwood C, Melvin C, Madayag RM, Bar-Or D. Matched pilot study examining cannabis-based dronabinol for acute pain following traumatic injury. Trauma Surg Acute Care Open 2020;5:e000391.
16. Takakuwa KM, Hergenrather JY, Shofer FS, Schears RM. The Impact of Medical Cannabis on Intermittent and Chronic Opioid Users with Back Pain: How Cannabis Diminished Prescription Opioid Usage. Cannabis Cannabinoid Res 2020;5:263-70.
17. Merlin JS, Samet JH, Cheng DM, et al. Marijuana Use and Its Associations With Pain, Opioid Dose, and HIV Viral Suppression Among Persons Living With HIV on Chronic Opioid Therapy. J Acquir Immune Defic Syndr 2019;82:195-201.
18. Pawasarat IM, Schultz EM, Frisby JC, et al. The Efficacy of Medical Marijuana in the Treatment of Cancer-Related Pain. J Palliat Med 2020;23:809-16.

19. Madden K, George A, van der Hoek NJ, Borim FM, Mammen G, Bhandari M. Cannabis for pain in orthopedics: a systematic review focusing on study methodology. Can J Surg 2019;62:369-80.
20. Zeyl V, Sawyer K, Wightman RS. What Do You Know About Maryjane? A Systematic Review of the Current Data on the THC:CBD Ratio. Subst Use Misuse 2020;55:1223-7.
21. Woo JJ, van Reekum EA, Rosic T, Samaan Z. Children and Youth Who Use Cannabis for Pain Relief: Benefits, Risks, and Perceptions. Adolesc Health Med Ther 2020;11:53-61.
22. Flannery KM, D'Souza G, Agarwal R. Perioperative Management of the Pediatric Patient on Medicinal Marijuana: What Anesthesiologists Should Know. Anesth Analg 2019;129:1339-43.

2 PAIN OUT project in Serbia: a bundle of measures for perioperative pain management

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Introduction

The recognized problems in pain management in developing countries include lack of budgets for pain management improvement programs, lack of acute pain team organization, and lack of protocols to systematize available resources for pain management[1,2]. We recognized additional problems like the absence of data on pain evaluation and pain treatment results. And here we are not alone, as it was noted earlier that the problems in pain management in developing and middle-income countries are "mirrored and compound problems of developed countries "[3].

Among barriers to adequate pain management in developing countries are "healthcare professionals' lack of empathy," "positive social appraisal of patients' ability to cope with pain," ack of proper education about pain in medical schools, and lack of adequate resources[4]. Our personal experience also shows the hospital management ambivalence toward pain therapy and acute pain service (APS) organization.

The actions defined previously include the patient's need for proper education about pain[4], including family, friends, hospital management, and society. Additionally, hospitals' policy adjustment is needed to provide high-quality postoperative pain management[4], suggesting perioperative action. A web-based quality improvement and research network addressing the management of postoperative pain. The PAIN OUT project international project includes hospitals from Europe, the USA, Africa, South East Asia. The European Commission initially funded it, but now it is a not-for-profit, academic project coordinated from Jena University Hospital, Germany.

PAIN OUT EFIC project is per definition of EFIC Project (Introducing the project to wards 20 02 17) "an initiative assisting healthcare providers in optimizing perioperative pain management in Europe." It is best described as The Pain Care and Outcomes

Improvement Project based on Plan–Do–Study–Act-like methodology, clinical peer review, and logic "learn from the best "[5].

PAIN OUT Methodology

During the project in Serbia, teams in the hospitals used standardized performance measurement tools developed by the PAIN OUT team[5]. We recruited 1-2 surgical wards from each hospital to work together with ten hospitals from each country, forming a "national network." The network in each country was led by a local collaborator, a "network leader." This is a 2-year project, and in the end, the teams will decide if and how to improve their practice through the project. The Serbian PAIN OUT Network consists of ten hospitals, including Military Medical Academy, Oncology Institute of Vojvodina, Sremska Kamenica, Prijepolje General Hospital, Center of Anesthesiology and Reanimation, University Clinical Centre of Serbia, Center for Physical Medicine and Rehabilitation, University Clinical Centre of Serbia, Clinic for Digestive Surgery, University Clinical Centre of Serbia, Institute for Cardiovascular Diseases Dedinje, National Cancer Research Centre of Serbia, Belgrade, University Clinical Centre Nis, and Clinical Hospital Center "Bezanijska Kosa, "Belgrade, Serbia (Figure 1).

Figure 1. Hospitals taking part in the project.

The PROCESS questionnaire consists of the following five sections administrative information, screening/inclusion criteria, demographics, pain-related medical history, and perioperative medications. PAIN OUT is based on patient-related outcomes (PRO). Patients fill out the questionnaire in their native language, and surveyors enter the demographic and perioperative data from the patient's chart and then enter them in a web-based repository. The standardized methodology is used throughout the sites, and final results are analyzed. Every hospital needs to provide Ethical committee approval,

and patients need to be informed and consented to for entering the study. Among the PRO is the intensity defined as least, worst, and time in severe pain.

A perioperative pain bundle

A "bundle" is a small set of evidence-based interventions for a defined patient population and care setting, and clinicians accept them as elements of care that should be delivered as usual practice [6,7]. The implementation of these elements could improve significantly clinical results compared to the performance of each element separately[6,7]. An example of bundle implementation is the ABCDEF bundle for critically ill patients[8]. Fundamentally, bundle elements should be widely available and straightforward to implement after appropriate clinical judgment[9]. Also, if not possible, one of the elements can be canceled. Bundles should not be considered "magic bullets"; they are regarded as strategies to improve patient care [6,7].

The Serbian PAIN OUT Network bundle consisted of four elements: information about pain therapy strategy available throughout the perioperative period, but especially preoperatively; intraoperative use of 1 to 2 nonopioid medications and continue their application on the ward with "around the clock" timings in the total daily dose, intraoperative regional anesthesia either peripheral and central nerve block or wound infiltration; postoperative pain assessment at least once per nurses shift, and additional analgesics application if needed and pain reassessment (Figure 2). The opioids were advised if pain scores were higher than 6. The pain reassessment after intravenous medication application was recommended after 30 minutes and after oral analgesics after 60 minutes. We opted to introduce oral analgesics use whenever possible, non-pharmacological methods, and work on communication skills among medical staff, patients, and families (Figure 3).

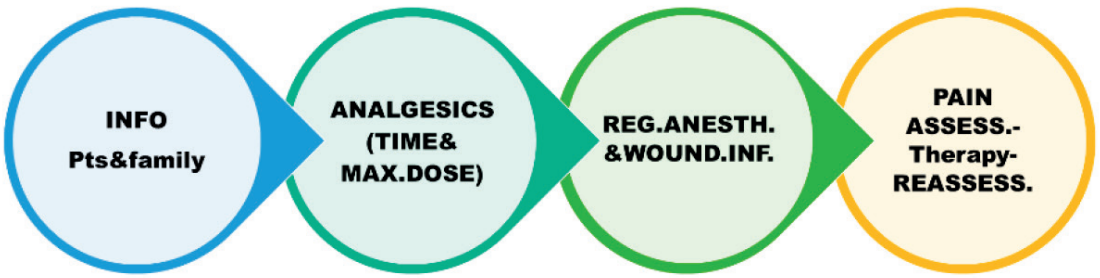

Figure 2. Perioperative pain management bundle elements suggested by PAIN OUT.

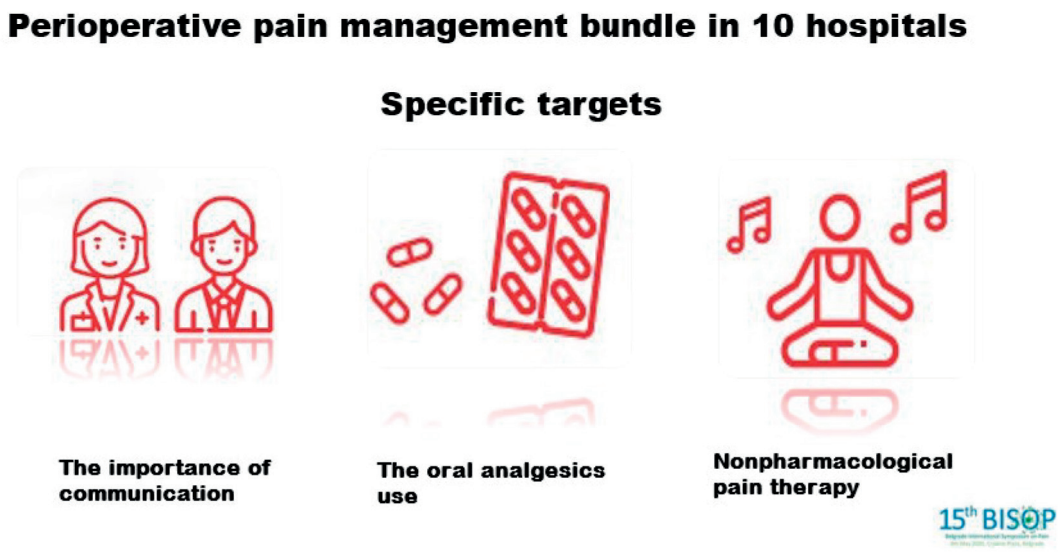

Figure 3. The introduction of "novel" principles in clinical practice in Serbian hospitals.

Work in progress

Our project started with Phase 1 from Jan to May 2018, when we collected the PRO on a fundamental level as the situation on pain therapy on the wards. During the interphase, we worked on the medical staff education in small groups or one-on-one bases and introduced the bundle. Phase 2 started in May 2019 and finished in February 2020.

For this study but also for broader use, we constructed several recommendations based on the internationally available literature, which were for the first time available in Serbian and include pain scale[9] (Figure 4), local anesthetic systemic toxicity guideline[10] (Figure 5), daily dosage for nonopioid medications available in Serbia[11] (Figure 6) and metamizole warning card[12] (Figure 7).

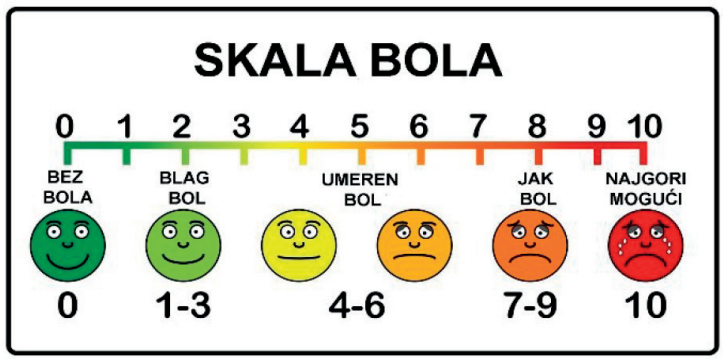

Figure 4. Information about postoperative pain-Numeric rating scale[9].

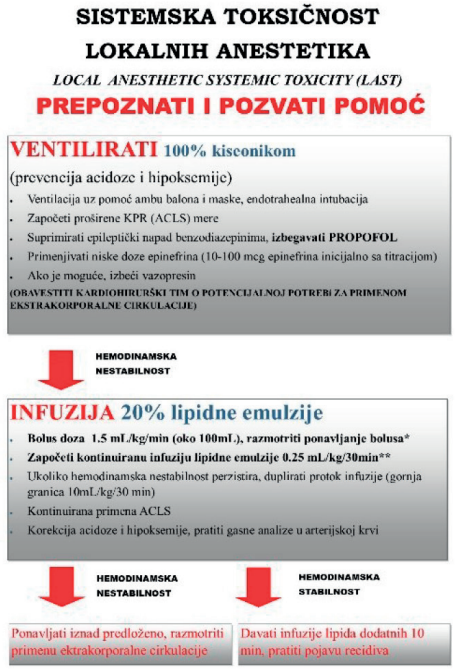

Figure 5. Local anesthetic systemic toxicity (LAST) guideline in Serbian language [10].

Serbian Pain Society

NEOPOIDNI ANALGETICI

Lek	Fabrički naziv	Način primene	Jedna doza (mg)	Trajanje efekta (h)	Maksimalna dnevna doza (mg)
Paracetamol	Febricet®, Panadol®, Panadol Advance®, Paracetamol Alkaloid®, Efferalgan ®	tableta, sirup	500-1000	4	4000
		Intravenski	1000	4	4000
Metamizol	Analgin®, Novalgetol®	tablcta/supozitorija	1000	4	4000
		intravenski	1250	4	4000-5000
Nefopam	Nefalgic®	intravenski, intramuskularno	20	-	120 Max 10 dana
Neselektivni nestoirdni antiinflamatorni lekovi (NSAIL)					
Ibuprofen	Argifen®, Argifen®forte, BlokMax®, Brufen®, Dolorofen®, Ibalgin®, Ibuprofen®, Ibumax	tableta/sirup	200-600	2-6	2400
Dikofenak	DicloRapid®, Diclofenac Duo®, Diclofenac retard®, Diklofenak ®, Naklofen® duo, Rapten duo®, Rapten-K®	tableta/ supozitorija	50-100	4-6	150
		intravenski		4-6	150
Ketoprofen	Ketonal ®, Ketonal®duo, Ketonal ®forte	tablcta	100-200 mg	4-6	200
		intravenski	-	-	-
Deksketoprofen	Dexomen ®, Dexomen ®inject	tableta	25	4-6	150
		intravenski	50		200
Ketorolak	Toradol®, Zodol®,	tableta, intravenski	30 inicijalno	4-6	150 mg prvog dana 120 mg nakon toga
			15-30 mg naredne doze	-	Max 5 dana
Acemetacin	Rantudil®forte	kapsula	60	-	180 Max 7 dana
Lornoxicam	Xefo®, Xefo®Rapid	tableta, intravenski, intramuskularno	8-16mg na 24h	-	16mg
COX-2 selektivni inhibitori					
Etoricoxib	Arcoxia ®, Etorapid®, Exxiv®	tableta	60-120	8-12	120

Tabelu priredili: Doc.dr Dušica Stamenkovic,anesteziolog; Dr Milijana Miljković, klinički farmakolog, Nikolina Milošević, student medicine, Vojnomedicinska akademija, Beograd.
Provera: Prof.Nebojša Ladević, Medicinski Fakultet Univerziteta u Beogradu

Figure 6. Nonopioid medications are available in the Serbian market, dosages, and different application formulas[11].

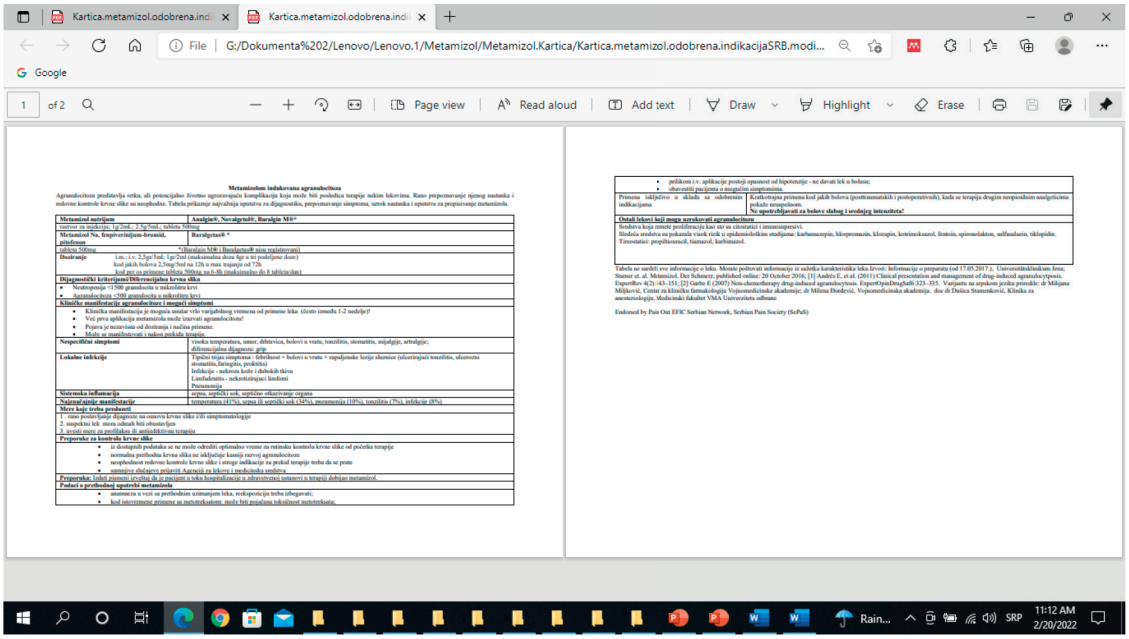

Figure 7. Metamizole use warning card in Serbian includes necessary information about medication and early side effects recognition instructions. The card is available per request from the authors[12].

All these guidelines were presented and available to use. Also, the authors introduced guidelines for different types of surgical procedures in the resources referenced here and summarized in the book dedicated to postoperative pain management[9].

Problems in perioperative pain management

We recognized a wide discrepancy among prescribed and given medications on the ward; the patients were rarely informed about postoperative pain treatment plans, wound infiltration, and regional anesthesia (spinal) were seldom used. In orthopedic patients, particular problems were recognized as once they are mobilized, their pain medications are restricted to NSAIDs per request. This is controversial since elderly pts have comorbidities frequently considered a contraindication for NSAIDs application[13].

The problem with pain therapy monitoring was alarming since no data about pain assessment existed in medical documentation. Considering the study, one of the problems was a misunderstanding of patients' specific questions/scales in the questionnaire. Despite the problems, we noticed the lack of interest in the clinical research-even among patients and family, and among medical staff lack of time for collecting and inputting data into a benchmarker – work overload.

Communication among the parts in the process

One of the fields identified as critical was missing information about perioperative pain to patients and their families. Additionally, team members' communication was not on the highest level. And it is recognized as a necessary part of the bundle in every field[6]. The poster resulted from the dr Suzana Bojic initiative and six-month process to construct the first version ever produced in Serbian hospitals; unfortunately, we didn't include patients, which will be addressed in the next version (Figure 8)[14].

Figure 8. Poster dedicated to patients and families presents information about perioperative pain management. It is available in Serbian, Cyrillic, Latin letters, and in english[13].

Communication among three actors in pain management needed improvement among all sides. The vital was education, and among all the materials that we used, we found that conversion on an on-to-one basis gave the best clinical results (Figure 9). However, we are aware that we need to implement much more effort in the future in communication.

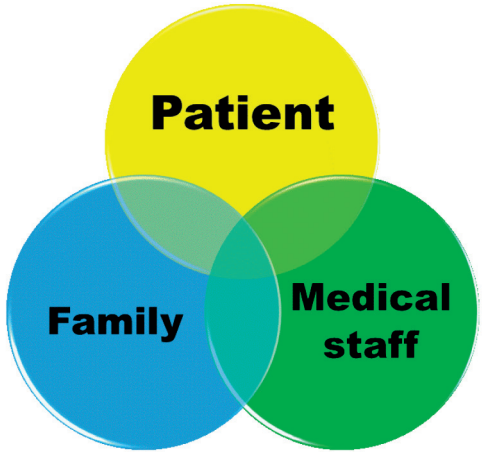

Figure 9. The vital missing part in pain management was communication among medical staff, patients, and family.

Action is needed

The essential elements of perioperative pain bundle measures proposed by PAIN OUT are perioperative information about pain therapy given to patients and families, regular implementation of 1 to 2 non-opioids medications in total daily dosage started intraoperatively and continued on the ward combined with regional analgesia techniques, and postoperative pain assessment and reassessment.

Key messages from our practice

A perioperative pain bundle is easy to apply and adjustable to individual patients' needs, hospital medication availability, and staff technical skills. This is in contrast with some other bundles[6]. Perioperative pain management is teamwork. Pain assessment and reassessment after treatment are essential for perioperative pain management. Record the results of pain measurement and therapy in medical documentation. Moderate pain needs to be treated with opioids. Enteral forms of analgesics should be a choice whenever possible. We advised against intramuscular injections of analgesics.

References:

1. Size M, Soyannwo OA, Justins DM. Pain management in developing countries. Anaesthesia. 2007;62 (Suppl 1):38-43.
2.Dahlman LE, Warfield CA. Pain management in developing counties. ASA Newsletter 2012; 76(6): 18-20.
3. Zaslansky R, Chapman CR, Baumbach P, Bytyqi A, Castro Lopes JM, Chetty S, Kopf A, Li L, Ern Ming L, Olawoye O, Rizza Parico J, Soyannwo O, Stamenkovic D, Wang H, Meissner W. Improving perioperative pain management: a preintervention and postintervention study in 7 developing countries. Pain Rep. 2019 Jan 25;4(1):e705.
4. Eshete MT, Baeumler PI, Siebeck M, Tesfaye M, Wonde D, Haileamlak A, Michael GG, Ayele Y, Irnich D. The views of patients, healthcare professionals, and hospital officials on barriers to and facilitators of quality pain management in Ethiopian hospitals: A qualitative study. PLoS One. 2019 Mar 14;14(3):e0213644.
5. http://pain-out.med.uni-jena.de/
6. Resar R, Pronovost P, Haraden C, Simmonds T, Rainey T, Nolan T. Using a bundle approach to improve ventilator care processes and reduce ventilator-associated pneumonia. Jt Comm J Qual Patient Saf. 2005 May;31(5):243-8.
7. Zaslansky R.Bundle overall version 12 12 18
8. Balas MC, Vasilevskis EE, Olsen KM, et al. Effectiveness and safety of the awakening and breathing coordination, delirium monitoring/management, and early exercise/mobility bundle. Crit Care Med. 2014;42(5):1024-1036.
9.Stamenković D. Monitoring bola. In Akutni postoperativni bol (*Postoperative pain management). Eds.* tamenković D, Ladjevic N. Medical Faculty University of Defence, Media Center, Belgrade, 2019, pp.59-80.

10.Slavković D, Kostić Z, Milošević N, Rančić N, Dragojević-Simić V, Stamenković D, Miljković M. Surgical wound infiltration by local anesthetic (wound infiltration). SJAIT 2019; 41(7-8): 143-155.doi:10.5937/sjait1908143S
11. Stamenković D, Miljkovic M, Milosevic N. Neopioidni analgetici (Prilog). In Akutni postoperativni bol (*Postoperative pain management). Eds.* tamenković D, Ladjevic N. Medical Faculty University of Defence, Media Center, Belgrade, 2019, pp.421.
12. Miljkovic M, Rancic N, Dragojevic-Simic V, Stamenkovic D. Metamizole for postoperative pain: PRO's and CON's. Proceedings 13th Belgrade International Symposium on Pain 2018, Belgrade, Serbia, May 18-19, 2018. p.69-77.
13.FDA. FDA Strengthens Warning of Heart Attack and Stroke Risk for Non-Steroidal Anti-Inflammatory Drugs | FDA Available online: https://www.fda.gov/consumers/consumer-updates/fda-strengthens-warning-heart-attack-and-stroke-risk-non-steroidal-anti-inflammatory-drugs (accessed on Jun 6, 2021).
14. Stamenkovic D. Postoperative pain management-information for patients and family, Serbian PainOut Network Initiative. 14th Belgrade International Symposium on Pain, Belgrade 17th to18th May 2019. Proceedings 86-93.

3 Perioperative pain management - the past, present and future - Military Medical Academy experience

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Abstract: Adequate perioperative analgesia is one of the main components of early recovery after surgery and is necessary in order to reduce the period of stress, and consequently, morbidity and mortality. The international PAIN OUT is a research project that collects data on outcomes reported from patients using the International Pain Outcome Questionnaire (IPO) and patients, clinical and treatment characteristics. In Military medical academy (MMA), as part of this project, were interwieved 550 patients in the general surgery ward and orthopedic ward, in two phases, the initial and postinterventional. The postintervenional phase included implementation of perioperative pain package (POP)- information about POP treatment options delivered to a patient and family preoperatively; application of the full daily dose of paracetamol and/or NSAIDs or metamizol, peripheral or epidural block or infiltration of a surgical wound; assessing, treating and re-evaluating pain in the postoperative period. Despite applied mesures no significant change in pain intensity was observed, but time spent in severe pain was significantly shorter. Patient-reported satisfaction with pain treatment on the postoperative day 1 was similar in both phases and the patientes reported higher satisfaction. Continuous assessment and reassessment of pain during the postoperative period, timely and valuable information for patients and family about postoperative pain and treatment, and multimodal analgesia improved the postoperative pain relief.

Introduction

Acute postoperative pain is present in patients 7 days after surgery. It occurs as a result of damage to the skin and organ structures, which leads to somatic visceral or neuropathic pain or a combination of several types of pain (1). Acute pain is the trigger of neuroendocrine, immune and anti-inflammatory responses. This leads to increased

levels of hormonal stress, catabolism with tissue loss, immunosuppression, increased myocardial oxygen demand that accompanies the onset of tachycardia and increased heart volume (2). In this way, the tendency towards thromboembolism, vasoconstriction, increased motility of the GIT, deterioration of lung function increases, and all as a result, there is an increase in morbidity and mortality (2). A causal-symptomatic solution is necessary in order to reduce the period of stress, and consequently, morbidity and mortality (2). Acute pain also causes short-term psychological changes. They can be influenced by timely conversation with the patient and providing an adequate explanation (2).

In the case of inadequately controlled postoperative pain after simple surgical interventions, chronic postoperative pain occurs in 10-15% of patients and lasts longer than 3 months after surgical intervention (1).

The Military Medical Academy (MMA) is involved in the international project PAIN OUT, which is a project aimed to improve the treatment of patients in the postoperative period. More than 80 hospitals around the world are involved in this project, which aims to develop and validate a system for measuring and feedback on the quality of outcomes and support decision-making in the treatment of pain.

Methods

The international PAIN OUT is a research project that collects data on outcomes reported from patients using the International Pain Outcome Questionnaire (IPO) and patients, clinical and treatment characteristics. The International Pain Outcomes questionnaire (IPO) comprises key patient-level outcomes of perioperative pain (POP) package includes pain intensity, physical and emotional functional interference, side effects, and perceptions of care. This study was conducted, as a part of PAIN OUT, in two wards, orthopedics and general surgery, after approval by the Regional Hospital Ethics Committee was obtained, and had two phases – initial and post-interventional. This research included data from 550 patients who were hospitalized in the MMA.

The International Pain Outcomes questionnaire comprises key patient-level outcomes of perioperative pain (POP) package includes pain intensity, physical and emotional functional interference, side effects, and perceptions of care (15). Patients evaluated patients' reported outcomes using a 11-point numerical rating scale (0 =no sensation, 10 =worst possible). Data were collected during the postoperative 1st day after orthopedic (n = 136; n = 136) and general surgery (n = 136; n = 142) during the initial and post-interventional phases of the study. Also, a comparison of the results of the initial and post - interventional phase was performed in the department of orthopedic and general surgery.

The initial phase lasted from January 15 to May 23, 2018, and included data from 271 patients (n=136 in the general surgery ward and n=136 patients in the traumatology and ortopedic ward) and the post-intervention phase lasted from April 1, 2019, to

March 11, 2020 and included data from 278 patients (n=142 on general surgery ward and n=136 patients on traumatology and ortopedic ward). The initial phase involved collecting data on the treatment of acute postoperative pain. In the post-interventional phase, the effectiveness of the perioperative pain package was implemented and tested. That includes information about POP treatment options delivered to a patient and family preoperatively; application of the full daily dose of paracetamol and/or NSAIDs or metamizol near the operation and continue in the ward; application of at least one of the following: peripheral or epidural block or infiltration of a surgical wound; assessing, treating and re-evaluating pain in the postoperative period.

Patient inclusion criteria are that the patient: 1) underwent surgery; 2) is 18 or older; 3) is on the first post-operative day; 4) has been back in the ward for at least 6 hours; and 5) agrees to participate in the survey. The aim of this study was to assess the change in patients' reported outcomes (PROs) data after the introduction of a POP improvement program.

Results

Demographic data comprise variables such as patient gender, age and are shown in Table 1. The total number of patients involved in the initial and postinterventional phase is shown.

Table 1. Demographic data.

Phase	**Initial n=136**	**Postinterventional n=142**	**p value**
General surgery			
Female n(%)	62 (22.3%)	65 (23.4%)	1.000*
Male n(%)	74 (26.6%)	77 (27.7%)	
Age (mean±SD)	59.17±13.56	59.96±15.52	0.641**
Traumatology and ortopedics			
	n=136	**n=136**	
Female n(%)	77 (28.3%)	87 (32.0%)	0.265*
Male n(%)	59 (21.7%)	49 (18%)	
Age (mean±SD)	67.39±14.96	70.04±12.42	0.112**

*Chi-square test **Independent sample test

Patients filled in the IPO on their own with no help from the surveyor, staff on the ward or family. However, when patients were incapable of doing so due to technical or medical reasons, they were interviewed. The percentage of interviewed patientes and the reasons for the interview are shown in Table 2. In the initial phase, a large percentage of patients didn't fill the IPO on their own. The most common reason for that was technical. In the general surgery ward, the patients were incapable of doing so due to having nasogastric tube, intravenous cannula, or were too weak after a surgery procedure. In the orthopedic ward the most frequent surgical procedures were total hip replacement and total knee replacement, so they could not take a suitable position. In the postinterventional phase, a significantly smaller number of patients were interviewed.

Table 2. The proportion of patients who were interviewed and reasons for the interview

Procedures	**General surgery**			**Ortopedic**		
Phase	**Initial n=136**	**Postintervent n=142**	**p value***	**Initial n=136**	**Postintervent n=136**	**p value***
Nºof interviewed pts	80 (59.7%)	50 (35.2)	<0.001	115 (84.6%)	89 (65.4%)	<0.001
technical reasons	47 (58.75%)	28 (56%)	1.000	96 (83.4%)	58 (65.17%)	0.004
too ill/weak	29 (36.23%)	6 (12%)	0.007	19 (16.52%)	3 (3.37%)	0.006
requested assistance	6 (7.5%)	16 (32%)	0.001	7 (6.09%)	25 (28.09%)	<0.001
did not understand scales	1 (1.25%)	0	1.000	4 (3.47%)	3 (3.37%)	1.000
too much pain	1 (1.25%)	0	1.000	2 (1.73%)	0	0.593

*Chi-square test

International Classification of Diseases version 9 surgical procedure (ICD-9-CM) codes were used for the classification of surgical procedures. The most frequent surgical procedures in the initial phase in the general surgery ward were complete thyroidectomy, open and other partial excision of the large intestine, and abdominoperineal resection of the rectum, retrospectively. In the postinterventional phase, the most frequent procedures were complete thyroidectomy, bilateral repair of inguinal hernia, then open and other partial excision of the large intestine and abdominoperineal resection of the rectum, retrospectively (Table 3.).

Table 3. The most frequent general surgery procedures in the initial and postinterventional phase.

Op code	Initial n=136	Postinterventional n=142	ICD9
06.4	31 (22.8%)	36 (26.0%)	complete thyroidectomy
53.1	9 (6.6%)	26 (18.3%)	bilateral repair of inguinal hernia
45.7	11 (8%)	15 (10.6%)	then open and other partial excision of the large intestine
48.5	11 (8%)	15 (10.6%)	abdominoperineal resection of the rectum

The most frequent procedures in the initial and postinterventional phase in the orthopedic and traumatology ward were total hip replacement, total knee replacement, closed reduction of fracture with internal fixation and partial hip replacement retrospectively. (Table 4.).

Table 4. The most frequent orthopedic procedures in the initial and postinterventional phase.

Op code	Initial n=136	Postinterventional n=136	ICD9
81.51	55 (40.4%)	51(37.5%)	total hip replacement
81.54	34 (25%)	40 (29.4%)	total knee replacement
79.1	28 (20.6%)	24 (17.7%)	closed reduction of fracture with internal fixation
81.52	10 (7.4%)	21 (15.4%)	partial hip replacement

Mean values of maximal pain in general surgery procedures were similar in both phases, but the time spent in severe pain was shorter in the postinterventional phase. That was the case in orthopedic procedures, also (Table 5).

Table 5. Pain intensity in general surgery and orthopedic procedures in the initial and postinterventional phase.

Procedures	General surgery			Ortopedic		
Phase	Initial n=136	Postintervent. n=142	P value*	Initial n=136	Postintervent. n=136	P value*
Max pain	5.52 ± 2.447	5.65 ±2.343	0,230	6.71±2.515	6.40±2.423	0.315
Time in severe pain	32 (25)%	20 (21)%	< 0,001	32(26)%	18 (27)%	< 0,001

*Independent sample test; mean±SD

Table 6 shows how postoperative pain affected activities in and out of bed on the first postoperative day. A significant difference is noticeable in surgical procedures where pain less affected the activity outside the bed less in the post-intervention phase. In addition, there is a significant difference in the reduction of pain that affected sleep in this phase in both procedures.

Table 6. Pain interference with activities in general surgery and ortopedic procedures in the initial and postinterventional phase.

Procedures	**General surgery**			**Ortopedic**		
Phase mean±SD	Initial n=136	Postintervent n=142	p value	Initial n=136	Postintervent n=136	p value
IntrfrBreath-Cough	3,74 ±3.54	3.84 ± 2.78	<0.001*	0.45±1.75	0.20±1.02	0.004*
IntrfrInbed	4.71 ±3.96	4.40 ± 2.66	0.006*	5.01±3.31	6.17±2.8	0.025*
IntrfrLeftbed n(%)	109 (80.1%)	112 (78.9%)	0.089**	41 (30.1%)	52 (38.2%)	0.201**
IntrfrOutbed	3.73 ±2.91	2.84 ± 2.31	0.001*	4.08±3.2	4.27±2.5	0.047*
IntrfrSleep	3.09 ±3.59	1.95 ± 2.76	<0.001*	4.54±4.24	3.38±3.45	<0.001*

*Independent sample test **Chi-square test

During the postoperative period, analgesics treatment-related adverse effect were monitored. The most common adverse effects were drowsiness in the initial phase and nausea in the postinterventional phase. Drowsiness was significantly lower in the postinterventional phase (Table 7). The nonpharmacologilac interventions used in post-operative period were talking to friends, talking to medical staff, walking, prayer. The use of nonpharmacological interventions was lower in the postinterventional phase.

Table 7. Treatment-related adverse effects and nonpharmacological interventions.

Adverse effects	**General surgery**			**Orthopedic**		
Phase mean±SD	Initial n=136	Postintervent n=142	p value*	Initial n=136	Postintervent n=136	p value*
Dizziness	25%	28.20%		22.10%	21.30%	
	0.88 ± 1.93	0.90 ± 1.76	0.905	0.93 ± 2.10	0.67 ± 0.62	0.235
Drowsiness	64.70%	37.30%		53.70%	28.70%	
	3.09 ± 3.19	1.57 ± 2.43	<0.001	2.60 ± 2.98	1.13 ± 2.11	<0.001

Itching	4.40%	1.40%		3.70%	3.70%	
	0.11 ± 0.55	0.01 ± 0.21	0.054	0.18 ± 0.99	0.06 ± 0.34	0.19
Nausea	46.30%	45.60%		41.20%	41.20%	
	2.25 ± 3.17	2.32 ± 3.09	0.859	2.22 ± 3.24	2.14 ± 3.08	0.833
Number of patients that had non-pharmacological interventions	14	7		13	4	

*Independent sample test

Despite the applied measures for the treatment of postoperative pain, there were patients who wanted more pain treatment, but in the second phase significantly less. Allowed participation was low in both phases. Patient-reported satisfaction with pain treatment on the postoperative day 1 was similar in both phases and the patientes reported higher satisfaction (Table 8.). Pain relief was higher in the post-interventional phase and was associated with higher satisfaction.

Table 8. Variables related to perception of care.

Procedure	**General surgery**			**Ortopedic**		
Phase	Initial n=136	Postintervent n=142	P value	Initial n=136	Postintervent n=136	P value
More treatment	18 (13.2%)	14 (9.9%)	0.677	39 (28.7%)	18 (13.2%)	0.006
Alwpart	5.58 ± 4.483	6.31 ± 4.542	0.179	5.46 ± 4.435	6.29 ± 4.509	0.123
Satisf	8.74 ± 1.945	8.82 ± 2.034	0.713	8.13 ± 2.557	8.57 ± 2.138	0.118
Relief	0.428 ±0.617	0.74 ± 0.371	<0.001	0.58 ± 0.48	0.74 ± 0.33	0.003

Chi-square test, Independent sample test

Dominant type of intraoperative anaesthesia was general. Regional anesthesia was represented in the orthopedics department, especially in the initial phase, but still insufficient. In the postinterventional phase intraoperative wound infiltration was used in most procedures (Table 9).

Table 9. Type of intraoperative anesthesia.

Procedures	**General surgery**			**Orthopedic**		
Phase	Initial n=136	Postintervent n=142	p value*	Initial n=136	Postintervent n=136	p value*
General anaesthesia	135 (99.3%)	142 (100%)	0,983	113 (83.1%)	127 (93.4%)	0.014
Regional anaesthesia – spinal	1 (0.7%)	0	0.98	23 (16.9%)	12	0.07
Intra-op wound infiltration	0	121 (85.2%)		0	124 (91.18%)	

Chi-square test

Table 10. showed the choice of pharmacological postoperative pain treatment, the use of nonopioids (diclofenac, ketoprofen, ketorolac), metamizole and paracetamol and opioids (sufentanyl, fentanyl, pethidine, morphine, tramadol).

In the general surgery ward the most frequently administered nonopioid in the initial phase were: intraoperatively - ketoprofen, in recovery – paracetamol, in the ward – diclofenac. The most frequently administered nonopioid in the postinterventional phase were: intraoperatively – metamizol, in recovery – metamizol and paracetamol, in the ward – metamizol. The most frequently administered opioid in initial phase were intraoperatively – fentanyl, in recovery – pethidine, in the ward only two patietes were treated with opioid analgesic (pethidine and tramadol), and in the postinterventional phase intraoperatively – sufentanil, in recovery and in the ward– pethidine.

In the orthopedic and traumatology ward the most frequently administered nonopioid in the initial phase were: intraoperatively and in recovery – ketoprofen, in the ward - diclofenac. The most frequently administered nonopioid in the postinterventional phase were: intraoperatively – metamizol, in recovery – paracetamol, in the ward – metamizol. The most frequently administered opioid in initial phase were intraoperatively – fentanyl, in recovery and in the ward – pethidine, and in the postinterventional phase intraoperatively – sufentanyl, in recovery and in the ward – pethidine.

Table 10. The choice of pharmacological postoperative pain treatment.

Procedures	**General surgery**				**Orthopedic**			
Drug Phase	Nonopioids Initial/ Postinterv	p value	Opioids Initial/ Postinterv	p value	Nonopioids Initial/ Postinterv	p value	Opioids Initial/ Postinterv	p value
Intraoperatively	86 (63.2%)/ 130 (91.5%)	<0.001	136 (100%)/ 142 (100%)	–	90(66.1%)/ 116 (85.3%)	<0.001	136 (100%)/ 136 (100%)	-
In recovery	51 (37.5%)/ 66 (46.5%)	0.163	62 (45.6%)/ 50 (35.2%)	0.063	84 (62.2%)/ 89 (65.4%)	0.621	31 (23%)/ 34 (25%)	0.777
On the ward	108 (79.4%)/ 135 (95.1%)	<0.001	2 (1.5%)/ 3 (2.1%)	0.964	131 (96.3%)/ 134 (98.5%)	0.569	4 (3%)/ 14 (10.3%)	0.028

* Chi-square test

Discussion

Pain management in the perioperative period refers to the measures before, during, and after a procedure that is intended to reduce or eliminate postoperative pain (3). The evidence suggests that less than half of patients who undergo surgery report adequate postoperative pain relief (4). Previous guidelines for pain management have not been a significant influence on exercise patterns or improvement of pain control in patients (5). Over the last 2 decades, attention has been increased to the need for better post-surgical pain management in order to improve clinical and economic outcomes (5). The causes of inadequate treatment of acute pain (as defined by the IASP - International Association for the Study of Pain) are: insufficient education of clinicians about the importance and need for adequate treatment of acute pain and the consequences of non-treatment; more than 50% of all hospitals in Europe do not have written guides or protocols for pain relief; in more than 50% of the hospitals pain is treated only at the request of the patient; there is a tendency to disregard the intensity of pain, and overreliance on opioid analgesia, which results in adverse effects and poor recovery, while also contributing to the „opioid epidemic" by the unnecessary discharge of patients on high doses of opioids supplied in large quantities (1,6).

Postoperative analgesia involves the use of non-pharmacological and pharmacological measures (2). Pharmacological therapy involves choosing drugs that act on different parts of the anatomical pain pathways. Analgesics act by inhibiting ascending pain signals, either in the periphery or centrally in the spinal cord and brain, and facilitating descending inhibitory spinal pathways. This leads to decreased nociceptive transmission to higher neurological centers (7).

Pharmacological therapy involves the use of non-steroidal anti-inflammatory drugs (NSAIDs), metamizole, paracetamol and opioid analgesics (2). Uncritical use of non-opioid analgesics, such as NSAIDs, may lead to side effects such as acute kidney injury, postoperative bleeding, or worsening of cardiac failure (6,7). The use of opioids in higher doses is associated with significant side effects that often impair the patient's post-surgical recovery (6). Multimodal analgesia aims to overcome this by using a combination of different analgesics and techniques, each with different modes and mechanisms of action in the peripheral and/or the central nervous system and might have additive or synergistic effects, to achieve better analgesia as well as to reduce side effects (6, 8). Thereby the patient's immediate postoperative recovery accelerates, reduces the dose of opioid analgesics and shortens the duration of hospitalization (9, 10, 11). The administration of infiltrative analgesia at the end of surgery showed a positive effect on the intensity of postoperative pain (11). Recommended doses of anesthetics for postoperative continuous wound infiltration do not lead to toxic effects that can be caused by local anesthetics (11). Also, the use of multimodal analgesia encourage the use of opiate-sparing techniques including regional analgesia (7).

PAIN OUT aims to improve the quality of pain management services provided to hospitalized patients after surgery and increase knowledge in this area (12). Thanks to the PAIN OUT project, our institution has implemented measures to provide better management of pain. These efforts have led to an improvement in some outcomes reported by patients associated with pain. The most significant difference is observed in the variable of time spent in severe pain. It is also present after surgical and orthopedic procedures. The reason for this may be that the analgesics in the post-intervention phase were dosed "per hour" and not at the request of the patient. Administration of full daily doses of analgesics, wound infiltration technique, as well as that the assessment and re-assessment of pain intensity in the postoperative period was continuously performed. The pain intensity was rated as moderate and was similar in both phases. Here we have some interesting findings; despite the pain intensity, intereference of pain on out-of-bed activities and sleep in the postinterventional phase was lower. Here we can hypothesize, that potentially our patients were better with pain measurement due to preoperative information about POP. Expectation of a peak-and-trough pattern of pain intensity may make temporary relief achieved with medication more relevant than overall pain intensity (13,14). Differences in pain perception and analgesic consumption are still tentative, and age and gender differences may be a contributing factor to pain sensation (15). Age has been suggested to have blunted the peripheral nociceptive function, decreasing pain in some contexts (15).

Associations of satisfaction with relief received and allowed participation were reported. Myles et al and Dolin et al observed patient satisfaction to be high in spite of experiencing moderate to severe pain and the reasons for this are complex (16, 17).

Availability of the staff for pain management or expressing an intention to provide relief, and informing patients preoperatively had positive influence on patient satisfaction (13).

A small number of the PAIN OUT patients reported that they tried nonpharmacological interventions for pain relief in both phases, but in the postinterventional phasese that number was smaller. There are several possible reasons for this finding. They could be: higher staff burnout, impossibility of implementation of nonpharmacological interventions, severe clinical condition of the patient.

Drowsiness is the most commonly reported adverse effect in initial phases while nausea is the most commonly reported adverse effect in the postinterventional phase. The frequency of reported nausea in the postoperative period was similar in both phases. The overall risk of postoperative nausea and vomiting after general anesthesia is reported to be approximately 30% (18). The general anasthesia was dominant in our study, while regional anesthesia was slightly represented. We found that all of our patients were given opioids intraoperatively, and most of them received nonopioids intraoperatively and in the recovery room. Patients received different analgesic postoperatively in the different doses. The administration of opioids might be a possible reason for postoperative nausea. Opioids inhibit peristaltic activity and delay gastric emptying and gastrointestional transit via activation of the bowel μ receptors, and has effects on central opioid receptors (19).

In the initial phase 63.2% of patientes in the general surgery ward recieved nonopioids (diclofenac, ketoprofen, ketorolac or metamizole or paracetamol or combination) intraoperatively, 37.5% in the recovery room, and 79.4% in the ward. In the postinterventional phase a significantly higher percentage of patients received neopioid intraoperatively (91,5%), in recovery (46,5%) and in the ward (95,1%). In the initial phase 66.1% of patientes in the orthopedic ward recieved nonopioids intraoperatively, 62,2% in the recovery room, and 96.3% in the ward. In the postinterventional phase a significantly higher percentage of patients received nonopioid intraoperatively (85.3%), and in the ward (98.5%). In the recovery that percentage was similar in both phases. Opioids (fentanyl, sufentanyl, morphine, pethidine and tramadol) use was present only intraoperatively and in a certain percentage in the recovery room. The administration of opioids was insufficient in the ward. The mean valule of maximal pain intensity after general surgery procedures was 5.52 ± 2.447 in the initial and 5.65 ±2.343 in the postinterventional phase. After orthopedic procedures the mean value was 6.71±2.515 in the initial and 6.40±2.42 in the postinterventional phase. We did not get significant diferences in pain intensity. The pain management was based on opioids intraoperatively, combination of NSAIDs, metamizol and paracetamol in recovery and in the ward. Some patientes recieved opioids in recovery room too, and only few patientes on the ward. All patients got wound infiltration intraoperatively in the postinterventional

phase, but that did not affect pain intensity. Time spent in severe pain was significantly shorter in this phase.

But Vallano et al observed that non-opioid analgesics were the preferred drugs for the treatment of postoperative pain (20). Balasubramanian at al in a prospective observational study concluded that high satisfaction and low Visual Analog Score were present in patients receiving a combination of NSAIDs and opioids compared to those who received only a combination of NSAIDs or opioids (15).

Conclusion

One of the main components of early recovery after surgery programs is the establishment of adequate perioperative analgesia. A combination of NSAIDs and opioids provide effective pain relief, high satisfaction and lesser sedation with least side effects following general surgery and orthopedic procedures. Continuous assesment and reassesment of pain during the postoperative period, timely and valuable information for patients and family about postoperative pain and treatment, and multimodal analgesia can go a long way in improving the quality and safety of postoperative pain relief.

Reference

1. Popović N, Lađević N, Stojanović M, Marković D, Ilić-Mostić T, Terzić B. Medical therapy acute postoperative pain. SJAIT 2014; 3 (4):209-214.
2. Malek J, Ševčik P, Bejšovece D, Gabrhelík T, Hnilicováa M, Křikava I et al. Postoperative Pain Management. Mladá fronta a. s. 2017; 9-19
3. American Society of Anesthesiologists (ASA) Committee on Standards and Practice Parameters .Practice Guidelines for Acute Pain Management in the Perioperative Setting Anesthesiology. 2012; 116:248 –73
4. Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: Results from a national survey suggest postoperative pain continues to be undermanaged. Anesth Analg,2003; 97:534-540
5. Gan TJ, Habib AS, Miller TE, White W, Apfelbaum JL. Incidence, patient satisfaction, and perceptions of post-surgical pain: results from a US national survey. Current Medical Research and Opinion, 2014;30 (1): 149–160.
6. Lee B, Schug SA, Joshi GP, Kehlet H, on behalf of the PROSPECT Working Group, Procedure-Specific Pain Management (PROSPECT) - An Update, Best Practice & Research Clinical Anaesthesiology, 2018; doi: 10.1016/j.bpa.2018.06.012.
7. Small C, Laycock H. Acute postoperative pain management. BJS 2020; 107: e70–e80. doi: 10.1002/bjs.11477
8. Chou R, Gordon BD, Leon-Casasola O, Rosenberg MJ, Bickler S, Brennan T et al. Guidelines on the Management of Postoperative Pain. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American

Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. The Journal of Pain, 2016; 17 (2): 131-157
9. Tilleul P, Aissou M, Bocquet F, Thiriat N, le Grelle O, Burke MJ, Hutton J, Beaussier M. Cost-effectiveness analysis comparing epidural, patient-controlled intravenous morphine, and continuous wound infiltration for postoperative pain management after open abdominal surgery. Br J Anaesth. 2012; 108(6):998–1005.
10. Xin Y, Hong Y, Yong LZ. Efficacy of postoperative continuous wound infiltration with local anesthesia after open hepatectomy. Clin J Pain. 2014; 30(7):571–6.
11. Slavković D, Kostić Z, Milošević N, Rančić N, Dragojević-Simić V, Stamenković D et al. Surgical wound infiltration by local anesthetic (wound infiltration). SJAIT 2019; 43 (7-8): 143-156
12. Zaslansky R et al. PAIN OUT: an international acute pain registry supporting clinicians in decision making and in quality improvement activities. Journal of Evaluation in Clinical Practice. 2014; doi:10.1111/jep.12205
13. Schwenkglenks M, Gerbershagen HJ, Taylor RS, Pogatzki-Zahn E, Komann M, Rothaug J et al. Correlates of satisfaction with pain treatment in the acute postoperative period: Results from the international PAIN OUT registry. PAIN, 2014.
14. McNeill JA, Sherwood GD, Starck PL, Nieto B. Pain management outcomes for hospitalized Hispanic patients. Pain Manag Nurs 2001;2:25–36.
15. Balasubramanian G, Vijayakumar C, Sistla SC, Badhe AS, Karthikeyan VS, Raj Kumar N, Singh SS. Postoperative analgesia following elective abdominal surgery: a prospective observational study Int Surg J 2017;4:2710-6
16. Dolin SJ, Cashman JN. Tolerability of acute postoperative pain management: nausea, vomiting, sedation, pruritus, and urinary retention. Evidence from published data. Br J Anaesth. 2005;95:584-91.
17. Myles PS, Williams DL, Hendrata M, Anderson H, Weeks AM. Patient satisfaction after anaesthesia and surgery: results of a prospective survey of 10,811 patients. Br J Anaesth. 2000;84:6-10.
18. Moraitis A, Hultin M, Wallden J. Risk of postoperative nausea and vomiting in hip and knee arthroplasty: a prospective cohort study after spinal anaesthesia including intrathecal morphine. BMC Anesthesiology 2020; 20:242. doi:10.1186/s12871-020-01154-z
19. Kovac, A. L. Updates in the Management of Postoperative Nausea and Vomiting. Advances in Anesthesia. 2018; doi:10.1016/j.aan.2018.07.004
20. Vallano A, Aguilera C, Arnau JM, Baños JE, Laporte JR. Management of postoperative pain in abdominal surgery in Spain. A multicentre drug utilization study. Br J Clin Pharmacol. 1999;47:667-73.

4 Snop mera u perioperativnoj kontroli bola kod uroloških procedura- iskustvo PainOut mreže u Srbiji /Perioperative Pain Management Bundle for urological Procedures-Serbian PAINOUT Network Experience

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Abstract

Introduction. Studies have proven that it is necessary to individualize the therapeutic approach to the treatment of acute postoperative pain, but so far it has not contributed to better pain control in developed countries. In 2013, the International Association for the Study of Pain (IASP) supported the formation of the Pain Out database- non-commercial project of academic importance, available to all physicians in Europe and the world. **Methodology.** After three-month observation phase of the project conducted in eight hospital centers in Serbia, the intervention phase of the project began. Previously agreed changes in the therapeutic approach were implemented in all hospital centers in intervention phase of the project. These changes in the therapeutic approach are referred to as "bundles" for better control of acute postoperative pain. The agreed measures, proven to be effective in the publications, included: information for the patient, recording the pain intensity, regular application of analgesic therapy, emphasizing the procedures of regional anesthesia (peripheral and central nerve blocks). We decided to try to increase the number of peripheral blocks for lumbotomy approach (infiltration of the wound with local anesthetic, as a single shot procedure performed by the same surgeon) and central nerve blocks (spinal, epidural). The use of analgesics per hour or continuously was already the standard procedure of the clinic. The procedure of informing patients began during the first contact with the anesthesiologist - at the pre-admission anesthesiology clinic, followed with the posters form information presented in the hall of the clinic. Recording of pain intensity in the standard check list was performed according to the agreement: at least four times after open surgical procedures and at least twice after endoscopic procedures. Before the observation phase started, it was decided to form two study wards - the open major ward (OM,)

and the endoscopic ward (E). The classification of operative procedures is coded according to the International Classification of Diseases, ICD-10 classification. **Results.** The first phase of the project included 149 patients, while in the second phase included 167 patients. In both phases, the majority of operative procedures was recorded in the OM group: 79.1% vs 71.3% compare to endoscopic 15.4% vs 15.0%. Within the OM group, the majority interventions were performed on the kidney (36.2% vs 50.3%). No statistically significant difference was found in the distribution of procedures in the two phases of the project (Chi-sqare test, p =2, 15). Regarding gender there was dominant representation of male patients compare with female (105 male / 44 female vs 118 male / 49 female), but no statistical difference between two populations of patients (Chi-sqare test p = 2.44). There was no difference regading age: 63.6 years vs 62.7 years. Comparing the prevalence of chronic pain in the preoperative period between the two examined patient populations of the two phases of the study, no statistically significant difference was found (p = 3,740 for OM surgery and p = 0,009 for endoscopic surgery). All OM procedures were performed under general anesthesia. Intraoperatively, the most common used opioid analgesic was fentanyl in both phases of the study (97.2% / 100%). In the first phase of the project, the wound infiltration procedure with local anesthetic was recorded in 2.7% of procedures, compare with 10,7% procedures of the seconed phase. In E surgery, operative procedures were performed predominantly under general anesthesia, but with a more significant presence of regional anesthesia - spinal anesthesia (10.3% / 31.2%). In postoperative period of OM surgery of the first phase the most common pharmacological modality of pain relief was the use of continuous intravenous analgesia consisting of tramadol and metamizole mixed in the same solution at the recommended maximum daily doses, while the analgesic regimen in the second phase of the project was analgesia in regular intervals regimen. Consequently,there was no a statistically significant difference in the recorded mean minimum and maximum pain intensity between the two phases of the project. The average duration of severe pain in first phase was twice as long as in the seconed phase for OM procedures. The applied analgesic therapy in both phases of the project caused minimal side effects - nausea, dizziness, drowsiness. Average 94.7% of the second phase patients were informed about postoperative measurement of pain intensity and modalities of pain treatment compared to 2.7% of patients from the first phase. In the endoscopic patient population, a greater reduction in pain intensity was observed in seconed phase compared to the first phase. In the OM population, a smaller reduction in pain intensity was observed in second phase compared to the first phase, but without the need for additional analgesia with equal satisfaction with the applied treatment. **Conclusion.** This project emphasized the importance of adequate treatment of acute postoperative pain and literally classified the pain as vital. This project pointed to less obvious risk factors for inadequate control of acute postoperative pain. Preoperative

psychological support to patients preparing for surgery could significantly supplement the pharmacotherapy of acute postoperative pain.

Uvod

Godinama unazad, mnogi istraživači ističu nedovoljno dobro lečen akutni postoperativni bol kao značajan problem u neposrednom postoperativnom toku [1,2]. Iako je označen kao značajan problem koji narušava kvalitet života pacijenta, odlaže mobilizaciju i povratak svakodnevnim aktivnostima, usporava zarastanje rana, učinjeni terapijski napori u lečenju aktunog postoperativnog bola se čine nedovoljnim [3]. Podaci ukazuju da se na godišnjem nivou 50% operisanih pacijenata žali na umereno jak do jak intenzitet bola neposredno nakon izvršene operativne procedure [4]. Studije su dokazale da je neophodna individualizacija terapijskog pristupa, ali ni ona nije doprinela boljoj kontroli bola u razvijenim zemljama Evrope i sveta [5,6,7]. Internacionalno udruženje za istraživanje bola (*IASP, International Assotiation for Study of Pain*) je 2013.godine podržalo formiranje Pain Out baze podataka, koja predstavlja nekomercijalni projekat od akademskog značaja, dostupan svim lekarima Evrope i sveta [8]. Inicijativu za formiranjem ovakvog projekta i kordinisanje projektom sprovode istaknuti stručnjaci u terapiji bola sa Univerzitetske klinike u Jeni (www.pain-out.eu).

Metodologija

Nakon tromesečne observacione faze projekta, sprovedene u osam bolničkih centara u Srbiji, započeta je druga, interventna faza, koja je trajala 01.04.2018 - 31.10.2020. U toku interventne faze, sprovedene su izmene terapijskog pristupa u svim bolničkim centrima, prethodno dogovorene i prilagođene načinu organizovanja zdravstevne službe u Srbiji. Ove izmene terapijskog pristupa su označene kao "bundle", snop mera u cilju bolje kontrole akutnog postoperativnog bola. Dogovorene mere, u publikacijama dokazane kao efikasne, obuhvatale su: informisanost pacijenta, beleženje jačine bola, regularne primene analgetske terapije, potenciranje postupaka regionalne anestezije (perifernih i centralnih nervnih blokova).

Analizom aktuelnog terapijskog pristupa na odeljenju anesteziologije i reanimatologije Klinike za urologiju Kliničkog centra Srbije, zaključili smo da se od predloženih mera već sprovode postupci regularne ili kontinuirane primene analgetske terapije, kao deo višegodišnjeg standardnog analgetskog protokola ovog odeljenja. Standardni analgetski pustupak podrazumeva primenu analgetske terapije u regularnim intervalima (samo neopioidne terapije ili kombinovane sa opioidom kod intravenske primene odnosno, kombinovanjem opioida i lokalnog anestetika kod epiduralne primene). Dogovorno, opredelili smo se da nastojimo da povećamo broj perifernih blokova kod lumbotomija (infiltracija rane lokalnim anestetikom, kao single shot procedura izvedena od strane istog hirurga) i centralnih nervnih blokova (spinal, epidural).Takođe, kod svih pacijenata je sprovedena informisanost u vezi sa lečenjem akutnog postopeativnog bola istim postupkom kao i beleženje jačine bola

prema numeričkoj skali (*NRS, Numeric Rating Scale*). Postupak informisanja pacijenata je započet tokom prvog kontakta sa anesteziologom- u predprijemnoj anesteziološkoj ambulanti. Inicijalni postupak se sastojao u postavljanju postera na vidno mesto u čekaonici ispred ambulante i razgovora sa pacijentom o metodu anesteziranja i lečenja akutnog postoperativnog bola. U hodniku svakog odeljenja klinike, postavljeni su isti posteri kao što je u čekaonici ambulante. Tokom preanestetičke vizite, pacijentima je dodatno pojašnjen postupak merenja jačine bola, predočena primena analgetske terapije, shodno prijavljenoj jačini bola. Beleženje jačine bola u postojeću terapijsku listu je sprovedeno prema dogovoru: minimum četiri puta kod otvorenih operativnih zahvata i minimum dva puta posle endoskopskih procedura. Višegodišnji sistem merenja jačine bola u ovom odeljenju podrazumeva da se jačina bola proverava više puta, ali ne i da se beleži.

Pre započinjanja observacione faze projekta, odlučeno je da se fomiraju dva studijska odeljenja- odeljenje otvorene velike hirurgije (OM, open major) i odeljenje endoskopije (E, endoscopic). Klasifikacija operativnih procedura je kodirana prema internacionalnoj klasifikaciji bolesti, ICD-10 classification. Ova klasifikacija ne obuhvata laparoskopske procedure u urologiji pa je u dogovoru sa glavnim kordinatorom projekta odlučeno da se ove procedure označe kao OM, uz napomenu o metodologiji izvođenja. U projekat su uključeni svi pacijenti koji su pristali na učešće u studiji, a koji se planiraju za operativno lečenje patološkog procesa bubrega, prostate i mokraćne bešike. Prvog postoperativnog dana, nakon vremena predviđenog za fizikalni tretman, sproveden je validirani upitnik na srpskom jeziku, čime se stekla jasnija slika o uticaju bola na dnevne aktivnosti. Svi podaci neophodni za unos u PainOut Benchmark su dobijeni iz upitnika i iz istorije bolesti pacijenta, prema protokolu.

Rezultati

U prvoj fazi projekta, učešće je zabeleženo kod 149 pacijenata, dok je u drugoj fazi u projekat uključeno 167 pacijenata. Zbog lakše sistematizacije i jasnijeg prikaza rezultata, sve operativne procedure iz OM grupe (open major) smo podelili prema poziciji hirurškog reza na: lumbotomije (interkostalni pristup), medijalne laparotomije (gornja i donja), infraumbilikalne medijalne laparotomije, laparoskopije. Pristupom preko lumbotomije su izvedene operativne procedure na bubregu. Pristupom preko medijalne laparotomije i infraumbilikalne laparotomije obavljene su operativne procedure na mokraćnoj bešici i prostati. U obe faze, najveći broj operativnih procedura je zabeležen u OM grupi: 79,2% u prvoj fazi i 71,3% u drugoj fazi projekta. U okviru OM grupe, najbrojnije su intervencije izvedene na bubregu (36,2% vs 50,3%) jer prema iskustvima istraživačkog tima, ove procedure prouzrokuju bol najvećeg intenziteta neposredno postoperativno, koji najviše korelira sa postoperativnim dnevnim aktivnostima i kvalitetom postoperativnog oporavka. U statističkom uzorku, značajno manje su zastupljene endoskopske procedure u obe faze projekta (15,4% vs 15,0%).

Tabela 1: Distribucija operativnih procedura prema fazama projekta

Hirurški pristup	Faza 1	Faza 2
Lumbotomija	54 (36,2%)	84 (50,3%)
Infraumbilikalni	37 (24,8%)	22 (13,2%)
Laparotomija	27 (18,2%)	13 (7,8%)
Laparoscopija	8 (5,4%)	12 (7,2%)
TURBT *	17 (11,4%)	13 (7,8%)
TURP **	3 (2,0%)	6 (3.6%)
PCNL ***	3 (2,0%)	6 (3,6%)
Σ	149 (100%)	167 (100%)

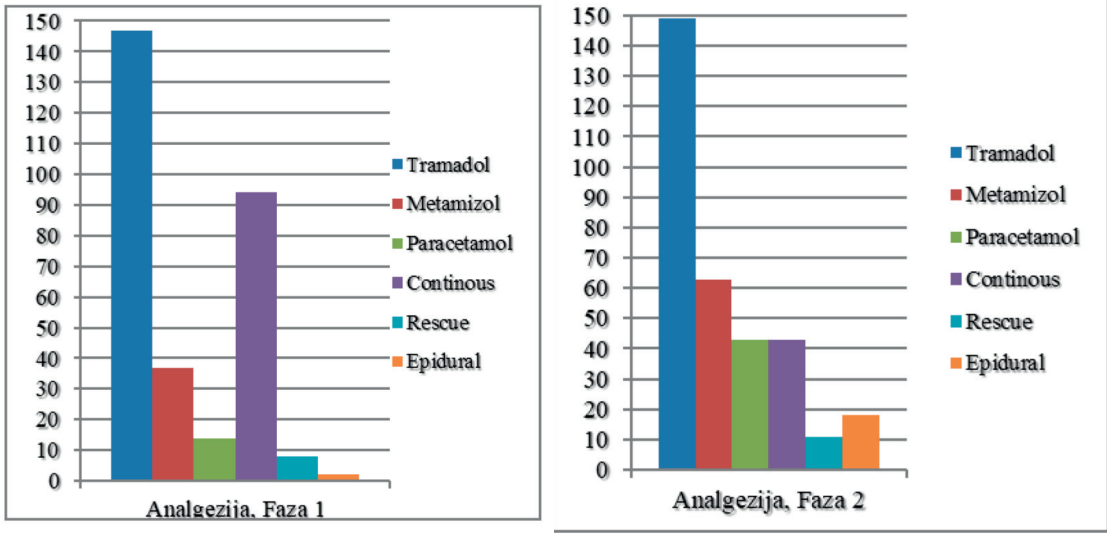
*TURBP- transurethral resection of bladder tumor, **TURP-transurethral resection of prostata, ***PCNL-precutanous nephrolitholapaxia

Primenom statističkog analitičkog metoda, nije nađena statistički značajna razlika u distribuciji operativnih procedura u dve faze projekta (Chi-sqare test, p =2, 15). U obe faze istraživanja, uključeni su pacijenti oba pola, uz dominantnu zastupljenost pacijenata muškog pola (105♂ / 44 ♀, 118 ♂/ 49 ♀), ali bez statsitičke razlike u distribuciji pacijenata po polu između dve populacije (Chi-sqare test p = 2,44). Prosečna starost pacijenta u fazi 1 je 63,6 godina, dok je prosečna starost pacijenata u drugoj fazi 62,7 godina, bez statisitički značajne razlike između istraživačkih grupa (T test, p = 0,001). Takođe, nije nađena ni statistički značajna razika u distribuciji prosečne telesne mase između dve hirurške grupe unutar svake populacije pacijenata niti među ispitivanim populacijama pacijenata (T test, p = 0,01). S obzirom da mnogi istraživači ističu veliki uticaj preoperativnog postojanja hroničnog bola na uspeh u lečenju akutnog postoperativnog bola [9], poređenjem zastupljenosti hroničnog bola u preoperativnom periodu između dve ispitivane populacije pacijenata u dve faze studije, nije nađena statistički značajna razlika, p = 3,740 za OM hirurgiju i p = 0,009 za endoskopsku hirurgiju. Sve OM procedure, izvedene su uslovima opšte endotrahealne anestezije. Prosečno 6% svih OM procedura čine laparoskopske procedure u obe faze studije. Intraoperativno, najzastupljenjiji opioidni analgetik je bio fentanil u obe faze studije (97,2% / 100%). Kombinovana anestezija bila je zastupljena kod 2,7% procedura u prvoj fazi i 14,8% procedura u drugoj fazi. Infiltracija rane lokalnim anestetikom je izvedena od strane istog hirurga kod operativnih procedura na bubregu, koje su izvedene preko pristupa kroz lumbotomiju. U prvoj fazi projekta, ovaj postupak je zabeležen kod 2,7% procedura, dok je u drugoj fazi ovaj postupak zabeležen kod 10,7% procedura. Nasuprot OM hirurgiji, kod E hirurgije, operativne procedure su izvedene dominantno u uslovima

opšte anestezije, ali uz značajniju zastupljenost regionalne anestezije- spinalne anestezije (10,3% / 31,2%).

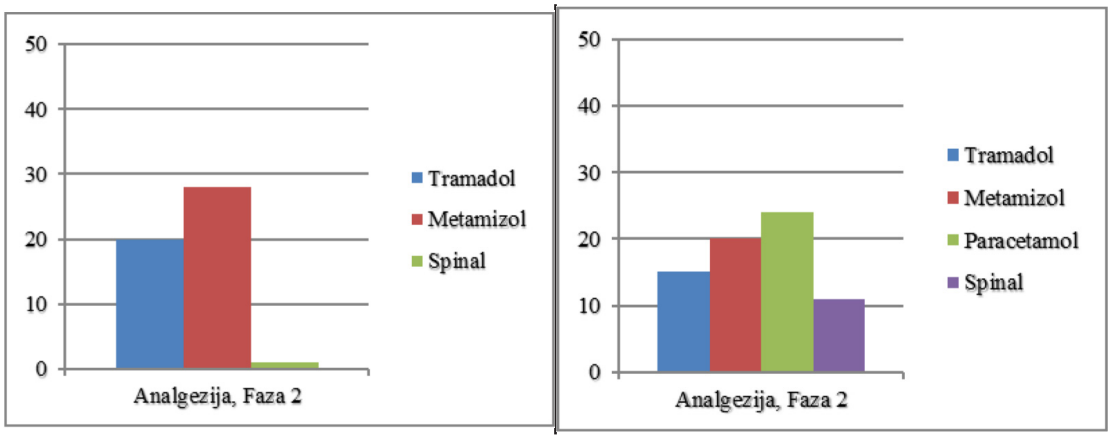
U postoperativnom periodu, kod OM hirurgije, najzastupljeniji farmakološki modalitet kupiranja bola u fazi 1 je bila primena kontinuirane intravenske analgezije koju su činili u istom rastvoru pomešani tramadol i metamizol u preporučenim maksimalni dnevnim dozama prema idelnoj telesnoj masi (tramadol 0,5mg/kg, metamizol 50mg/kg). Nasuprot ovome, izbor analgetskog režima u drugoj fazi projekta je predstavljala frakcionirana analgezija primenjena po satu koju je dominantno činila kombinacija tramadola i paracetamola ili metamizola. Zapaženo je značajno povećanje zastupljenosti epiduralne analgezije (**Grafikon 1, Grafikon 2**).

Grafikon 1 i 2: Izbor analgetske terapije u postoperativnom periodu kod Open Major procedura prema fazama projekta



Ovakav analgetski izbor nije imao za posledicu statistički značajnu razliku u zabeleženoj prosečnoj minimalnoj i maksimalnoj jačini bola između dve faze projekta. Ali, kod pacijenata koji su prijavili jak postoperativni bol, prosečno trajanje jakog bola u fazi 1 je bilo dvostruko duže u poređenju sa fazom 2. U postoperativnom periodu faze 1, paracetamol nije bio analgetski izbor, dok je u fazi 2 bio najzastupljeniji (**Grafikon 3, Grafikon 4**), što se nije odrazilo na prosečno zabeleženu prosečnu jačinu bola. Akutni postoperativni bol jakog intenziteta nije bio zabeležen kod ove populacije pacijenata ni u jednoj fazi.

Grafikon 3 i 4: Izbor analgetske terapije kod endoskopskih procedura prema fazama projekta



Procena i beleženje jačine bola je obavljano kroz sposobnosti pacijenta da izvede dublji udah i da se nakašlje, da ustane iz postelje i da nakon ustajanja iz postelje obavi osnovne aktivnosti u cilju održavanja higijene- da se umije, očešlja, obrije, čime je dodatno pokušana "objektivizacija " izmerenih vrednosti. Bol je na ove aktivnosti malo uticao u obe faze projekta (**Tabela 2**).

Tabela 2: Interferencija jačine bola sa dnevnim aktivnostima pacijenta prvog postoperativnog dana (0- bez, 10-najveća moguća)

Faza	Kašljanje/Dublje disanje	Ustajanje iz kreveta	Aktivnosti van kreveta
1	1,90 E, 2,91 OM	92% E, 75% OM	2,14 E, 3,37 OM
2	1,07 E, 3,16 OM	98% E, 89% OM	1,48 E 4,13 OM

Primenjena analgetska terapija u obe faze projekta je prouzrokovala minimalno ispoljene neželjene efekte- mučninu, vrtoglavicu, pospanost (**Tabela 3**).

Tabela 3: Intenzitet neželjenih efekata primenjene analgetske terapije

Faza	Mučnina	Vrtoglavica	Pospanost
1	0,74 E 1,94 OM	0 E 0,84 OM	0,5 E 1,58 OM
2	1,22 E 1,70 OM	0,13 E 0,47 OM	1,27 E 1,39 OM

Oko 94,7% pacijenata faze 2 je preoperativno primilo informaciju o postoperativnom merenju jačine bola i o modalitetima lečenja bola. U prvoj fazi projekta, 2,7% pacijenata je primilo istu informaciju preoperativno.

Tabela 4: Utisak pacijenta o primenjenom tretmanu bola

Faza	Redukcija bola, %	Još analgetika,%	Zadovoljstvo, 0-10
1	67,18 E 80,95 OM	15,2 E 22,1 OM	8,07 E 8,64 OM
2	88,02 E 77,17 OM	8,8 E 20,5 OM	9,69 E 8,60 OM

Kod endoskopske populacije pacijenata, zabeležena je veća redukcija jačine bola u fazi 2 u poređenju sa fazom 1, manja potreba za dodatnom analgetskom terapijom, osim ordinirane, i veće zadovoljstvo primenjenim analgetskim tretmanom. Nasuprot njima, u OM populaciji je u fazi 2 zabeležena manja redukcija jačine bola, ali bez potrebe za dodatnom analgezijom uz podjednaku satisfakciju primenjenim tretmanom (**Tabela 4**).

Zaključak

Ovaj projekat je naglasio značaj adekvatnog lečenja akutnog postoperativnog bola i doslovno ga svrstao u vitalne znake. U poređenju sa prvom fazom, u drugoj fazi projekta se nakon kratkotrajne edukacije pacijenata jasno izdvojila lakoća kojom pacijenti interpretiraju jačinu bola, odgovarajući na pitanja, čime smo dobijali verodostojniji podatak o jačini bola.Ovaj projekat je ukazao na manje očigledne faktore rizika za neadekvatnu kontrolu bola. U OM grupi pacijenata druge faze se u poređenju sa istom grupom prve faze beleži prosečno lošija kontrola bola, ali podjednako zadovoljstvo primenjenom terapijom, što bi moglo da ukaže na pozitivan psihološki učinak informisanja. S toga, preoperativna psihološka podrška pacijenata koji se pripremaju za operativni zahvat bi mogla značajno da dopuni farmakoterapiju akutnog postoperativnog bola.

Literatura

1. Wu C, Raja S.Treatment of acute postoperative pain. Lancet 2011;377:2215-2225
2. Meara JG,Leather AJ,Hagander L et al.Global surgery 2030:evidence and solutions for achieving health, welfare and economic development. Lancet 2015;386:569-624
3. Gerbershagen H,Aduckthil S,Van Wijck A, et al.Pain intensity on the First Day after surgery: a prospective cohort study.Anesthesiology 2013;118:934-44
4. Taylor RS, Ullrich K, Regan S, et al. The impact of early postoperative pain on health--related quality of life. Pain Pract 2012;13:515-523
5. Sommer M, Rijke M,van Kleef M. The prevalence of postoperative pain in sample of 1490 surgical inpatients. Eur J Anaesthesiol 2008;25:267-74

6. Melnyk M, Casey RG, Black P, Koupparis AJ. Enhanced recovery after surgery (ERAS) protocols:Time to change practice? CAn Urol Assoc J 2011;5:342-348
7. Lavandhomme P.Why me?The problem of chronic pain after surgery. Br J Pain 2017;11:162-165
8. Zaslansky R, Rothaug J, Chapman CR, et al. PAIN OUT:The making of international acute pain registry. Eur J Pain 2015;19:490-502
9. Hinrichs-Rocker A,Schulz K,Jarvinen I et al.Psychosocial predictors and corelates for chronic post-surgical pain-a systematic review.Eur J Paun 2009;13:719-30

Experience with perioperative pain management bundle for orthopedic surgery-team work

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Abstract

Anesthesia for orthopedic surgeries today is very challenging for anesthesiologists since most of these surgeries tend to be performed as one day surgery, which places new demands on the choice of procedure, patient, type of anesthesia, adequate discharge time and control of postoperative pain. Total hip and knee arthroplasty, as leading orthopedic procedure, are followed by severe pain, especially in the first 24 hours postoperatively and during active movements. Early mobilization and physical therapy contribute to the rapid and complete recovery of these patients. Intraoperative periarticular local infiltrations and peripheral nerve blocks are becoming more frequent in the postoperative pain control as part of multimodal concept.

Peripheral nerve blocks have been used as an anesthetic technique for decades. Ultrasound-guided peripheral nerve blocks have become a standard technique that, in addition to its greater efficiency, also provides the use of a smaller amount of local anesthetic and reduces the incidence of complications. By enabling a better understanding of the site and dose of local anesthetic administration, ultrasound guided peripheral nerve blocks today provide the highest degree of success and safety.

Uvod

Anestezija za ortopedske operacije danas, predstavlja veliki izazov za anesteziologa kako u pogledu preoperativne pripreme i vođenja anestezije, tako i sa aspekta postoperativne terapije bola. Izazov zavisi od kompleksnosti i/ili hitnosti intervencije, vezane za rekonstrukciju različitih anatomskih struktura kao i intraoperativnog gubitka krvi posebno kod pacijenata sa brojnim komorbiditetima[1]. Ova hirurgija zahteva takođe naročitu pažnju u prevenciji tromboembolijskih komplikacija kako u perioperativnom, ali pre svega u postoperativnom periodu posebno kod pacijenata sa imobilizacijom[1-3].

Takođe veliki značaj ima prevencija ali i lečenje posttraumatskih kognitivnih poremećaja i delirijuma naročito kod starijih pacijenata. Poslednjih godina, postoji tendencija da se većina ortopedskih operacija radi u ambulantnim uslovima što postavlja nove zahteve kako u izboru procedure, pacijenta, tipa anestezije, adekvatnom vremenu otpusta i postoperativnoj kontroli bola [2–4]. Ranom mobilizaciom i fizikalnom terapijom doprinosi se brzom i kompletnom oporavku ortopedskih pacijenata [1-5].

Ugradnja totalne proteze kuka i kolena značajno doprinosi poboljšanju kvaliteta života i smanjenju bola kod pacijenata sa bolestima ovih zglobova [1]. Povećanju ukupnog broja proteza koje se ugrade s jedne strane, doprinosi i starenje svetske populacije, ali i sve veći broj pacijenata sa nekoliko različitih tipova implantiranih proteza u telu. Tako danas artroplastike kuka i kolena postaju vodeće ortopedske procedure[1]. One su praćene izuzetno jakim bolom naročito u prva 24h postoperativno i tokom aktivnih pokreta[5]. Prepoznajući značaj kontrole bola ne samo intraoperativno već i postoperativno a u cilju prevencije pojave hroničnog bola, kod ovih pacijenata još uvek se traga za pravim rešenjem[5]. Danas se primenjuje multimodalni pristup i u okviru njega i preemtivna analgezija ali bez standarda kada su ovi pacijenti u pitanju. Takođe deo ovog koncepta je i sve češća primena periartikularne lokalne infiltracije i perifernih nervnih blokova[1,5-8] .

Lokalni anestetici

Lokalni anestetici su lekovi koji se veoma dugo, efikasno i bezbezdno primenjuju. Svoje dejstvo ostvaruju reverzibilnom blokadom natrijumskih kanala u aksonima nervnih ćelija sprečavajući tako propagaciju nervnih impulsa [1,9].

Nakon ubrizgavanja lokalnog anestetika samo mali procenat dospeva do membrane nerva[1,9]. Anestetik se inicijalno širi duž struktura sa najmanje otpora, koje deluju i kao fizičke barijere sprečavajući njegovo dalje difundovanje, dok jedan deo biva apsorbovan u cirkulaciju[1,9]. Stoga je veoma značajno njegovo davanje u neposrednoj blizini nervne strukture koja se želi blokirati kako bi se sa minimalnom dozom obezbedila adekvatna anestezija za što duži vremenski period[1,9]. Ponašanje lokalnog anestetika u tkivima, brzina početka delovanja kao i trajanje efekta određeni su fizičko-hemijskim karakteristikama: rastvorljivošću u mastima, vezivanjem za proteine, pKa, vazodilatacijom[1,9].

Mehanizam delovanja

Lokalni anestetik ostvaruje efekat nakon ulaska u nervnu ćeliju, reverzibilnim vezivanjem za alfa subjedinicu voltažno zavisnih natrijumskih kanala dovodeći do konformacionih promena kojima se sprečava dalji ulazak jona Na^+ u unutrašnjost ćelije[1,9]. Da bi došlo do ovog vezivanja kanal mora biti u otvorenom stanju a lokalni anestetik u jonizovanoj formi. Lokalni anestetici pored natrijumskih kanala mogu blokirati i druge kanale u različitom stepenu, pre svega kalijumske i kalcijumske ali i N-metil-D-aspartat receptore[1,9]. Lokalni anestetik svoj efekat prvo ostvaruje na vlaknima manjeg dijametra, zatim tankim B i C i na kraju na A delta vlaknima. Stoga se prvo blokiraju vlakna kojima se prenosi bolni nadražaj, zatim ona kojima se prenosi senzibilitet i na kraju motorna[1,9].

Administracija lokalnih anestetika

Primena lokalnih anestetika u okviru regionalne anestezije ima za cilj da se sa minimalnom dozom obezbedi adekvatna analgezija za što duži vremenski period. Ovo se postiže uzimajući u obzir individualne karakteristike bolesnika, maksimalno dozvoljenu dozu anestetika (na osnovu telesne težine bolesnika), mogućnost primene vazokontriktora, brzinu i tehniku administracije kao i prokrvljenost lokalnog tkiva. Rastvori lokalnih anestetika najčešće su 0,5%, 1% ili 2%[1,9]. Ukoliko je neophodno analgeziranje više operativnih polja kod jednog bolesnika, u cilju povećavanja volumena a ne doze primenjenog lokalnog anestetika, najčešće se prave razblaženja i to 0,25%, 0,125% ili 0,0625%[1,9]. Dodavanjem vazokstriktora (adrenalin 1:200000) rastvoru lokalnog anestetika usporava se apsorpcija i produžava efekat uz bolju hemostazu operativnog polja. Neophodna je posebna opreznost pri primeni vazokonstriktora kod bolesnika sa poremećajima srčanog ritma dok su kontraindikovani za anesteziranje distalnih delova tela vaskularizovanih terminalnim arteriolama[1,9].

Toksičnost lokalnog anestetika je povezana sa maksimalnom koncentracijom u plazmi. Cirkulišući nivo je određen brzinom apsorpcije, distribucije i metabolizma koje variraju od anestetika do anestetika[1,9]. Metabolizam lokalnog anestetika zavisi od njegove hemijske strukture prisustva amidne ili estarske veze[1,9]. Primena lokalnih anestetika se smatra sigurnom ukoliko se daje adekvatna doza na odgovarajućem mestu[1,9]. Neželjeni efekti ,koji nisu tako retki, u kliničkoj praksi se najčešće pogrešno svrstavaju u alergijske reakcije. Lokalne i sistemske toksične reakcije nastaju kao rezultat primenjene velike doze ali i zadesne intravaskularne ili intratekalne primene[1,9].

Periartikularna infiltracija

Periartikularna infiltracija koristi se kao deo multimodalnog koncepta analgezije u ortopedskoj hirurgiji najčešće kod artoplastika kolena. Ona podrazumeva infiltraciju rastvora lokalnog anestetika intraoperativno tokom različitih faza rada. Kod ugradnje totalne proteze kolena koristi se 120 ml rastvora koji pored lokalnog anestetika (0.5% bupivacaine ili levobupivacaine 3mg/kg) sadrži i opioid (morfin 5mg), NSAIL (ketorolak 30 mg) i adrenalin (100-300mcg). Prvih 60 ml se infiltriše neposredno pre cementiranja proteze i podrazumeva infiltraciju zadnje kapsule kako posterolateralne, tako i posteromedijalne strane. Sa posebnom pažnjom se infiltriše centralni deo (bez duboke aplikacije rastvora), uz obaveznu aspiraciju pri svakom ubodu[10-12]. U ovoj fazi se infiltriše tkivo medijalnog i lateralnog femoralnog recesusa, kao i medijalna i lateralna kapsula u projekciji ranijeg meniskokapsularnog spoja. Sledeća faza se izvodi po završetku cementiranja protetskih komponenata. Tako se 40 ml pripremljenog rastvora infiltriše duž lateralne i medijalne strane artrotomije kao i retropatelarno masno tkivo. Nakon rekonstrukcije zglobne kapsule subkutano masno tkivo se infiltriše sa preostalih 20 ml [10-12].

Periartikularna infiltracija dovodi do smanjenja postoperativnog bola kao i potrošnje opioida ali ne obezbeđuje adekvatnu analgeziju u postoperativnom periodu

posebno pri izvođenju aktivnih pokreta [13]. Mnogo bolji analgetski efekti postižu se primenom perifernih nervnih blokova[13].

Periferni nervni blokovi

Periferni nervni blokovi u poslednje vreme postaju deo multimodalnog koncepta analgezije naročito u ortopedskoj hirurgiji, zahvaljujući brojnim prednostima, koje se odnose pre svega na kardiorespiratornu stabilnost, minimalnu pripremu pacijenta, dobru postoperativnu kontolu bola kao i smanjenju upotrebu opioida, redukciju postoperativne mučnine i povraćanja kao i broja bolničkih dana, prevenciji ponovnog prijema pacijenata, bržem otpustu pacijenta, ranoj rehabilitacija i smanjenju ukupnih troškova ali pre svega zadovoljstvu pacijenata [14,15]. U skladu sa svim ovim prednostima ne iznenađuje njihova sve šira primena u svakodnevnoj praksi poslednjih godina [15]. Uvođenje nervnog stimulatora u rutinsku anesteziološku praksu, a u poslednjih dvadesetak godina i ultrazvuka, omogućilo je značajno širu primenu perifernih nervnih blokova, uz visok stepen uspešnosti, ali i sigurnosti za pacijenta [16]. Nervnim stimulatorom se generiše električni impuls niskog inteziteta (do 5 mA), kratkog trajanja (0,05–1 ms) i frekvence (1–2 Hz). U cilju što boljeg pozicioniranja igle, a bez kontakta sa nervom, preporučuje se jačina 0,2–0,3 mA, 0,1 ms, 2 Hz [17]. Međutim, u poređenju sa nervnim stimulatorom, blokovi perifernih nerava vođeni ultrazvukom imaju određene prednosti, pre svega u kvalitetu bloka, količini upotrebljenog lokalnog anestetika, manjoj neprijatnosti za pacijenta, kao i manjoj učestalosti punkcije krvnog suda [17]. Da bi se omogućila vizuelizacija nervnih struktura, u zavisnosti od dubine, koriste se dve sonde: linearna (frekvence 5–18m Hz) za površne strukture do 6 cm i konveksna (frekvence 2,5–5 MHz) za dublje strukture [1,17] .

Međutim povrede nerava iako retke, ipak su moguće i najčešće nastaju kao rezultat direktnog oštećenja iglom, toksičnog efekta anestetika ili kao sekundarna komplikacija usled krvarenja ili infekcije. Izuzetno je važno njihovo rano prepoznavanje jer oporavak nerva zavisi od ranog prepoznvanja i započinjanje terapije [18-21]. Imajući u vidu da klinički značajan blok može da nastane davanjem < 1 ml lokalnog anestetika pod kontrolom ultrazvuka definisane su tri tehnike : 1. intraneuralna –kod proksimalnih nervnih struktura se ne preporučuje jer usled male količine vezivnog tkiva u njima, može doći do lezije nerva ; 2. intrapleksus (sub-perineuralna) koja može biti perineuralna (kada se okružuje svaki pojedinačni nerv) ili perivaskularna (lokalni anestetik se daje u omotač oko arterije) 3. peri-pleksus (ekstrafascijalna) – podrazumeva davanje lokalnog anestetika van pleksusa, u slučaju interskalenskog bloka između skalenskih mišića [22-28].

Pre izvođenja svakog perifernog nervnog bloka, neophodna je pažljiva procena anatomskih odnosa kod svakog pacijenta i njihova detaljna analiza. Nakon provere neurološkog statusa u regiji od interesa detaljno se objašnjava postupak pacijentu u cilju bolje saradnje ali i upoznavanje sa mogućim neželjenim efektima i komplikacijama. Nakon dezifenkcije kože pristupa se izvođenju bloka [29,30].

Blok se može izvesti pojedinačnim davanjem lokalnog anestetika ili postavljanjem katetera perineuralno u cilju kontinuiranog davanja[15]. Poželjan analgetski efekat u cilju postoperativne kontrole bola koji se postiže primenom perifernog nervnog bloka trebao bi da bude što duži. Davanjem lokalnog anestetika u jednoj dozi, obezbeđen je analgetski efekat do 24 sata[15]. S druge strane plasiranje katetera u neposrednoj blizini nerva i kontinuirano davanje lokalnog anestetika može biti komplikovano opstrukcijom katetera, migracijom kao i curenjem lokalnog anestetika pored katetra ali i njegovim akcidentalnim ispadanjem. Takođe iako retko na prisustvo katetera može doći do razvoja lokalne inflamacije i infekcije. Bakterijska kolonizacija katetera , koji stoji duže od 48 h, smatra se da postoji kod 69% pacijenata koji su prethodno primali antibiotsku terapiju ili su dijabetičari [15, 30,31]. Adekvatan izbor pacijenata kao i njihova edukacija u cilju rukovanja sa kateterom, ograničava njegovu primenu kao i neophodnost 24h dostupnosti medicinske pomoći u cilju otklanjanja bilo kakvih komplikacija[30,31].

Adekvatan izbor anestezije ali i postoperativne analgetske terapije kada su u pitanju artroplastike, zahteva izbor perifernog nervnog bloka kojim se postiže analgezija u odsustvu mišićne slabosti a u cilju rane rehabilitacije pacijenta. Složenosti ovog pitanja doprinosi i veliki interindividualni anatomski varijabilliteti struktura [32,33].

Tako je kada su u pitanju artroplastike kolena, femoralni nervni blok dugo godina bio osnov postoperativne analgezije. Njegova analgetska efikasnost je potvrđena i kod artroskopija kolena ali i mišićna slabost koja nije bila željeni klinički efekat[35] .

Postavljajući nove zahteve u rehabilitaciji ovih pacijenata, koji se pre svega odnose na ranu aktivnu a ne pasivnu rehabilitaciju, navelo je mnoge kliničare u potragu za različitim modalitetima analgetske terapije. Smanjenjem doze lokalnog anestetika, postiže se diferenciranje bloka sa adekvatnim analgetskim efektom ali i očuvanjem mišićne slabosti. Kao alternativa bloku n.femoralis-a predložen je blok aduktor kanala. Ovim blokom kod artroplastika kolena postignuta je adekvatna rana mobilizacija bez razlike u analgetskoj efikasnosti u odnosu na femoralni blok[38]. Kompleksnosti njegovog izvođenja doprinose značajne razlike u pogledu objašnjenja neuronskih struktura u samom aduktor kanalu kao i „idealno" mesto za primenu anestetika. Davanje velike količine lokalnog anestetika u distalnom delu aduktor kanala, takođe može dovesti do mišićne slabosti i to potkolenice i stopala, usled širenja u poplitealnu jamu i blokade n.ishiadicus-a[38] .

Zaključak

U zaključku možemo reći da periferni nervni blokovi vođeni ultrazvuom danas predstavljaju svakodnevnu praksu rada anesteziologa. Oni obezbeđuju najviši stepen uspešnosti, ali i sigurnosti za pacijenta. Učestalost toksičnih efekata lokalnih anestetika ali i povrede nerava ukoliko se izvode pod kontrolom ultrazvuka su zanemarljive. Ali uprkos brojnim dokumentovanim podacima o prednostima njihove primene, periferni nervni blokovi u kontroli postoperativnog bola ne primenjuju se dovoljno često. Njihovo

izvođenje zahteva poznavanje relativno jednostavne tehnike i mogu se primeniti kod gotovo svih pacijenata, izuzev onih sa alergijom na lokalne anestetike. Adekvatanim izborom perifernog nervnog bloka trebalo bi obezbediti adekvatnu analgeziju u odsustvu mišićne slabosti a u cilju rane rehabilitacije pacijenta.

Literatura

1. Miller R. Miller's anesthesia. 9th edition, Philadelphia, Elsevier; 2019.
2. Fournier M, Brolin T, Azar F, Stephens R, Throckmorton T. Identifying appropriate candidates for ambulatory outpatient shoulder arthroplasty: validation of a patient selection algorithm. J Shoulder Elbow Surg. 2018; (18):S1058–2746.
3. Leggott K, Martin M, Sklar D et al. Transformation of anesthesia for ambulatory orthopedic surgery: A mixed-methods study of a diffusion of innovation in healthcare. Healthc (Amst). 2016; 4(3):181–7.
4. Ludwin D. Setting up an ambulatory regional anesthesia program for orthopedic surgery. Anesthesiol Clin. 2014; 32(4):911–21.
5. Kukreja P, Feinstein J, Kalagara HK et al. Summary of the anatomy and current regional anesthesia practices for postoperative pain management in total knee arthroplasty. Cureus. 2018; 10(6):e2755.
6. Elkassabany N, Abraham D, Huang S et al. Patient education and anesthesia choice for total knee arthroplasty. Patient Educ Couns. 2017; 100(9):1709–1713.
7. Liu S, Chen X, Yu C et al. Comparison of periarticular anesthesia with liposomal bupivacaine with femoral nerve block for pain control after total knee arthroplasty: A PRISMA-compliant meta-analysis. Medicine (Baltimore). 2017; 96(13):e6462 doi:
8. Berninger MT, Friederichs J, Leidinger W et al. Effect of local infiltration analgesia, peripheral nerve blocks, general and spinal anesthesia on early functional recovery and pain control in unicompartmenatl knee artroplasty BMC Musculoskelet Disord. 2018; 19(1):249
9. Butterworth J., Mackey D., Wasnick J. Morgan and Mikhail's Clinical Anesthesiology, 6th edition. New York, Chicago, McGraw-Hill, 2018.
10. Shpangehl M., Clarke H. Peri-operative pain management for total knee replacements – Mayo Clinic Available: www.youtube.com/watch?v=R0Q4adIYF-Q.
11. Chung A, Spangehl M. Peripheral nerve blocks vs periarticular injections in total knee arthroplasty. J Arthroplasty. 2018; 33(11):3383–3388.
12. Horlocker TT, Hebl JR, Gali B et al. Anesthetic, patient, and surgical risk factors for neurologic complications after prolonged total tourniquet time during total knee arthroplasty. Anesth Analg. 2006; 102(3):950–5
13. Kim DH, Beathe JC, Lin Y, YaDeau JT, Maalouf DB, Goytizolo E, Garnett C, Ranawat AS, Su EP, Mayman DJ, Memtsoudis SG. Addition of Infiltration Between the Popliteal Artery and the Capsule of the Posterior Knee and Adductor Canal Block

to Periarticular Injection Enhances Postoperative Pain Control in Total Knee Arthroplasty: A Randomized Controlled Trial Anesth Analg 2019 Aug;129(2):526-535
14.Brattwall M, Jildenstal P, WarrénStomberg M, Jakobsson JG. Upper extremity nerve block: how can benefit, duration, and safety be improved? An update. F1000Res. 2016 May 18.
15. Joshi G, Gandhi K, Shah N, Gadsden J, Corman SL. Peripheral nerve blocks in the management of postoperative pain: challenges and opportunities. J Clin Anesth. 2016 Dec; 35:524–529.
16. . Gelfand HJ, Ouanes JP, Lesley MR, et al. Analgesic efficacy of ultrasound-guided regional anesthesia: a meta-analysis. J Clin Anesth. 2011; 23(2):90–6.
17. Guay J: The neurostimulator for brachial plexus blockade by the axillary approach: a metaanalysis on its efficacy to increase the success rate. Ann Fr Anesth Reanim. 2005; 24(3):239–43.
18. Sehmbi H,Madjdpour C, Shah UJ et al. Ultrasound guided distal peripheral nerve block of the upper limb: A technical review. J Anaesthesiol ClinPharmacol. 2015; 31(3):296–307.
19. Guay J. The neurostimulator for brachial plexus blockade by the axillary approach: a metaanalysis on its efficacy to increase the success rate. Ann FrAnesth Reanim. 2005; 24(3):239–43.
20. Farber SJ, Saheb-Al-Zamani M, Zieske L, Laurido-Soto O, Bery A, Hunter D, Johnson P, Mackinnon SE. Peripheral nerve injury after local anesthetic injection. Anesth Analg. 2013; 117(3):731–9.
21. Tran dQ, Dugani S, Pham K, Al-Shaafi A, Finlayson RJ. A randomized comparison between subepineural and conventional ultrasound-guided popliteal sciatic nerve block. Reg Anesth Pain Med. 2011; 36:548–52
22. Missair A, Weisman RS, Suarez MR, Yang R, Gebhard RE. A 3-dimensional ultrasound study of local anesthetic spread during lateral popliteal nerve block: what is the ideal end point for needle tip position? Reg Anesth Pain Med. 2012; 37:627–32.
23. Perlas A, Wong P, Abdallah F, Hazrati LN, Tse C, Chan V. Ultrasound-guided popliteal block through a common paraneural sheath versus conventional injection: a prospective, randomized, double-blind study. Reg Anesth Pain Med. 2013; 38:218–25.
24. Karmakar MK, Shariat AN, Pangthipampai P, Chen J. High-definition ultrasound imaging defines the paraneural sheath and the fascial compartments surrounding the sciatic nerve at the popliteal fossa. Regional Anesthesia and Pain Medicine 2013; 38:447–51
25. Bigeleisen PE. Nerve puncture and apparent intraneural injection during ultrasound-guided axillary block does not invariably result in neurologic injury. Anesthesiology. 2006; 105:779–83. 26. Andersen HL, Andersen SL, Tranum-Jensen J. Injection inside the paraneural sheath of the sciatic nerve: direct comparison

among ultrasound imaging, macroscopic anatomy, and histologic analysis. Reg Anesth Pain Med. 2012; 37:410–4.
27. Abdallah FW, Chan VW. The Paraneural Compartment: A New Destination? Regional Anesthesia and Pain Medicine. 2013; 38:375–7
28. Bernucci F, Gonzalez AP, Finlayson RJ, Tran de QH. A prospective, randomized comparison between perivascular and perineural ultrasound-guided axillary brachial plexus block. Reg Anesth Pain Med. 2012; 37:473–7.
29. Fredrickson MJ, Wolstencroft P, Kejriwal R, Yoon A, Boland MR, Chinchanwala S. Single versus triple injection ultrasound-guided infraclavicular block: confirmation of the effectiveness of the single injection technique. Anesth Analg. 2010; 111:1325–7.
30. Spence BC, Beach ML, Gallagher JD, Sites BD. Ultrasound-guided interscalene blocks: understanding where to inject the local anaesthetic. Anaesthesia. 2011; 66:509–14.
31. Marhofer D, Marhofer P, Triffterer L, Leonhardt M, Weber M, Zeitlinger M. Dislocation rates of perineural catheters: a volunteer study. Br J Anaesth. 2013; 111:800–6.
32. Neal JM, Salinas FV, Choi DS. Local anesthetic-induced myotoxicity after continuous adductor canal block. Reg Anesth Pain Med. 2016; 41(6):723–727.
33. Liu Q, Chelly JE, Williams JP, Gold MS. Impact of peripheral nerve block with low dose local anesthetics on analgesia and functional outcomes following total knee arthroplasty: a retrospective study. Pain Med. 2015;16(5):998–1006.
34.Lenart MJ, Wong K, Gupta RK, Mercaldo ND, SchildcroutJS, Michaels D, et al. The impact of peripheral nerve techniques on hospital stay following major orthopedic surgery.
Pain Med. 2012; 13:828–34.
35.Chan EY, Fransen M, Sathappan S, Chua NH, Chan YH, Chua N. Comparing the analgesia effects of single-injection and continuous femoral nerve blocks with patient controlled analgesia after total knee arthroplasty. J Arthroplasty.2013; 28:608–13.
36. Tulgar S, Selvi O, Senturk O, Serifsoy TE, Sanel S, Meydaneri S. Evaluation of analgesic regimens in total knee arthroplasty, retrospective study.North Clin Istanb. 2017 Aug 25;4(2):124-130.
37. Abdallah FW, Madjdpour C, Brull R Is sciatic nerve block advantageous when combined with femoral nerve block for postoperative analgesia following total knee arthroplasty? a meta-analysis. Can J Anaesth. 2016 May;63(5):552-68.
38. Gao F, Ma J, Sun W, Guo W, Li Z, Wang W. Adductor Canal Block Versus Femoral Nerve Block for Analgesia After Total Knee Arthroplasty: A Systematic Review and Meta-analysis.Clin J Pain. 2017 Apr;33(4):356-368.

6 Perioperative pain management bundle for abdominal oncology surgery

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Introduction

Insufficient management of acute pain may lead to poor patient outcomes and potentially life-threatening complications. Pain relief after surgery continues to be a major medical challenge. The goal of postoperative pain management is to reduce or eliminate pain and discomfort with a minimum of side effects.

Major colorectal surgery induces severe and prolonged postoperative pain, especially during mobilization, which does not only reduce comfort but can also lead to serious local and systemic complications. Provision of pain relief allows patients to cough, breathe deeply, allows early introduction of oral feeding and faster and more efficient mobilization. Pain, increased sympathetic tone, use of systemic opioid analgesia and intestinal neuroinflamatory processes negatively affect gastrointestinal motility and prolong the duration of postoperative ileus.

Opioid analgesia remains the mainstay of postoperative pain management strategies after colorectal surgery despite being associated with many adverse effects. Perioperative opioid overuse contributes to various side effects and complications after colorectal surgery, including post-operative ileus, postoperative nausea and vomiting, itching, urinary retention, hypotension, respiratory depression, confusion and hallucinations, tolerance, prolonged hospital length of stay and increased healthcare costs. It is recommended the use of patient-controlled delivery systems, if possible, so that dosage is individualized rather than standardized.

According to new guidelines the key is to avoid opioid overuse and apply multimodal analgesia in combination with epidural analgesia when indicated. Multimodal analgesia is a combination of various opiod-sparing medications and different analgesia techniques; the benefit of using a multimodal approach to pain management is based on the concept that several multiple pain reducing mechanisms will improve pain control

while avoiding the side effects of each drug. Studies have demonstrated the benefits of a combination of opioid-sparing drugs in the preoperative (gabapentin, acetaminophen, celecoxib), intraoperative (lidocaine and magnesium infusions, ketorolac, transversus abdominis plane block), and postoperative (gabapentin, acetaminophen, celecoxib) phase of colorectal surgery. These protocols are increasingly being incorporated into enhanced recovery after surgery pathways (ERAS) after colorectal surgery.

The ERAS approach recommends multimodal analgesia in combination with thoracic epidural analgesia (TEA) with low dose of local anaesthetic and opioids as the gold standard technique for analgesia in patients undergoing open colorectal surgery. In fact, when compared with parenteral opioids, TEA provides better analgesia during the first 72 postoperative hours, faster recovery of gastrointestinal function and reduced postoperative cardiac and respiratory complications. Epidural anaesthesia is an effective analgesic method, but it does not suit all population groups, such as patients with coagulation disorders. The risk–benefit equation has shifted away from epidural analgesia and in favour of less invasive but equally effective and safer regional anaesthesia techniques. Some authors suggested that epidural analgesia can no longer be considered the 'gold standard' as a routine method for the management of postoperative pain after colorectal surgery.

Laparoscopic surgery has gradually replaced traditional laparotomy because it has many advantages, such as less bleeding, faster recovery and fewer complications. The most recent ERAS guidelines for colorectal surgery state that TEA can be used in the context of laparoscopic colorectal surgery, but it is not recommended in that setting; spinal analgesia, wall blocks, or lidocaine intravenous infusion should be preferred.

In recent years, several infiltrative techniques have received increasing attention as part of multimodal regimens to treat postoperative pain. These techniques can be single dose or catheter techniques and are usually surgeon administered. The ease of use and safety of local anaesthetics has been well recognised for decades. Collectively, they serve as one of the most important classes of drugs in perioperative pain management. The main advantage of local anaesthetics is that they directly act on the tissue to which they are applied and do not have the adverse effects of opioids. Simple surgeon-delivered techniques such as wound infiltration, preperitoneal/intraperitoneal administration, transversus abdominis plane (TAP) block and local infiltration analgesia as single administration or with catheters placed under direct vision and in collaboration with anaesthesiologists. Direct application of local anaesthetics to the surgical site is a rational approach to block pain transmission from afferent nociceptive barrage. Local anaesthetics also inhibit the inflammatory response to injury and may, therefore, reduce the risk of hyperalgesia. The technique is simple and inexpensive, and has a good safety profile.

Recently, potential links between postoperative NSAID use and anastomotic breakdown have been suggested by observational studies. At the present time, evidence

supports regular doses of NSAIDs in the postoperative period as an effective component of a multimodal, opioid-sparing regime to manage acute pain.

Results

PAIN OUT is an international quality improvement and research network focusing on perioperative pain management in adults and children in the clinical routine. "Working with a healthcare providers to optimize management of perioperative pain" is subproject of the PAIN OUT network. The team from Oncology Institute of Vojvodina joined the project in 2017. The greatest improvement in postoperative analgesia was achieved in patients after colorectal surgery.

In the first project phase (2018.) 63 adult patients completed a high-standardized questionnaire after colorectal surgery, so we collected data of the intensity and characteristics of the postoperative pain. In first phase there was a discrepancy between the severity of postoperative pain at one side and a high satisfaction with analgesia among patients on the other side. At Serbia Mid project workshop we discussed our findings and decided to try to improve analgesia by: preoperative patient and family consultation about pain treatment options, infiltration of the surgical wound, applying full daily doses of paracetamole and/or NSAIDs (first dose close to end of surgery and continue on the ward), and assessing and treating pain every 2-3 hours after surgery. We informed anesthesiologists, surgeons and nurses in our hospital about this project. These interventions were implemented in clinical practice and after few months we started the second phase (2019.). In the second project phase 86 adult patients after colorectal surgery completed the same questionnaire. We performed assessment of pain and wound infiltration in all patients (changed from 1% to 100%!).

We noticed an impressive reduction in the mean worst pain intensity (6,43/3,37) between the first and the second phase. Also in pain interference with coughing/taking deep breath (2,57/1,31) and with activities in bed (4,1/2,85), time in severe pain (38,10%/26,23%) and relief after analgetic therapy (67,62%/86,60%). There were no statistically significant differences in adverse effects (nausea, drowsiness, itch) between the two project phases, except dizziness which was significantly rarer in the second project phase.

The most common reason for dissatisfaction of patients after surgery is inadequate analgesia, so patient satisfaction has become an indicator of the quality of medical care. Satisfaction scores were significantly better in the second phase compared with the first phase during the first postoperative day (8,79/9,36).

Patients in our study spent significantly less time out of bed than in other studies. The reason could be the methods of work of our medical staff and even patients themselves. Patients sometimes were not ready to activate despite satisfactory analgesia and information about the benefits of early mobilization.

Conclusion

Effective analgesia has a potential to improve postoperative recovery and outcomes, and has long-lasting positive effects on functional capacity and quality of life of patients. It is necessary to improve perioperative pain management in routine clinical practice. Our results suggest that solution of inadequacy of postoperative pain management does not actually lie in the usage of expensive medication or development and use of new techniques, but rather in combination of clinically proven techniques and optimal utilization of the already available drugs. It is very important to upgrade the role of surgical ward nurses and to develop close cooperation with surgeons for improving management of pain and quality of postoperative pain therapy.Future directions for effective perioperative multimodal analgesia include in exploring strategies for chronic pain prevention, potential to modulate cancer-recurrence and use of enhanced recovery in perioperative period.

References:

1. Rawal N. Current issues in postoperative pain management. Eur J Anaesthesiol. 2016; 33:160-71.
2. Gustafsson UO, Scott MJ, Hubner M, Nygren J, Dematines N, Fancis N et al. Guidelines for perioperative care in elective colorectal surgery: enhanced recovery after surgery (ERAS) society recommendations: 2018. World J Surg. 2019;43:659-95.
3. Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T et al. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain. 2016;17:131-57.
4. Yap R, Nassif G, Hwang G, Mendez A, Erkan A, Kelly J, Debeche-Adams T, Albert M, Monson J. Achieving Opioid-Free major colorectal surgery: is it possible? Dig Surg. 2020; 30:1-7.
5. Mujukian A, Truong A, Tran H, Shane R, Fleshner P, Zaghiyan K. A Standardized Multimodal Analgesia Protocol Reduces Perioperative Opioid Use in Minimally Invasive Colorectal Surgery. J Gastrointest Surg. 2019 . [Epub ahead of print]
6. Rutegård M, Westermark S, Kverneng Hultberg D, Haapamäki M, Matthiessen P, Rutegård J. Non-steroidal anti-inflammatory drug use and risk of anastomotic leakage after anterior resection: a protocol-based study. Dig Surg. 2016;33:129-35.
7. Wei S, Yu-Han Z, Wei-Wei J, Hai Y. The effects of intravenous lidocaine on wound pain and gastrointestinal function recovery after laparoscopic colorectal surgery. Int Wound J. 2019;1–12.
8. Kverneng Hultberg D, Angenete E, Lydrup ML, Rutegård J, Matthiessen P, Rutegård M. Nonsteroidal anti-inflammatory drugs and the risk of anastomotic leakage after anterior resection for rectal cancer. Eur J Surg Oncol. 2017;43:1908-1914.

9. Naito M, Sato T, Nakamura T, Yamanshi T, Miura H et al. Pain management using acetaminophen throughout postoperative course of laparoscopic colorectal surgery: A case-matched control study. Ann Med Surg 2017;17:38-42.
10. Eto K, Kondo I, Kosuge M , Ohkuma M , Haruki K, et al. Enhanced recovery after surgery programs for laparoscopic colorectal resection may not need thoracic epidural analgesia. Anticancer Res 2017;37:1359-64.

Surgeon's perspective of perioperative pain management for abdominal surgery/Hirurško viđenje snopa mera na terapiju perioperativnog bola u abdominalnoj hirurgiji

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Uvod

Prema procenama na godišnjem nivou se operiše oko 200 miliona pacijenata širom sveta, kod kojih u neposrednom postoperativnom toku, ako su svesni, dominira postoperativni bol (1). Akutni hirurški bol nastaje zbog lokalnog oštećenja tkiva hirurškom incizijom, kojom se pokreće kaskada inflamatornog procesa i nervnog oštećenja (2). Iz tog razloga bol se javlja u čak 80% operisanih bolesnika (3). Visok procenat bolesnika sa postoperativnim bolom ukazuje da ovaj problem predstavlja globalan problem u hirurgiji uprkos primeni mnogobrojnih vodiča o postoperativnom bolu (4). Intenzitet bola u postoperativnom period može biti različit a njegov nivo može zavisiti od vrste operacija, od anestezije ili analgezije koja se primenjuje kao i od praga osetljivosti samog bolesnika na bol (3). Jaki, akutni postoperativni bolovi mogu ukazivati na rane postoperativne komplikacije ili najaviti hronični postoperativni bol, što za krajnji rezultata ima pogoršanje kvaliteta života (5). Loše praćenje i kontrolisanje postoperativnog bola može biti povezano i sa povećanjem morbiditeta, produženim vremenom oporavka i prolongiranim korišćenjem opioidnih analgetika (2). Operacije žučne kese i kila (bilo klasičnim, bilo laparoskopskim putem) su dve najčešće operacije u opštoj hirurgiji (6,7,8). Pri holecistektomiji i operaciji ventralnih kila preporučuje se opšta endotrahealna anestezija uz standrdni monitoring (9). Za operaciju ingvinalne kile primenjuje se opšta, zatim regionalna anestezija ili infiltracija anestetika na mestu incizije. U postoperativnom toku analgezija obuhvata primenu manjih doza opioidnih u kombinaciji sa neopioidnim analgeticima. Bol nastala prilikom ove dve vrste operacija je kompleksna pa se preporučuje multimodalni pristup (10).

Cilj ovog rada je da se proceni nivo postoperativnog bola u zavisnosti od primene anestetika i analgetika u intraoperativnom kao i u neposrednom postoperativnom periodu kod bolesnika kojima je urađena operacija žučne kese ili kile.

Materijal i metode

Prikupljanje podataka sprovedeno je u okviru multinacionalnog i interdisciplinarnog projekta PAIN OUT registra postoperativnog akutnog bola. Urađena je prospektivna, kohortna klinička studija otvorenog tipa. Cilj ove kliničke studije je bio unapređenje lečenja postoperativnog bola, kako tokom same studije, tako i nakon završetka studije, odnosno da se implementiraju klinički vodiči koji bi značajno unapredili lečenje postoperativnog bola u budućnosti na osnovu studijskih rezultata. Učestvovalo je 200 medicinskih ustanova širom sveta. Jedan od medicinskih centara, uključen u formiranje registra bio je Kliničko-bolnički centar „Bežanijska kosa", koji je dobio i odobrenje svog Etičkog odbora (odobreno dana 08.09.2017. broj 7622/3). U našem centru je uključeno ukupno 188 bolesnika, starosti 18 ili više godina kojima su u ovoj ustanovi na Odeljenju za hirurgiju urađene sledeće operacije: operacija žučne kese- holecistektomja (klasična ili laparoskopska) ili kile-plastika (ingvinalne regije ili prednjeg trbušnog zida). Svi su imali potpisani pristanak informisanog pacijenta za uključivanje u registar PAINOUT. Obrađeni su u dve faze u vremenskom periodu od 01. oktobra 2017. do 01. aprila 2019. (I faza) i od 02. aprila 2019. do 14. marta 2020. godine (II faza). U prvoj fazi su evidentirani podaci o upotrebi anestetika intraoperativno i analgetika postoperativno dok u drugoj fazi je osim parametara praćenih za vreme prve faze dodatno intraoperativno aplicirana infiltraciona anestezija u predelu hirurške incizije. Pre samog započinjanja II faze na osnovu rezultata iz I faze urađena je dodatna obuka lekara koji su radili anesteziju i analgeziju ovih pacijenata. Isključujući kriterijumi su bili: kognitivne bolesti,, nekomunikativni bolesnici ili odbijanje bolesnika da učestvuje u istraživanju.

Korišćena su dva upitnika odakle su sumirani podaci: a) upitnik za bolesnike - korišćen za procenu percepcije pacijenata o postoperativnom bolu sa skalama za procenjivanje jačine bola, aktivnosti, emocija, neželjenih efekata analgetske terapije, kao i percepcije nege i terapije; b) procesni upitnk za dobijanje demografskih i kliničkih podataka koji uključuju starost, pol, komorbiditete, vrstu operacije, trajanje operacije, vrste anestezije i analgetika, tokom intra i postoperativnog perioda.

Dobijene podatke su saradnici (studijski lekari) iz ova dva upitnika u papirnom obliku dalje unosili u mrežu registra PAIN OUT. Tako su učesnicima ovog projekta dostupne povratne informacije o svojim rezultataima koje dalje mogu porediti sa drugim. Statistička analiza podataka je urađena u statističkom kompjuterskom programu, *IBM SPSS Statistics*, verzija 26. Atributivne varijable su predstavljene u obliku frekvenci pojedinih kategorija, a kontinualne varijable u obliku srednje vrednosti ± standardne devijacije. Statistička značajnost između pojedinih kategorija atributivnih varijabli je testirana *Chi-square* testom, dok je za razlike u kontinualnim varijablama korišćen *Independent Samples* test za nezavisne uzroke.

Rezultati

Istraživanje je obuhvatilo dve faze u kojima je analizirano 188 bolesnika (84 kojima je urađena operacija kile i 104 operisanih zbog kalkuloze žučne kese). Od svih

holecistektomisanih u prvoj fazi bilo je 66 bolesnika a u drugoj fazi 38 bolesnika. U grupi operisanih zbog kile, 63 bolesnika je bilo u prvoj fazi, a 21 bolesnik u drugoj fazi. Kod operacija žučne kese tokom obe faze studije više je bilo žena, oko 70%, dok je prosečna starost u obe faze bila oko 51 godinu starosti. Kod operacija kile tokom obe faze studije više je bilo muškaraca, preko 75%, dok je prosečna starost ispitanika u prvoj fazi bila oko 54 a u drugoj oko 59 godina starosti.

Tabela 1. Intraoperativna primena anestetika kod ispitanika operisanih od kile i žučne kese tokom dve faze istraživanja

Operacija žučne kese	I faza (n=66)	II faza (n=38)	p vrednost*
Opšta anestezija	64(97,0%)	36(97,3%)	p=1,000
Vrsta anestezije: inhalaciona/ intravenska	50(78,1%)/14(21,9%)	22(61,1%)/14(38,9%)	p=0,689
Regionalna anestezija	2(3,0%)	0	p=0,772
Infiltracija rane	1(1,5%)	38(100%)	p<0,001
Operacija kile	I faza (n=63)	II faza (n=21)	
Opšta anestezija	46(73,0%)	17(81,0%)	p=0,663
Vrsta anestezije: inhalaciona/ intravenska	39(84,8%)/7(15,2%)	8(47,1%)/9(52,9%)	p=0,002
Regionalna anestezija	16(25,4%)	4(20,0%)	p=0,848
Infiltracija rane	1(1,6%)	21(100%)	p<0,001

*- Chi-square test

Opšta anestezija ordinirana je kod najvećeg broja bolesnika (100) kod operacije žučne kese, osim kod dva u prvoj fazi i jednog u drugoj fazi studije, tako da nije bilo razlika u odnosu na fazu studije (Tabela 1).Kod operacije kile 25% bolesnik nije dobilo opštu anesteziju (17 u I fazi a 4 u II fazi). I kod operacije žučne kese i kod operacije kile u prvoj fazi samo je po jednom bolesniku infiltrovan anestetik, dok su u drugoj fazi svi dobili (p<0,001; p<0,001).

Holecistektomisani bolesnici su neopioidne i opiodine analgetike, u sobi za oporavak, statistički značajno češće dobijali u drugoj fazi ispitivanja (p=0,048; p=0,012), dok kod operisanih od kile nije nađena statistički značajna razlika između faza, ali su i ovde češće ordinirani analgetici u II fazi studije (p=0,223; p=0,575) (Tabela 2).

Tabela 2. Primena analgetika u sobi za oporavak kod ispitanika operisanih od kile i žučne kese tokom dve faze studije

Operacija žučne kese	I faza	II faza	p vrednost*
Neopioidi	12(18,2%)	15(39,5%)	p=0,048
Opioid	5(7,6%)	11(28,9%)	p=0,012
Operacija kile	I faza	II faza	
Neopioidi	18(28,6%)	10(47,6%)	p=0,223
Opioid	7(11,1%)	4(19,0%)	p=0,575

*- Chi-square test

Na hirurškom odeljenju većina bolesnika je dobila neopioidne analgetike u obe ispitivane grupe, tokom obe faze, tako da nema statistički značajne razlike između faza i kod operacija žučne kese i kod operacija kile. Analizom upotrebe opioidnih analgetika na odeljenju hirurgije nije nađena statistički značajna razlika, mada su holecistektomisani skoro duplo češće dobijali opioidne analgetike u II fazi u odnosu na I fazu (Tabela 3).

Tabela 3. Primena analgetika na odeljenju kod ispitanika operisanih od kile i žučne kese tokom dve faze studije

Operacija žučne kese	I faza	II faza	p vrednost*
Neopioidi	65(98,5%)	37(97,4%)	p=0,689
Opioid	19(28,8%)	17(45,9%)	p=0,124
Operacija kile	I faza	II faza	
Neopioidi	61(96,8%)	21(100%)	p=0,764
Opioid	26(41,3%)	8(40,0%)	p=1,000

*- Chi-square test

Ispitujući jačinu maksimalnog bola kod operacije žučne kese i kod operacije kile nije nađena značajna razlika između prve i druge faze, mada je bol u II fazi bio veći u obe grupe (p=0,228, p=0,196) (Tabela 4). Ako analiziramo uticaj bola na aktivnosti (disanje, kašalj, ustajanje i spavanje) onda vidimo da nije nađena razlika ni u jednoj varijabli između faza kako kod operacije žučne kese, tako i kod operacije kile. Prosečna bol u drugoj fazi smanjila se u skoro svim kategorijama.

Tabela 4. Jačina bola i uticaj bola na funkcionisanje pacijenta operisanih od kile i žučne kese tokom dve faze studije; vrednosti su prikazane kao srednja vrednost ± standardna devijacija

Operacija žučne kese	I faza	II faza	p vrednost*
Maksimalan bol	4,17±2,51	4,74±1,90	p=0,228
Bol pri dubokom udahu/ kašlju	2,83±2,96	2,08±2,33	p=0,181
Bol pri aktivnost u krevetu	4,05±2,94	3,39±2,12	p=0,235
Bol pri ustajanju iz kreveta	3,23±2,61	2,97±1,72	p=0,606
Bol u snu	1,70±2,35	1,92±2,29	p=0,638
Operacija kile	I faza	II faza	
Maksimalan bol	4,06±2,71	4,90±2,02	p=0,196
Bol pri dubokom udahu/ kašlju	2,21±2,77	2,05±2,08	p=0,811
Bol pri aktivnosti u krevetu	4,06±3,19	3,29±2,55	p=0,314
Bol pri ustajanju iz kreveta	4,02±2,99	3,80±1,40	p=0,753
Bol u snu	2,06±2,80	2,19±2,64	p=0,856

*- Independent Samples Test

U našoj studiji nađena je značajna razlika pojave pospanosti i svraba kod operacija žučne kese, dok je kod operacija kile uočena značajna razlika u pojavi svraba i mučnine (Tabela 5).

Tabela 5. Distribucija pacijenata sa neželjenim reakcijama na analgetike kod pacijenta operisanih od kile i žučne kese tokom dve faze studije; vrednosti su prikazane kao srednja vrednost ± standardna devijacija

Operacija žučne kese	I faza	II faza	p vrednost*	I faza	II faza	p vrednost**
Vrtoglavica	22 (33,3%)	16 (42,1%)	p=0,166	1,15±2,19	0,84±1,24	p=0,427
Pospanost	55 (83,3%)	23 (60,5%)	p=0,023	3,56±2,76	1,58±1,90	p<0,001
Svrab	3 (4,5%)	12 (31,6%)	p=0,002	0,08±0,40	0,45±0,79	p=0,002
Mučnina	29 (43,9%)	21 (55,3%)	p=0,757	1,62±2,66	1,55±2,15	p=0,893
Operacija kile	I faza	II faza		I faza	II faza	

Vrtoglavica	20 (31,7%)	7 (33,3%)	p=0,228	1,00±2,01	1,19±2,18	p=0,714
Pospanost	42 (66,7%)	14 (66,7%)	p=0,790	2,62±2,91	2,71±3,05	p=0,898
Svrab	6 (9,5%)	11 (52,4%)	p=0,003	0,14±0,56	1,24±1,84	p<0,001
Mučnina	19 (30,2%)	15 (71,4%)	p=0,012	1,08±2,26	2,76±2,96	p=0,008

*- Chi-square test; **- Independent Samples Test

Većina neželjenih efekata se češće javljala u drugoj fazi studije, ali ako se pogleda njihov intenzitet, onda se može videti da je kod operisanih od žučne kese uglavnom u drugoj fazi u odnosu na prvu fazu došlo do smanjenja, dok je kod operacije kila došlo do povećanja intenziteta.

Diskusija

U poslednje dve decenije objavljen je veliki broj novih saznanja u pogledu upravljanja postoperativnim bolom. Novi farmaceutski preprati i tehnologije za akutni bol dodatno su stavljeni u upotrebu. Međutim, velika istraživanja za procenu upravljanja i kontrole postoperativnog bola pokazali su mali napredak u terapiji ove vrste bola (11).

Oboljevanje od kalkuloze žučne kese literaturno se kreće u odnosu 3:1 do 4:1 u korist ženskog pola (12), dok je u našem uzorku taj odnos bio 2:1. S druge strane, muškarci imaju veću prevalenciju ingvinalne kile u poređenju sa ženama svih starosnih grupa što se objašnjava različitom anatomijom prednjeg trbušnog zida (13), što je pokazano i u našem istraživanju gde je tokom prve faze bilo 5 puta više a tokom druge faze 3 puta više muških pacijenata.

Idealna anestezija pruža dobru perioperativnu i postoperativnu analgeziju, stvara optimalne uslove za operaciju, povezana je sa manje komplikacija, pomaže u ranom otpuštanju bolesnika iz bolnice i finansijski je isplativa (14, 15). U našem istraživanju opšta anestezija je bila ordinirana kod 100 bolesnika kojima je operisana žučna kesa, a samo troje su dobili regionalni blok. Od ovog broja 72 bolesnika je rađeno u inhalacionoj anesteziji, a 28 bolesnika je dobilo intravensku anesteziju. Operacije kile u našem istraživanju rađene su u većem delu u opštoj endotrahealnoj anesteziji (63 bolesnik) a u nešto manjem broju u regionalnom bloku (21 bolesnik). Preporuke iz literature prednost daju opštoj i lokalnoj anesteziji u odnosu na regionalnu, naročito kod pacijenata starijih od 65 godina, jer je ona povezana sa većom incidencom postoperativnih komplikacija kao što su infarkt miokarda, pneumonija ili venska tromboza (16). U našem istraživanju u drugoj fazi kod svih ispitanika obe grupe, rađena je infiltracija rane lokalnim anestetikom, tehnikom *single shot by surgeon* (Chi-square test; p<0,001). Primenom ovakve subkutane tehnike može se objasniti nedovoljni analgetski efekat lokalne infiltracione anesetzije i potrebe za ranim ponavljanjem doza analgetika, opioidnih i neopioidnih, već u sobi za oporavak. Gebershagen i saradnici su takođe utvrdili da su

bolesnici prijavljivali jači bol nakon manje hirurške intervencije, što ukazuje na to da se takvim bolesnicima intraoperativno nedovoljno davalo analgetika u odnosu na velike abdominalne operacije (25). Takođe je pokazano da je kombinovana subkutana i subfascijalna infiltracija dovela je do smanjenja ranog postoperativnog bola, manje potrebe za dodatim analgeticima i produžila vreme za ponavljanje doza analgetika (27).

Naši bolesnici kojima je operisana žučna kesa, u sobi za oporavak, neopioidne analgetike su statistički češće dobijali u drugoj fazi (Chi-square test; p=0,048). Bolesnici kojima je operisana kila, u sobi za oporavak, neopioidne analgetike su statistički neznačajno češće dobijali u drugoj fazi (Chi-square test; p=0,223). Primena opioida je značajnije manja u odnosu na neopiodne analgetike. U jednoj ranijoj studiji na pacijentima kod kojih je rađena holecistektomija i operacije kile, pokazano je da se javio umeren do jak bol nakon 24 sata od operacije, što se poklapa sa prvom mobilizacijom (28).

Na odeljenju većina naših pacijenata dobila je neopioidne analgetike u obe grupe kako nakon operacije žučne kese tako i nakon operacije kile, kako u prvoj fazi, tako i u drugoj fazi. Ovo možemo objasniti činjenicom da su se sistemski ordinirani opioidi intraoperativno izmetabolisali, a dejstvo lokalnog anestetika prošlo.

Gebershagen et al. analizirao je rezultate bola tokom 24 sata nakon operacije kod velikog broja ispitanika koji su podvrgnuti različitim operacijama, uključujući i abdominalne. Srednji skor bola za ovu poslednju grupu bio je 4, pri kretanju a njihov najveći intenzitet bola bio je 5 (25). U našem istraživanju, maksimalna bol kod operacije žučne kese i kod operacije kile nije se značajno razlikovala između prve i druge faze studije (p=0,228, p=0,196). Pacijenti su tokom druge faze prijavili jaču prosečnu bol nego u prvoj fazi. Ako analiziramo uticaj bola na aktivnosti (jačinu bola pri kretanju, dubokom disanju, kašljanju i spavanju) onda vidimo da nije nađena razlika ni u jednoj varijabli između faza kako kod operacije žučne kese, tako i kod operacije kile. Međutim, ono što se zapaža, jeste da se prosečna bol u drugoj fazi smanjila u skoro svim kategorijama, što se može objasniti time das u primenjene različite mere analgezije intraoperativno i u ranom postoperativnom periodu u sobi za oporavak dale klinički zadovoljavajuće rezultate (20).

Postoperativna mučnina i povraćanje su najčešće komplikacije nakon anestezije i operacije. Neželjeni efekti su izuzetno česti kod terapije opioidima. Između 50% i 80% pacijenata u kliničkim ispitivanjima iskusi bar jedan neželjeni efekat terapije opioidima. Međutim, u svakodnevnoj upotrebi incidenca može biti i značajno veća. Najčešća neželjena dejstva primene opioida su povraćanje, vrtoglavica, svrab i pospanost. U našoj studiji nađena je značajna razlika pojave pospanosti i svraba kod operacija žučne kese, odnosno pojave svraba i mučnine kod operisanih od kila, uglavnom sa povećanjem tokom druge faze studije usled češćeg korišćenja analgetske terapije. Zbog pojave neželjenih efekata opioida, primenu treba smanjiti na najmanju moguću količinu a da se pri tome postigne zadovoljavajući analgetski efekat (21).

Zaključak

Sigurna i efikasna kontrola postoperativnog bola kod abdominalnih intervencija trebalo bi da se zasniva na planu koji je prilagođen pojedincu i hirurškom zahvatu. Idealno bi bilo da u postoperativnom pristupu terapiji bola primenimo multimodalni pristup. Anesteziolozi koji sprovode perioperativnu terapiju bola trebali bi da koriste terapijske opcije epiduralne ili intratekalne primene opioida, sistemsku primenu opioida (engl. *Patient control analgaesia - PCA*) i regionalne tehnike, nakon detaljnog razmatranja rizika i koristi za svakog pacijenta pojedinačno. Ove modalitete treba koristiti pre primene imtramuskularnih opioida, koji se ordiniraju „po potrebi".

Literatura

1. Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, Gawande AA. An estimation of the global volume of surgery: a modelling strategy based on available data. Lancet. 2008;372(9633):139-44.
2. Gupta A, Kaur K, Sharma S, Goyal S, Arora S, Murthy RS. Clinical aspects of acute post-operative pain management & its assessment. J Adv Pharm Technol Res. 2010;1(2):97-108.
3. Gan TJ. Poorly controlled postoperative pain: prevalence, consequences, and prevention. J Pain Res. 2017;10:2287-98.
4. Schnabel A, Yahiaoui-Doktor M, Meissner W, Zahn PK, Pogatzki-Zahn EM. Predicting poor postoperative acute pain outcome in adults: an international, multicentre database analysis of risk factors in 50,005 patients. Pain Rep. 2020;5(4):e831.
5. Zaslansky R, Chapman CR, Baumbach P, Bytyqi A, Castro Lopes JM, Chetty S, Kopf A, Li L, Ern Ming L, Olawoye O, Rizza Parico J, Soyannwo O, Stamenkovic D, Wang H, Meissner W. Improving perioperative pain management: a preintervention and postintervention study in 7 developing countries. Pain Rep. 2019;4(1):e705.
6. Stinton LM, Shaffer EA. Epidemiology of gallbladder disease: cholelithiasis and cancer. Gut Liver. 2012;6(2):172-87.
7. Jenkins JT, O'Dwyer PJ. Inguinal hernias. BMJ. 2008;336(7638):269-72.
8. Agresta F, Campanile FC, Vettoretto N, Silecchia G, Bergamini C, Maida P, Lombari P, Narilli P, Marchi D, Carrara A, Esposito MG, Fiume S, Miranda G, Barlera S, Davoli M; Italian Surgical Societies Working Group. Laparoscopic cholecystectomy: consensus conference-based guidelines. Langenbecks Arch Surg. 2015;400(4):429-53.
9. Tzovaras G, Fafoulakis F, Pratsas K, Georgopoulou S, Stamatiou G, Hatzitheofilou C. Spinal vs general anesthesia for laparoscopic cholecystectomy: interim analysis of a controlled randomized trial. Arch Surg. 2008;143(5):497-501.
10. Malenković V, Zorić S, Ranđelović TD. Advantageous usage combined spinal, epidural and general anesthesia versus general anesthesia in abdominal surgery. Srp Arh Celok Lek. 2003;131(5-6):232-7.

11. Sjövall S, Kokki M, Kokki H. Laparoscopic surgery: a narrative review of pharmacotherapy in pain management. Drugs. 2015;75(16):1867-89.
12. Pariente A, Erlinger S. Cholelithiasis and obesity: epidemiology, pathophysiology, clinical manifestation and prevention. Hepato-gastro & Oncologiae Digestive. 2017;24(1):18-25.
13. Burcharth J, Pedersen M, Bisgaard T, Pedersen C, Rosenberg J. Nationwide prevalence of groin hernia repair. PLoS One. 2013;8(1):e54367.
14. Nordin P, Zetterström H, Carlsson P, Nilsson E. Cost-effectiveness analysis of local, regional and general anaesthesia for inguinal hernia repair using data from a randomized clinical trial. Br J Surg. 2007;94(4):500-5.
15. Joshi GP, Rawal N, Kehlet H; PROSPECT collaboration, Bonnet F, Camu F, Fischer HB, Neugebauer EA, Schug SA, Simanski CJ. Evidence-based management of postoperative pain in adults undergoing open inguinal hernia surgery. Br J Surg. 2012;99(2):168-85.
16. Miserez M, Peeters E, Aufenacker T, Bouillot JL, Campanelli G, Conze J, Fortelny R, Heikkinen T, Jorgensen LN, Kukleta J, Morales-Conde S, Nordin P, Schumpelick V, Smedberg S, Smietanski M, Weber G, Simons MP. Update with level 1 studies of the European Hernia Society guidelines on the treatment of inguinal hernia in adult patients. Hernia. 2014;18(2):151-63.
17. El-Radaideh KM, Al-Ghazo MA, Bani-Hani KE. Combined subfascial and subcutaneous bupivacaine instillation for inguinal hernia wounds. Asian J Surg. 2006;29(4):242-6.
18. Loizides S, Gurusamy KS, Nagendran M, Rossi M, Guerrini GP, Davidson BR. Wound infiltration with local anaesthetic agents for laparoscopic cholecystectomy. Cochrane Database Syst Rev. 2014;(3):CD007049.
19. Gerbershagen HJ, Aduckathil S, van Wijck AJ, Peelen LM, Kalkman CJ, Meissner W. Pain intensity on the first day after surgery: a prospective cohort study comparing 179 surgical procedures. Anesthesiology. 2013;118(4):934-44.
20. Shadangi BK, Garg R, Pandey R. A randomized, placebo-controlled, double blind study of the analgesic efficacy of extraperitoneal wound instillation of bupivacaine and morphine in abdominal surgeries. Anaesth Pain Int Care. 2012;16(2):169-73.
21. Opioid Therapy for Chronic Pain Working Group, Department of Veterans Affairs & Department of Defense. VA/DoD Clinical Practice Guideline for Opioid Therapy for Chronic Pain. Version 3.0; 2017. Available at: https://www.healthquality.va.gov/guidelines/Pain/cot/

8 Regional hospital experience with the perioperative pain management bundle/Iskustvo regionalne bolnice u primeni snopa mera za perioperativnu terapiju bola

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Uvod

Terapija akutnog postoperativnog bola je široko prihvaćen pokazatelj visokog stepena zdravstvene zaštite i predstavlja jedan od glavnih činilaca koji utiču na pacijentovo zadovoljstvo lečenjem. Iako su uvedene nove analgetske tehnike, lekovi kao i nacionalni vodiči, akutni postoperativni bol i dalje ostaje ozbiljan klinički problem među populacijom hospitalizovanih pacijenta, doprinoseći na taj način razvoju hroničnih bolnih sindroma i zavisnosti od opioidnih lekova [1,2]. Incidencija hroničnih bolnih stanja nakon operativnih zahvata varira između 10-50 % a njihova pojava je u direktnoj vezi sa vremenom provedenim u jakim bolovima u prvom postoperativnom danu [3,4].

Materijal i metod

U ovom radu prikazani su rezultati druge „intervencione" faze istraživanja nakon uvođenja snopa mera za unapređenje perioperativnog tretmana bola. Pored toga uradjena je i delimična komparacija rezultata druge faze sa rezultatima prve „baseline" faze Pain Out studije. Na sastanku održanom 29.juna 2018.godine u okviru „Serbian PainOut EFIC Network-a", dogovoreno je da sve bolnice koje učestvuju u okviru ovog projekta prihvate primenu „bundle" sistema.

Rezultati

U opštoj bolnici Prijepolje u intervencionoj fazi PainOut studije obuhvaćene su dve grupe pacijenata: pacijenti podvrgnuti opšte hirurškim operacijama i pacijentkinje podvrgnute ginekološkim i obstetricijskim procedurama. U drugoj fazi istraživanja u periodu od 01.04.2020. god. do 31.12.2020. god. uključeno je 187 bolesnika, od toga 95 sa odeljenja opšte hirurgije i 92 pacijentkinje sa odeljenja ginekologije i akušerstva. Iz studije su isključena 2 pacijenta jer nisu želeli da učestvuju u istraživanju.

Prosečna starost bolesnika u grupi pacijenata opšte hirurgije iznosila je 49,26 godina, dok je u grupi pacijentkinja iz odeljenja ginekologije i akušerstva iznosila 34,57

godina. U grupi opšta hirurgija 74 pacijenta su podvrgnuti opštoj endotrahealnoj anesteziji, dok je 21 pacijent podvrgnut regionalnoj anesteziji (od toga 17 spinalnih anestezija i 4 epiduralne „single shot" anestezije). Kod 47 pacijenata iz grupe opšte hirurije urađena je laparoskopska holecistektomija, što je ujedno najčešća operacija u ovoj grupi. U grupi ginekologije i akušerstva 62 intervencije su urađene u opštoj endotrahealnoj anesteziji, dok je 28 urađeno u regionalnoj anesteziji. Najčešća intervencija u ovoj grupi bio je Craski rez koji je urađen kod 73 pacijentkinje. Distribucija tipa hirurških zahvata kojima su podvrgnuti pacijenti obe grupe prikazani su u tabelama 1.i 2.

Tabela 1. Distribucija tipa hirurških zahvata u grupi „opšta hirurgija"

Operativni zahvat	**Broj pacijenata (%)**
Laparoskopska holecistektomija	48 (50,5%)
Hernioplastika ingvinalne kile	30 (31,6%)
Apendektomija	7 (7,4%)
Hernioplastika umbilikalne kile	2 (2,1%)
Otvorena holecistektomija	3 (3,1%)
Resekcija kolona	1 (1,1%)
Parcijalna resekcija tankog creva	1 (1,1%)
Laparoskopska apendektomija	1 (1,1%)
Ekscizija hemoroida	1 (1,1%)
Hernioplastika ventralne kile	1 (1,1%)
Ukupno	**95**

Tabela 2. Distribucija tipa hirurških zahvata u grupi „ginekologija i akušerstvo"

Operativni zahvat	**Broj pacijenata (%)**
Carski rez	74 (78,7%)
Operacija prolapsa materice	8 (8.5)
Totalna abdominalna histerektomija	4 (4.3%)
Unilateralna salpingektomija (vanmaterična trudnoća)	3 (3,2%)
Destrukcija ovarijalnih cisti	5 (5,3%)
Ukupno	**94**

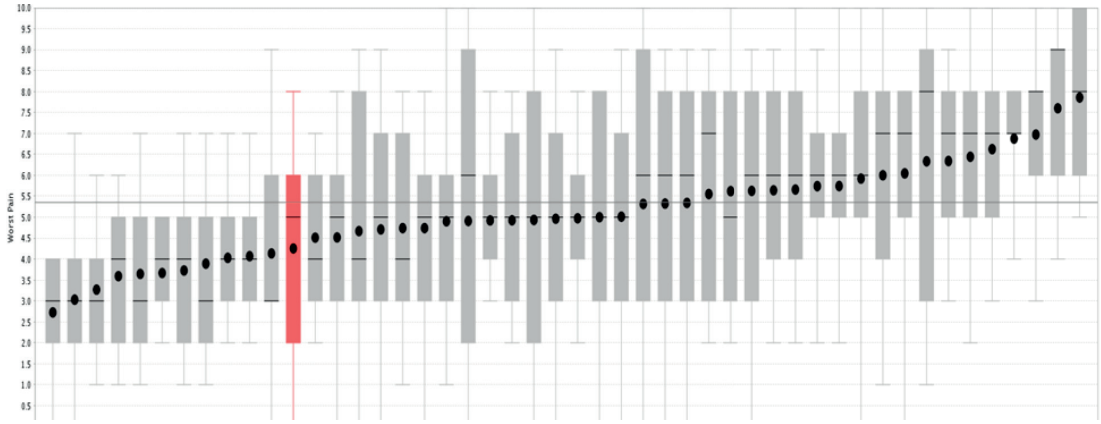
Informacije o primenjenim elementima snopa za perioperativnu terapiju bola prikazane su u tabeli 3.

Tabela 3. Učestalost i prosečne vrednosti elemenata snopa primenjenih u ispitivanim grupama

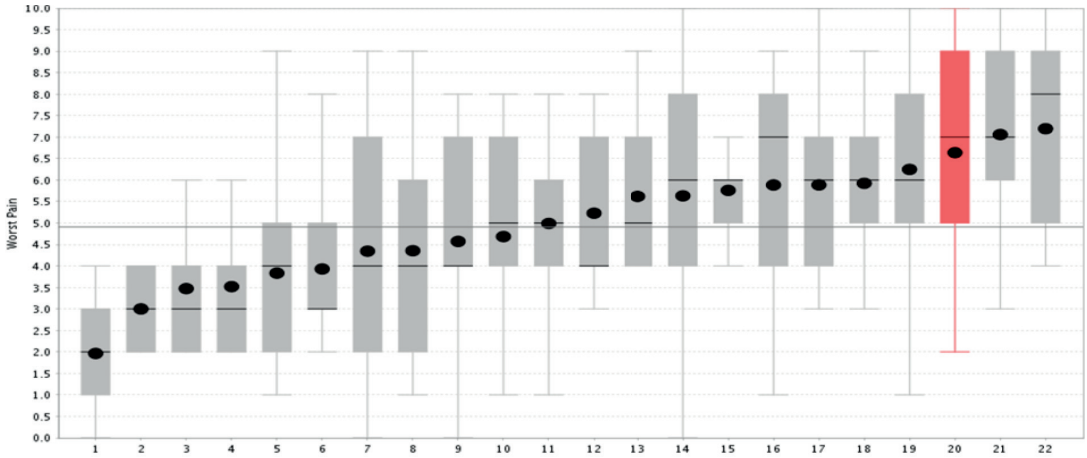
Primenjene mere snopa	Opšta hirurgija	Ginekologija i akušerstvo
Informisanost pacijenata o tretmanu bola, N(%)	59 (62.1%)	43 (46.7%)
Intraoperativno primenjeni neopiodini anagetici, DA, N(%)	14 (14.7%)	7 (7,6%)
Intraoperativno dati opioidi, DA, N(%)	92 (96,8%)	91 (98.9%)
Intraoperativno Fentanyl μg, mean (SD)	217 (54,28)	191.4 (31.46)
Infiltracija rane, DA, N (%)	63 (66.3%)	59 (64.1%)
Neopioidi dati u sobi za oporavak, DA, N (%)	47 (49.5%)	78 (84.8%)
Opioidi dati u sobi za oporavak, DA, N(%)	51 (53.7)	13 (14.1%)
Neopioidi dati na odeljenju, DA, N (%)	83 (87.4%)	90 (97.8)
Opioidi dati na odeljenju, DA, N (%)	60 (63.2%)	17 (18.5%)
Procena bola, mean (SD)	2.75 (1.30)	1.33 (1.43)
Ponovna procena bola nakon datog analgetika, mean (SD)	1.24 (0.90)	0.42 (0.87)

Prosečne vrednosti najgoreg bola prvog postoperativnog dana kod ispitivanih grupa pacijenata opšte bolnice Prijepolje u odnosu na slične grupe pacijenata ostalih bolnica uključenih u PainOut projekat prikazane su u grafikonima 1. i 2.

Grafikon 1. Prosečne vrednosti najgoreg bola prvog postoperativnog dana. Odeljenje opšte hirurgije



Grafikon 2. Prosečne vrednosti najgoreg bola prvog postoperativnog dana. Odeljenje ginekologije i akušerstva.



Na pitanje koliko često ste osećali jak bol nakon operacije, u grupi opšte hirurških pacijenata prosečna vrednost vremena provedenog u jakim bolovima iznosila je 22,7%, dok su pacijentkinje iz odeljenja ginekologije i akušerstva u proseku provele 40,7% vremena u jakim bolovima. Prosečne vrednosti uticaja bola na obavljanje aktivnosti u krevetu i van njega u grupi „opšta hirurgija" bile su: 3,60 odnosno 2,76, dok su u grupi „ginekologija i akušerstvo" iznosile: 5.98 odnosno 4.73.

Najčešće primenjivani anagetici na odeljenju kod grupe „opšta hirurgija" bili su: Tramadol (63,2%, mean 84,15 mg), Ketoprofen (45,3, mean 130 mg), Metamizol (41,1, mean 2,85 gr). Najčešće primenjivani analgetici na odeljenju grupe ginekologija i akušerstvo bili su: Metamizol (75%, mean 3,07 gr), Diklofen (34,8%, mean 98,43 mg), Ketorolac (25%, mean 42,17 mg).

Pacijentova procena uspeha terapije dobijena je kroz odgovore na pitanja „Za koliko Vam je otklonjen bol u postoperativnom periodu?" i „Zaokružite jedan broj koji najbolje pokazuje koliko ste zadovoljni sa rezultatima Vašeg tretmana protiv bola posle operacije**". Kod pacijenata u Odeljenju opšte hirurgije bol je otklonjen 73,43%, a pacijenti su zadovoljstvo tretmana protiv bola ocenili prosečnom ocenom 9.27**. Pacijentkinjama na odeljenju ginekologije i akušerstva bol je otklonjen 68,68%, dok je prosečna vrednost zadovoljstva terapije postoperativnog bola iznosila 8.82. Informisanost pacijenata o terapiji perioperativnog bola procenjena je kroz pitanje: „Da li ste primili neke informacije o mogućim opcijama tretmana protiv bola?" U grupi opšte hirurških pacijenata sa DA je odgovorilo 63% pacijenata,dok je u grupi pacijentkinja odeljenja ginekologije i akušerstva sa DA odgovorilo 51% pacijentkinja.

Zaključak

U našoj studiji primenom snopa mera tokom intervencione faze, uspeli smo donekle da snizimo bolne skorove u neposrednom postoperativnom toku, ali i da unapredimo skorove koji se tiču pacijentove percepcije nege.

Značajno je unapređen i parameter koji se tiče informisanosti pacijenata o mogućim opcijama tretmana bola. Elementi snopa koji se do sada nisu primenjivali u svakodnevnoj kliničkoj praksi u našoj bolnici, sada se primenjuju rutinski.Pain-out studija nam je pomogla da podignemo svest medju lekarima i medicinskim sestrama Opšte bolnice u Prijepolju o akutnog postoperativnog bola i njegovim komplikacijama ukoliko se neblagovremeno i neadekvatno tretira

9 Perioperative pain management bundle for breast surgery procedures

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Abstract

PAIN OUT project of the European pain federation (EFIC) is aimed at collecting data and improving the quality of the post-operative pain therapy in a highly standardised way. The project was conducted in Serbia in ten institutions and in two phases from 2017-2020. Patients who had a breast surgery at the National Cancer Research Centre of Serbia were approached by investigators on the first post-operative day and if they met inclusion criteria, they were asked to answer two questionnaires consisting of patient reported outcomes and process data. During the PAIN OUT project, it was possible to increase the availability of information of the available pain therapy for the patients. As a result of that, our patients have spent significantly less time feeling strong pain, pain was evaluated more often and the patients themselves asked for analgesic therapy more frequently.

Key words: postoperative pain therapy, breast surgery, pain management.

Introduction

PAIN OUT project of the European pain federation (EFIC) is aimed at collecting data and improving the quality of the post-operative pain therapy in a highly standardised way. The project was implemented in Europe, Americas, Africa and South East Asia so far. At the present moment, it is a non-profit, academic project coordinated from the Jena University Hospital, Germany. [1]

The project was conducted in Serbia in ten institutions and in two phases from 2017-2020. The first phase consisted of collecting the baseline data, data analysis, intervention planning, preparing a report and implementation of intervention. After that, data was collected again as part of the second phase which also included data analysis and final report preparation.

The National cancer research centre of Serbia participated in the project as one of these ten institutions.

Material and methods

Both phases of the PAIN OUT project were conducted at the Section of Breast Surgery, Department of Medical Oncology of the National Cancer Research Centre of Serbia in Belgrade. Patients who had a breast surgery were approached by investigators on the first post-operative day and if they met inclusion criteria, they were asked to answer two questionnaires consisting of patient reported outcomes and process data. Between the two phases, common intervention measures for all institutions participating in the project were agreed on and implemented. These measures were the following:

Increasing the availability of information of the post-operative pain therapy to the patients

Increasing the use of NSAIDs, metamizole, acetaminophen

Increasing the use of technique of infiltration of the operative wound/regional anesthesia techniques

Increasing the quantification of pain intensity measurement

Other measures whose implementation was also planned were: reducing the intramuscular administration of analgesics, finding a safe way to administer opioids in the ward, increasing the analgesiscs administration in the recovery/ward etc.

Data for the phase two at the National Cancer Research Centre of Serbia were collected from April 1st to June 30th 2020. All patients who had breast surgery on the days when the data were collected were approached and if they met the inclusion criteria, they were asked to fill in the standardised questionnaire, available in Serbian and other languages.

The inclusion criteria were the following:

1. Adult patients
2. Patient who gave oral or written consent
3. Patient on the first post-operative day.

Therefore, the exclusion criteria were the following:

1. Underage patient
2. Patient who refused to give consent to participating in the survey
3. Patient who is not in his first post-operative day.

Data were inputted into the web-based software by the trained surveyors.

Results

In both phases approximately the same number of patients was included. In the 2nd phase of the project in our institution, there were no male patients, unlike the 1st phase. Male patients also suffer from the breast cancer but much less frequently than the female patients.

Patients of both phases were of the approximately same age and body weight which is presented in the Table I.

The results in our institution show that there is a reduction of both the least and the worst post-operative pain in phase 2 compared to phase 1.There is a statistically significant reduction of the percentage of time that the patient spent feeling strong pain in phase 2 ($p < 0.05$). The values for the pain intensity, that is the least pain, the worst pain and the time spent in pain is presented in Figure 1.

Interference of pain with activities in bed, as well as interference with sleep and pain intensity during deep breathing or coughing and interference with activities out of bed were evaluated and rated by similar numerical values in both phases and there was no statistical significance between the values in the two phases ($p > 0.05$). Patients in both phases were able to get out of bed on the first post-operative day and there was no statistical significance between these values in phase 1 and 2, either ($p > 0.05$). Mean values of the evaluation of pain interference with activities in and out of bed, pain intensity during deep breathing or coughing and proportion of time out of bed are presented in Table II.

Patients evaluated interference of emotions with similar and rather low values for both phases. Mean values representing how much the patients felt helpless or anxious in both phases are presented in Figure 2.

Regarding adverse effects of the therapy, patients in both phases reported itching rarely, nausea was reported with similar frequency in both phases while drowsiness occurred more frequently in the phase 1 and dizziness more frequently in the phase 2. Mean values of evaluation of the reported adverse effects for both phases is presented in Figure 3.

Patients evaluated perception of care with very good values in both phases. Satisfaction with received pain therapy, allowed participation in the therapy and whether the patient wanted to have gotten more pain therapy was evaluated with similar values in both phases. Relief after the administered pain therapy was evaluated with significantly higher value in phase 2, compared to phase 1 ($p<0.05$). Presentation of evaluation of the perception of care for phase 1 and 2 is presented in Table III.

The type of administered therapy is also similar in both phases. Opioid analgesics, administered most frequently in the operating room or in the ward is the base of the therapy, when opioid analgesics are required. Other techniques like wound infiltration, regional anaesthesia and non-pharmaceutical methods were used much less frequently in both phases. The use of therapeutical methods is presented in Figure IV.

Conclusion

Patients who have undergone breast surgery in the National cancer research centre of Serbia evaluated the satisfaction of the administered post-operative pain therapy in phase 1 with high mean value of 8.74 so it would have been very difficult to significantly

increase this value in the phase 2. However, it does not mean that there is no opportunity to improve various aspects of the post-operative pain therapy for breast surgery patients in our institution. During the PAIN OUT project, it was possible to increase the availability of information of the available pain therapy for the patients. As a result of that, our patients have spent significantly less time feeling strong pain, pain was evaluated more often and the patients themselves asked for analgesic therapy more frequently.

As one of the secondary goals, in our institution, we managed to significantly reduce intramuscular administration of opioid analgesics and to exchange it for continuous infusion of opioid analgesics which presents safe, but also more comfortable mode of therapy administration, both for patients and the medical staff, especially in the ward.

Wound infiltration and regional anaesthesia, most of all intermittent and continuous nerve blocks, offer new possibilities for extensive breast surgery, especially in patients of older age with other comorbidities which increase risk for general anaesthesia.

References

1.PAIN OUT: About Pain out. Jena: Jena University Hospital, Germany. [cited 2020 Oct 10]. Available from http://pain-out.med.uni-jena.de/

Conflicts of interest.—None to declare.

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Table 1. Demographic data included in phase 1 and phase 2.

	Phase 1	Phase 2
No of patients	131	130
Gender (%)	99.2% female	100% female
Age (mean±SD)	56.76 ± 12.06	60.35 ± 12.86
Weight (kg)	72.06 ± 15.38	69.42 ± 9.02

Table 2. Mean values of pain interference with activities in bed, coughing/taking deep breath, sleep, proportion out of bed, activities out of bed in phase 1 and phase 2

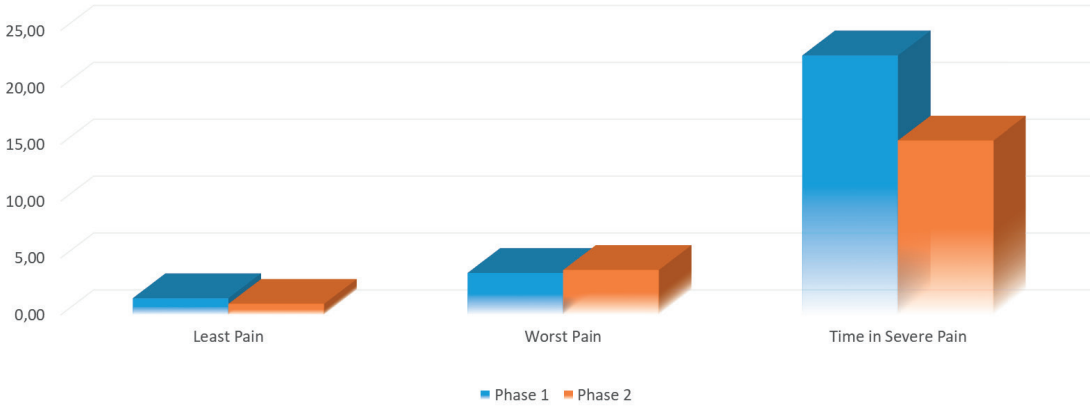
	Phase 1	Phase 2
Activities in bed (mean ± SD)	3.48 ± 3.10	3.21 ± 2.01
Coughing / taking deep breath (mean ± SD)	1.20 ± 2.33	2.68 ± 1.88

Sleep (mean ± SD)	1.82 ± 2.29	0.98 ± 1.24
Proportion out of bed (%)	92 YES	100 YES
Activities out of bed (mean ± SD)	1.68 ± 1.99	3.51 ± 1.93

Table 3. Mean values for the perception of care in phase 1 and phase 2

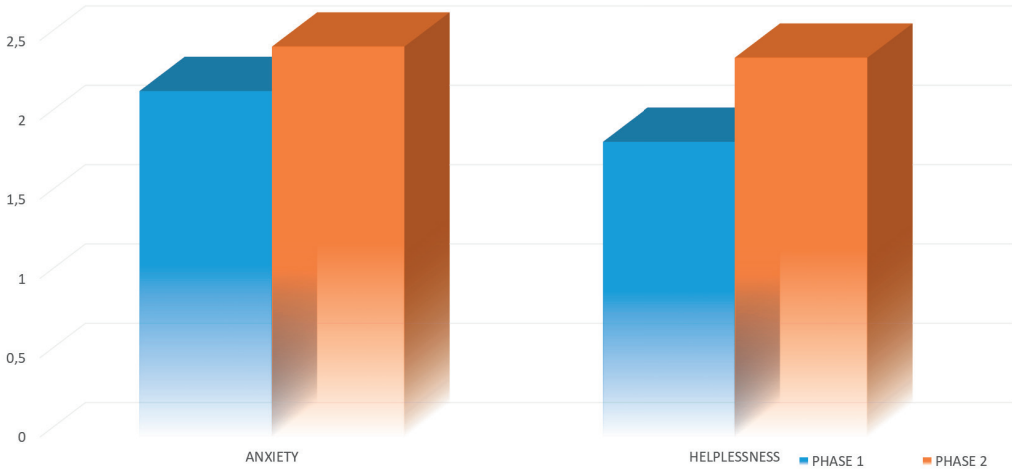
	PHASE 1	PHASE 2
Pain relief (mean ± SD)	65.40 ± 30.48	79.38 ± 16.79
Allowed participation (mean ± SD)	6.09 ± 3.94	6.99 ± 2.14
Satisfaction (mean ± SD)	8.74 ± 1.94	8.46 ± 1.51
Wish more treatement (mean ± SD)	89% NO	85% NO
Receipt of information (mean ± SD)	59% YES	86% YES

Figure 1. Mean values of the least pain, the worst pain and time in severe pain in phase 1 and phase 2.



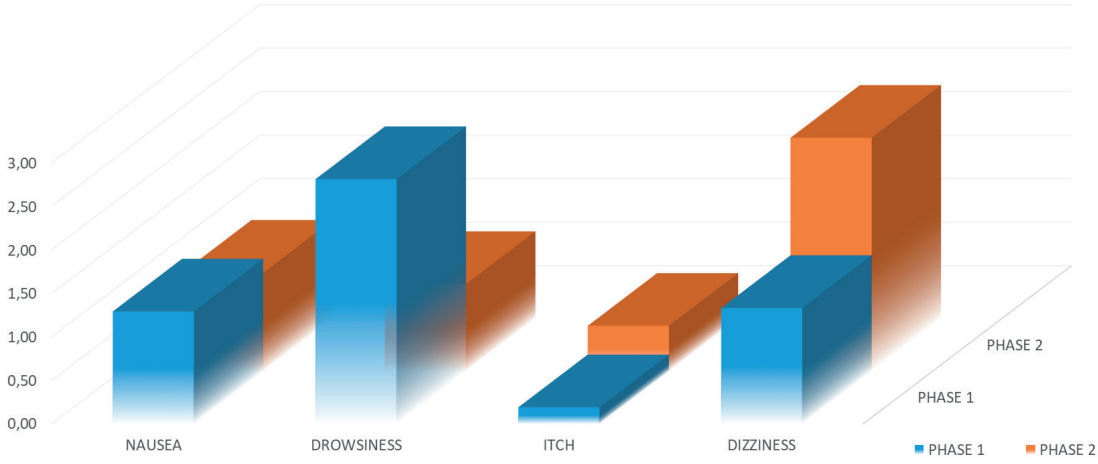
Graph 1. Presentation of mean values of the least pain, worst pain and time in severe pain for phase 1 and 2

Figure 2. Mean values of the anxiety and helplessness for phase 1 and 2.



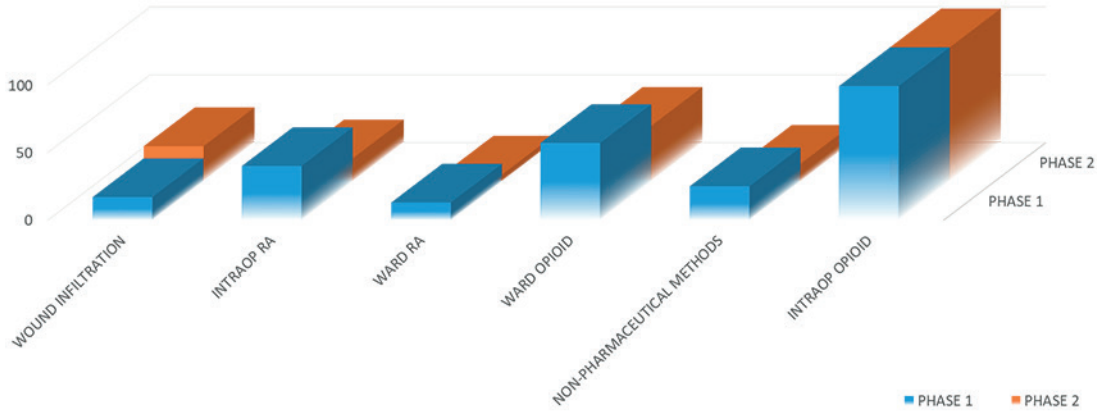
Graph 2. Presentation of mean values of the anxiety and helplessness for phase 1 and 2

Figure 3. Mean values of nausea, drowsiness, itching and dizziness for phase 1 and 2.



Graph 3. Presentation of mean values of nausea, drowsiness, itching and dizziness for phase 1 and 2

Figure 4. Mean values of the wound infiltration, intraoperative RA, ward RA, ward opioid use, non-pharmaceutical methods and intraoperative opioid use for phase 1 and 2



Graph 4. Presentation of mean values of the wound infiltration, intraoperative RA, ward RA, ward opioid use, non-pharmaceutical methods and intraoperative opioid use for phase 1 and 2

Combination of bilateral pectoral nerve block and bilateral erector spinae plane block for one-stage gender affirmation surgery, female to male – report of two cases

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Abstract

It is estimated that there are almost 25 million transgender persons living worldwide, of whom one million resides in the United States of America (USA). Physicians rely on an array of international clinical guidelines for effective preoperative preparation of patients undergoing gender affirmation surgery. Depending on the patient cases, i.e. female to male (FtM) or male to female (MtF), surgical procedures differ. FtM surgical approach is comprised of bilateral transgender mastectomy with chest reconstruction and "bottom" procedures consisting of hysterectomy, vaginectomy, metoidioplasty or phalloplasty. University Children's Hospital in Belgrade is one of the leading centers for gender affirmation surgery with 10-12 procedures done annually. From an anesthesiological aspect, prevention of thromboembolism, hemorrhage and pain managementare crucial. Achieving analgesia in these surgical procedures differs from i.v. opioid and NSAIL use to neuraxial blocks. We here present two patient cases in order to depict the role of peripheral nerve blocks, i.e. "single dose" bilateral pectoralis nerve (PECS) block and bilateral errector spinae plane (ESP) block in FtM gender affirmation surgery.

Key words: PECS block, ESP block, gender affirmation surgery, FtM

Introduction

The first description of pectoralis nerve (PECS) block presented in detail in 2012, following its successful use in breast surgery. Depending on the site of anesthetic application, a distinction between PECS I and PECS II block can be made. PECS block is a "single injection" superficial block of the anterior thoracic wall[1]. Application of a local anesthetic blocks pectoral nerves, intercostobrachial nerve, intercostal nerves and long thoracic nerve, thus achieving analgesia during breast surgery or any other surgical procedures involving the anterior thoracic wall.

During PECS I block local anesthetic is administered at the level of the third rib in the interfascial plane between pectoralis major muscle and pectoralis minor muscle. PECS II block is an extension of the PECS I procedure, where a local anesthetic is applied at the level of the third or fourth rib, beneath the serratus anterior muscle fascia, with the needle preferably making contact with the bone. This route of administration allows the local anesthetic to be distributed beneath the suspensory ligament of axilla (Gerdy's ligament). Gerdy's ligament is a thin fascia which connects the axillary and clavipectoral fascia and partially attaches itself to pectoral muscles, shaping the concavity of the axilla. The nerve block involves anterior cutaneous branches of intercostal nerves, long thoracic nerves C5-C7 and the intercostobrachial nerve, which is a cutaneous branch of the T2 intercostal nerve [2]. Indications for PECS I and PECS II block are various ranging from partial or total mastectomy with or without axillar resection, tumor resections, anterior thoracotomy, surgical procedures in the anterior shoulder region, silicone implant placement surgery, cardiac pacemaker and cardioverter defibrillator implantation to rib fractures [3]. Contraindications are usually rare, varying from local infections at the site of block application to patient's refusal to undergo the procedure. However, the use of anticoagulant therapy is not considered to be a contraindication, but requires additional precaution of anesthesiologists. Achieving complete analgesia during some surgical procedures demands combination of PECS block with serratus plane block, supraclavicular brachial plexus block or erector spinae plane (ESP) block.

ESP block is a novel peripheral paraspinal fascial plane block, first described as treatment of chronic neuropathic pain and applied in two patients who uderwent video-assisted thoracoscopic surgery [4]. In this procedure an anesthetic is administered between the erector spinae muscle and the superior margin of the vertebral transverse process. Upon application, the local anesthetic diffuses both in cranial and caudal direction through intertransverse connective tissue, paravertebral towards front and back branches of spinal nerves. Indications for this procedure are numerous encompassing thoracic, abdominal, orthopedic and urologic surgery and pain management. ESP block can be performed in different regions ranging from cervical to lumbosacral vertebral levels, but also in single or multiple levels during one procedure. Additionally, this intervention can be executed bilaterally and in combination with perineural catheter placement for postoperative continuous analgesia. ESP block is an effective alternative to epidural anesthesia and paravertebral block procedure [5].

Case reports

We report on two patient cases of FtM gender affirmation surgery. Upon implementing general endotracheal anesthesia (GETA) protocol in both patients, a combination of two peripheral block procedures were performed, i.e. PECS I and PECS II block for mastectomy and ESP block for "bottom" surgical procedures. Prior to these operations, the patients underwent hysterectomy with adnexectomy.

Case 1

A 24-year-old patient (body weight 60 kg) was admitted to the urology department of the University Children's Hospital for a planned bilateral mastectomy and "bottom" procedure as a part of FtM gender affirmation surgery and gender dysphoria treatment. The patient is a non-smoker and does not report any comorbidities, allergies as well as opioid and alcohol consumption. Standard preoperative protocol was followed, the patient was clinically assessed, laboratory tests were performed, antibiotics and anticoagulants were administered as prophylaxis and necessary blood products were obtained. The usual GETA protocol was implemented. The surgical procedure lasted 5 hours and vital parameters were monitored throughout the operation.

Postoperative pain management was achieved by means of two peripheral block modalities: bilateral PECS I and PECS II block for bilateral mastectomy and bilateral L2 ESP block for the "bottom" surgical procedure. Having in mind that the two peripheral blocks are volume-dependent, special attention was given to the maximal dose of anesthetics. According to aforementioned principle, Levobupivacaine (AbbVie S.r.l., Aprilia, Italy) 0.25%, 25 ml /62.5 mg was used for PECS I and PECS II block. Bilateral ESP block was achieved utilizing a mixture of Lidocaine (Galenika a.d., Belgrade, Serbia) 1.2% 10ml/120 mg, Levobupivacaine (AbbVie S.r.l., Aprilia, Italy) 0.25% 23 ml/ 57.5 mg and 4 mg od Dexametazon (Galenika a.d., Belgrade, Serbia).

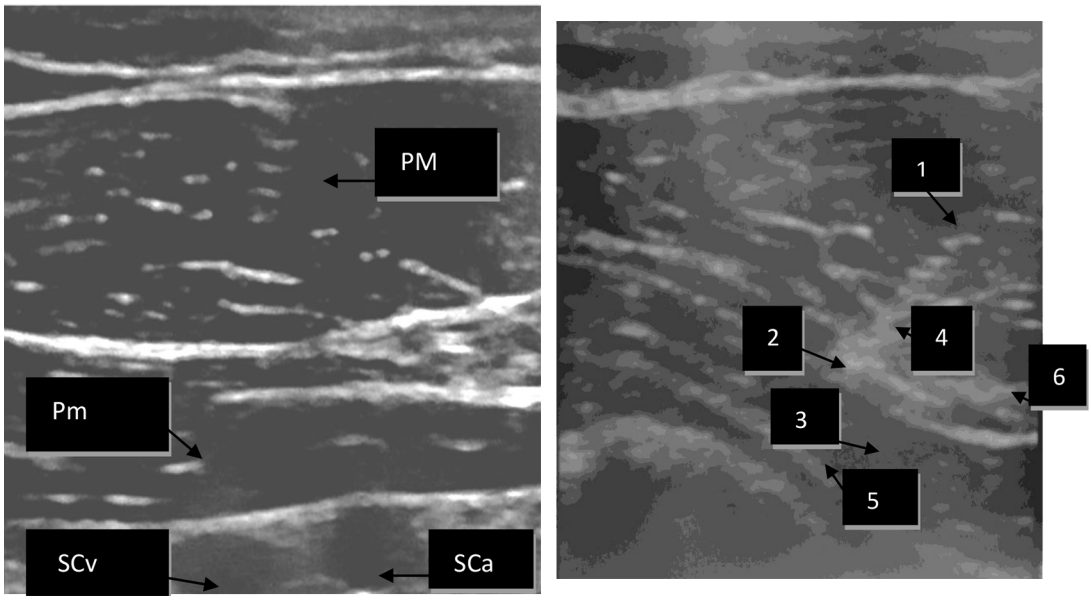

Figure 1. Pectoralis major(PM), Pectoralis minor(Pm), Fig.2 PM(1), Pm(2), serratus ant.(3), LA(4), subclavian artery and vein(SCv/a) IV rib(5), needle(6)

After surgery, during recovery from anesthesia the patient was hemodynamically stable, breathing rate was normal and pain was absent – Numeric Rate Pain Scale (NPRS)

was 0 (NPRS: 0 – no pain, 1-3 – mild intensity pain, 4-6 – moderate intensity pain, 7-10 – severe intensity pain). Upon surgery, in the intensive care unit and on the urology ward, the patient was prescribed 2.5 g/ 5 ml of metamizole i.v. (Novalgetol, Galenika a.d., Belgrade, Serbia) and 100 mg of Tramadol i.v. (Hemofarm a.d., Vršac, Serbia), both maximally every 8 hours, if circumstances required. Twelve hours upon surgery, NRPS was 2 and metamizole was administered, after which pain never occurred again and there was no need for Tramadol. On the first postoperative day, food and beverages were given perorally without the occurrence of nausea and vomiting. Seven days after the surgical procedure, the patient was discharged from the hospital in good physical state.

Case 2

A 26-year-old patient (body weight 50 kg) was admitted to the urology department for a planned FtM gender affirmation surgery as a part of gender dysphoria treatment. The patient is a non-smoker and was earlier treated for *H. pylori* infection, reports no allergies and opioid and alcohol consumption. Upon induction of anesthesia, following appropriate GETA protocols, the surgical procedure started and lasted for 6 hours. The dose of local anesthetics was corrected, as the dose of 0.25% 40 ml/ 100 mg Levobupivacaine (AbbVie S.r.l., Aprilia, Italy), was partitioned, i.e. 50 mg for bilateral PECS block and 50 mg for bilateral ESP block. Additionally, bilateral ESP block required 4 mg of Dexametazon (Galenika a.d., Belgrade, Serbia) and 1.2% 10ml /120 mg of Lidocaine (Galenika a.d., Belgrade, Serbia).

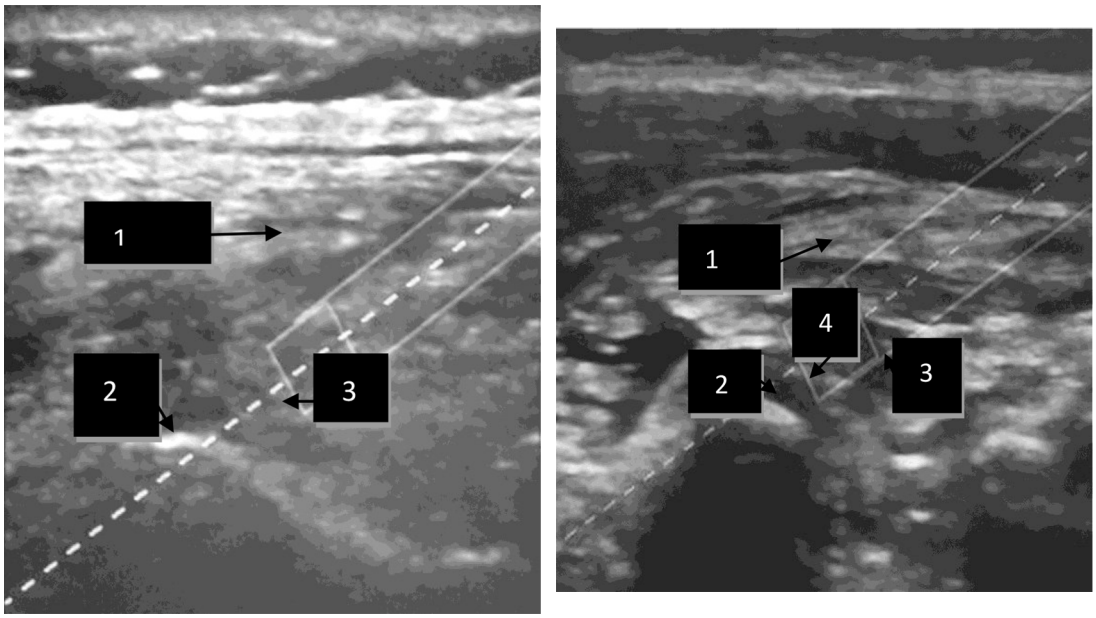

Figure 3. Erector spinae muscule(1), Fig.4 Erector spinae m.(1), PT(2), needle(3), Processus transverses(2), needle(3) local anesthetic (4)

Immediately after surgery, the patient was hemodynamically stable, with regular breathing rate and no pain (NRPS=0). Sixteen hours upon the procedure NRPS was 4, so the patient was given 5 ml/ 2.5g of metamizole i.v. (Novalgetol, Galenika a.d., Belgrade, Serbia), after which the pain did not reoccur. During the first postoperative day, the patient was allowed to take food and beverages orally and there was no nausea and vomiting. Eight days after the surgical procedure the patient was discharged from the hospital in stabile physical condition.

Discussion

It is well known there are contemporary, international recommendations and clearly defined protocols for preoperative preparation of transgender persons. University of San Francisco, one of the leading centers in this area of expertise, published the guidelines for the primary and gender-affirming care of transgender and gender non-binary people[6]. Perioperative examination and preparation of patients requires a multimodal expert approach ranging from psychiatrists, endocrinologists to anesthesiologists and surgeons. From an anesthesiologists point of view, standard clinical assessment and analysis of every patient case, should be accompanied by an effective acute pain management and chronic pain prevention strategy. One plausible idea for achieving better postoperative analgesia in transgender persons was application of minimally invasive peripheral block techniques in combination with postoperative use of NSAIL.

Pectoralis nerve (PECS) block provides adequate analgesic effect in the first 24 hours after a mastectomy due to breast cancer [7]. Several retrospective and a few prospective randomized studies showed that patient groups who were treated with PECS block received significantly lower doses of opioids intra- and postoperatively and that the incidence of nausea and vomiting was reduced in these patients as well [8, 9].

Erector spinae plane (ESP) block applied in T7 vertebral level allows for the distribution of the local anesthetic to L2-L3 region, so a "single dose" exerts its effect on the entire abdominal region[10]. A clinical study of ESP block effectiveness performed by Hamed et al. reported that patients who were treated with ESP block after elective hysterectomy needed significantly smaller doses of Fentanyl in comparison to a patient group that did not have this analgesic procedure. Additionally, the results show smaller incidence of nausea and vomiting in patients treated with ESP block[11]. Yamak et al. performed bilateral ESP block in T9 vertebral level after an emergency Cesarean delivery and recognized that this procedure is highly effective in acute pain management[12].

Compared to neuraxial blocks, these two procedures, i.e. PECS block and ESP block are less complicated, thus reducing the risk of injury of vital blood vessels and nerves and infection. Furthermore, these procedures can be used in patients on anticoagulant therapy.Although PECS block and ESP block are relatively novel procedures, studies and reports on these analgesic methods are scarce. However, clinical experience hitherto puts an emphasis on the effectiveness of analgesia achieved by these two

techniques. If applied preoperatively, these techniques will significantly decrease the amount of Fentanyl used during the surgical procedure. On the other hand, in patients treated with these methods postoperatively, the need for opioid use declines, nausea and vomiting are rare, pain management allows early patient verticalization and better breathing pattern, thus reducing the risk of thromboembolism and pneumonia. Ultimately, mortality rates decrease and the length of hospitalization significantly reduces.

Conclusion

Gender affirming surgery in transgender persons is comprised of several segments and therefore is performed in two acts. Also, it carries certain risks such as acute hemorrhage, large hematomas, severe acute pain and/or persistent chronic pain. Our goal was to be among the first to implement novel techniques of regional anesthesia in order to provide quality postoperative analgesia. Additionaly, by using PECS and ESP block methods we strive to reduce the utilization of opioids, prevent nausea and vomiting and achieve early patient verticalization, thus reducing the risk of thromboembolism. Based on the experience presented in these case reports we think that PECS I and PECS II block and ESP block are potentially exceptional pain management strategies in transgender patients undergoing gender affirmation surgery, but we are also aware that more studies on these techniques are necessary.

References

1. Blanco R. The 'pecs block': a novel technique for providing analgesia after breast surgery. Anaesthesia. 2011;66(9):847-8.
2. Parras T, Blanco R. Regional anaesthesia Tutorial 346: PECS blocks: World Federation of Societies of Anesthesiologists; 2017 [31.01.2017.]. Available from: www.wfsahq.org/resources/anaesthesia-tutorial-of-the-week.
3. Blanco R, Fajardo M, Parras Maldonado T. Ultrasound description of Pecs II (modified Pecs I): a novel approach to breast surgery. Revista espanola de anestesiologia y reanimacion. 2012;59(9):470-5.
4. Forero M, Adhikary SD, Lopez H, Tsui C, Chin KJ. The Erector Spinae Plane Block: A Novel Analgesic Technique in Thoracic Neuropathic Pain. Regional anesthesia and pain medicine. 2016;41(5):621-7.
5. Porkashanian A, Narayanan M, Venkataraju A. Regional anaesthesia Tutorial 414: The erector spinae plane block: a review of current evidence: World Federation of Societies of Anaesthesiologists; 2019 [3 December 2019]. Available from: www.wfsahq.org/resources/anaesthesia-tutorial-of-the-week.
6. Deutsch MB. Guidelines for the Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People. San Francisco: Center of Excellence for Transgender Health, Department of Family and Community Medicine, 2016.
7. Yuki I, Ueshima H, Otake H, Kitamura A. PECS Block Provides Effective Postopera-

tive Pain Management for Breast Cancer Surgery—A Retrospective Study. International Journal of Clinical Medicine. 2017;8:198-203.
8. Kim DH, Kim S, Kim CS. Efficacy of Pectoral Nerve Block Type II for Breast-Conserving Surgery and Sentinel Lymph Node Biopsy: A Prospective Randomized Controlled Study. 2018;2018:4315931.
9. Kumar S, Goel D, Sharma SK, Ahmad S, Dwivedi P, Deo N, et al. A randomised controlled study of the post-operative analgesic efficacy of ultrasound-guided pectoral nerve block in the first 24 h after modified radical mastectomy. Indian journal of anaesthesia. 2018;62(6):436-42.
10. Chin KJ, Adhikary S, Sarwani N, Forero M. The analgesic efficacy of pre-operative bilateral erector spinae plane (ESP) blocks in patients having ventral hernia repair. Anaesthesia. 2017;72(4):452-60.
11. Hamed MA, Goda AS, Basiony MM, Fargaly OS, Abdelhady MA. Erector spinae plane block for postoperative analgesia in patients undergoing total abdominal hysterectomy: a randomized controlled study original study. Journal of pain research. 2019;12:1393-8.
12. Yamak Altinpulluk E, Garcia Simon D, Fajardo-Perez M. Erector spinae plane block for analgesia after lower segment caesarean section: Case report. Revista espanola de anestesiologia y reanimacion. 2018;65(5):284-6.

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PROCEEDINGS

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Radiofrekventna ablacija vođena ultrazvukom- prikazi slučaja/Ultrasound Guided Radiofrequency Ablation – Case Presentations

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Abstract

Uvod: Radiofrekventna ablacija (RFA) je minimalno invanzivna procedura, kojom se radiofrekventni talasi od pulsnog generatora preko elektrode sa aktivnim vrhom isporučuju do tkiva. Usled stvaranja toplote dolazi do termokoagulacije sa akutnim inflamatornim odgovorom, nekrozom ćelija i fibrozom usled taloženja kolagenih vlakana. Položaj elektrode u tkivu mora biti potvrđen različitim radiološkim tehnikama od kojih se najčešće koriste fluoroskopija i ultrazvuk. Osteoartritis kolena (KOA) je praćen izuzetno jakim bolom usled destrukcije hrskavice i koštanih struktura, dovodeći do različitog stepena invaliditeta. RFA-om tri genikularna nerva, vođenom ultrazvukom, postiže se adekvatan analgetski efekat kod ovih pacijenata. **Zaključak**: Prednosti RFA vođene ultrazvukom u odnosu na fluoroskopiju ogledaju se u: realnoj slici položaja anatomskih struktura i jasnoj vizuelizaciji položaja igle u odnosu na njih; pokretnosti i dostupnosti ultrazvučnih aparata u odnosu na fluoroskop; odsustvu ponavljanih zračenja pacijenata i osoblja i znatno kraćem trajanju procedure.

Keywords: radiofrekventna ablacija (RFA), osteoartritis, genikularni nervi, terapija bola

Uvod

Radiofrekventna ablacija (RFA) je minimalno invanzivna procedura, koja je prvi put uspešno korišćena u terapiji hroničnog bola kod neuralgije n.trigeminus-a 1970 god. i od tada spisak indikacija za ovu proceduru je značajno proširen (1). Danas postoje tri različita tipa uređaja za radiofrekventnu ablaciju: konvencionalni (toplota) RFA koji se često naziva samo RFA, „cooled" RFA i pulsni RFA (1).

RFA dovodi do generisanja elektromagnetnog polja pomoću pulsnog generatora koje se preko elektrode sa aktivnim vrhom isporučuje do tkiva (1,2)(Slika 1). Aktivni

vrh igle može biti dužine 8mm, 10 mm i 12 mm, u zavisnosti od željenog područja lezije (1). Vrh elektrode zagreva lokalno tkivo do temperature obično veće od 47°C (u rasponu od 70°C do 90°C) u trajanju od 120 – 130 sekundi, generisano kroz elektromagnetno polje frekvencije 250 kHz (3,4). Položaj elektrode u tkivu mora biti potvrđen različitim radiološkim tehnikama od kojih se najčešće koriste fluoroskopija i ultrazvuk (1,2).

Slika 1. Generator za radiofrekventnu ablaciju

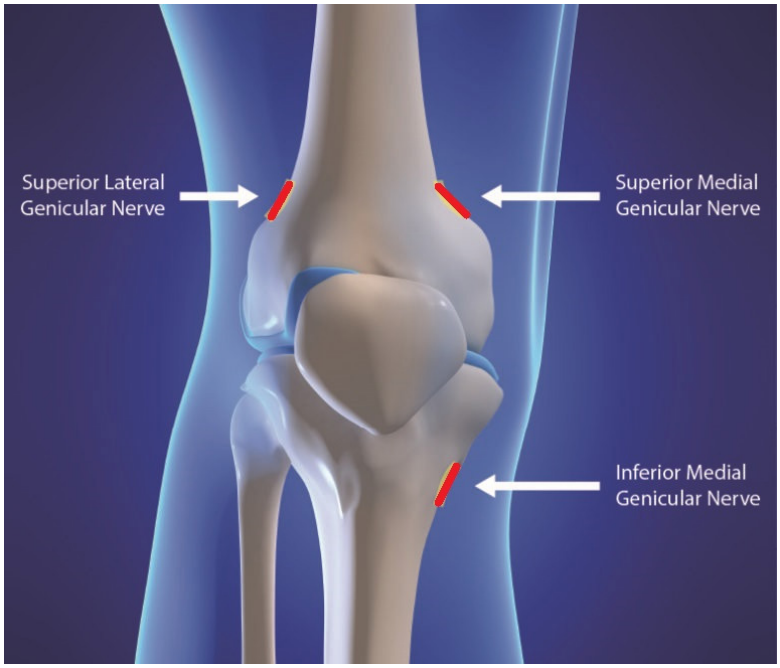
RFA zastavlja nociceptivni (A-δ i C vlakna) bolni impuls sa periferije do centralnog nervnog sistema bez uništenja motornih ili senzornih (A-β) vlakana (3). Ublažavanje bola nastaje kao rezultat destrukcije u snabdevanju senzornog nerva ali i zbog ekspresije gena c-Fos u lamini I i II dorzalnog roga usled izloženosti nerva električnom polju (5). Usled stvaranja toplote dolazi do termokoagulacije sa akutnim inflamatornim odgovorom, nekrozom ćelija i fibrozom usled taloženja kolagenih vlakana. Taj proces traje tokom tri nedelje nakon procedure i na njega se može uticati samo u akutnoj fazi primenom kortikosteroida. Kratkoročni efekati kortikosteroida na ovaj proces su rezultat smanjenja imflamatornog odgovora ali njihova primena je za sada bezpotvrđenih dugoročnih efekata (6). Bazalna lamina Schvannovih ćelija može biti očuvane nakon RFA ukoliko se koristi toplota do 45°C , omogućavajući regeneraciju nerva (3,7,8). Pored toga, RFA proizvodi lokalno električno polje, što je smatra se da promoviše neuromodulaciju inhibicijom ekscitatornih C-vlakana (8,9). Stepen termokoagulacije je određen dužinom vrha, prečnikom igle, provodnim medijumom, korišćenom temperaturom i dužinom trajanja RFA (1).

Pulsna RFA je uvedena 1998 god. kao alternativa konvencionalnoj RFA (1,2). Znatno je manje bolna procedura gde nakon postizanja temperature maksimum od 42°, zaustavlja se sprovodljivost i time smanjuje stepen oštećenja tkiva i vrši preciznija ablacija nerava (2). Pulsnom RFA generiše se impuls amplitude od 45 V u trajanju od po 20 milisekundi svakih 500 milisekundi (dva puta u sekundi) (10). Generator može

da modifikuje parametre u realnom vremenu da bi se postigla željena lokalna temperatura tkiva (2). Prednost pulsne RFA u odnosu na konvencionalnu RFA je u znatno manjim ireverzibilnim oštećenjima tkiva sa sličnim efektima na nervnu provodljivost (1,2). Međutim, trajanje efekta je znatno kraće i može zahtevati češće ponavljanje procedure kako bi se dobio isti efekat (11).

RFA hlađenjem („cooled") je još jedan modalitet RFA, uveden od 1996 god., kojom se hladan fiziološki rastvor propušta kroz iglu dovodeći do smanjenja lokalne temperature (1,2). Hladna voda menja ne samo toplotu u tkivu na oko 60°C, već i ukupnu veličinu, oblik i projekciju lezija u poređenju sa konvencionalnim RFA (12). RFA hlađenjem daje mogućnost stvaranja više područja neuronskih lezija, što može omogućiti znatno duže trajanje efekta u odnosu na konvencionalnu RFA (1,5,12).

Osteoartritis kolena (KOA) je veoma česta bolest koja dovodeći do različitog stepena invaliditeta doprinosi velikom ekonomskom opterećenju društva (13,14). Destrukcija hrskavice i koštanih struktura praćena je izuzetno jakim bolom kod ovih pacijenata. Ublažavanje bola i poboljšanje funkcije kolena predstavljaju glavne terapijske ciljeve koji se postižu farmakološkim i/ili nefarmakološkim metodama (15). Ugradnja totalne proteze kolena (TKA) je definitivni i najčešće primenjeni način lečenja (14). Međutim 20% pacijenata navodi bol kao glavni razlog nezadovoljstva nakon ove procedure (1,16). S druge strane kod pacijenata koji ne žele ili kod kojih se ne može ugraditi totalna proteza kolena konzervativnom terapijom za sada nisu postignuti adekvatni analgetski rezultati (14,16). RFA kao minimalno invanzivna tehnika od nedavno se koristi u terapiji bola kod ovih pacijenata (17,18). Prva istraživanja koja govore o njenoj efikasnosti datiraju iz 2011 god. kada se ablacijom genikularnih nerava postigla adekvatna kontrola bola (17). Fluoroskopija je trenutno najčešće korišćena metoda za vođenje RFA (18,19,20). Međutim sve više kliničkih istraživanja govore i prednost daju RFA-i vođenu ultrazvukom koja takođe omogućava jasnu lokalizaciju tri senzorna genikularna nerva: superior laterat, superior medial i inferior medial (Slika 2) (18-23). Zbog blizine peronealnog nerva i moguće njegove lezije donji lateralni genikularni nerv se ne blokira (18-23). Huang i sar.su metaanalizom koja je uključivala 8 studija i 256 pacijenata, sa različitim vremenom praćenja nakon terapije, pokazali analgetsku efikasnost RFA vođene ultrazvukom i funkcionalni oporavak kolena kod pacijenata sa KOA (14). Bolji efekti postignuti su RFA genikularnih nerava u odnosu na intraartikularnu ili RFA ishijadičnog nerva (14). Takođe je pokazano da analgetska efikasnost ultrazvučno vođene RFA terapije na pacijentima sa KOA se održava minimum 24 nedelje. S druge strane incidenca neželjenih događaja je bila veoma niska (2,33%) nakon ultrazvučno vođene RFA. Tako su 3 pacijenta imala ekhimozu na mestu procedure, dva pacijenta hipoesteziju, i jedan pacijent ukočenost od 256 lečenih pacijenata (24,25). Svi simptomi su se značajno poboljšali ili su nestali u narednih 6 meseci. Još jednu od prednosti RFA vođene ultrazvukom pokazali su Sari i sar., postrignuvši iste terapijske efekte kao sa RFA fluoroskopijom uz znatno skaćenje vremena trajanja procedure (26).



Slika 2. Mesto RFA genikularnih nerava

Zaključak

Uzimajući sve u obzir u zaključku možemo reći da RFA vođena ultrazvukom ima nekoliko prednosti u odnosu na fluoroskopiju. Te prednosti se ogledaju pre svega u dobijanju realne slike položaja anatomskih struktura i jasnoj vizuelizaciji položaja igle u odnosu na njih u realnom vremenu. Takođe u činjenici da su ultrazvučni aparati pokretni i dostupniji u odnosu na fluoroskop, da ne dovode do ponavljanih ili produženih zračenja niti pacijenata ni osoblja i da izvođenje procedure traje znatno kraće.

Konflikt interesa. Ne postoji konflikt interesa.

Zahvalnost. Posebnu zahvalnost dugujemo dr Ender Sir.

Reference

1. Cheppalli N, Bhandarkar AW, Sambandham S, Oloyede SF. Safety and Efficacy of Genicular Nerve Radiofrequency Ablation for Management of Painful Total Knee Replacement: A Systematic Review.Cureus. 2021 Nov 11;13(11):e19489. doi: 10.7759/cureus.19489.
2. Gupta A, Huettner DP, Dukewich M.Comparative Effectiveness Review of Cooled Versus Pulsed Radiofrequency Ablation for the Treatment of Knee Osteoarthritis: A Systematic Review.Pain Physician. 2017 Mar;20(3):155-171

3. Kapural L, Mekhail N. Radiofrequency ablation for chronic pain control. Curr Pain Headache Rep 2001; 5:517-525.
4. Choi WJ, Hwang SJ, Song JG, Leem JG, Kang YU, Park PH, Shin JW. Radiofrequency treatment relieves chronic knee osteoarthritis pain: A double-blind randomized controlled trial. Pain 2011; 152:481-487.
5. Van Zundert J, de Louw AJ, Joosten EA, et al.: Pulsed and continuous radiofrequency current adjacent to the cervical dorsal root ganglion of the rat induces late cellular activity in the dorsal horn. Anesthesiology.2005, 102:125-31
6. Abd-Elsayed A, Loebertman M, Huynh P, Urits I, Viswanath O, Sehgal N.The Long-Term Efficacy of Radiofrequency Ablation With and Without Steroid Injection. Psychopharmacol Bull. 2020 Oct 15;50(4 Suppl 1):11-16
7. Cosman ER, Jr., Cosman ER, Sr. Electric and thermal field effects in tissue around radiofrequency electrodes. Pain Med 2005; 6:405-424.
8. Smith HP, McWhorter JM, Challa VR. Radiofrequency neurolysis in a clinical model. Neuropathological correlation. J Neurosurg 1981; 55:246-253.
9. Slappendel R, Crul BJ, Braak GJ, Geurts JW, Booij LH, Voerman VF, de Boo T. The efficacy of radiofrequency lesioning of the cervical spinal dorsal root ganglion in a double blinded randomized study: No difference between 40 degrees C and 67 degrees C treatments. Pain 1997; 73:159-163
10. Cahana A, Van Zundert J, Macrea L, van Kleef M, Sluijter M. Pulsed radiofrequency: Current clinical and biological literature available. Pain Med 2006; 7:411-423
11. Pangarkar S, Miedema ML. Pulsed versus conventional radio frequency ablation for lumbar facet joint dysfunction. Curr Phys Med Rehabil Rep 2014; 2:61-65
12. Menzies RD, Hawkins JK. Analgesia and improved performance in a patient treated by cooled radiofrequency for pain and dysfunction postbilateral total knee replacement. Pain Pract 2015; 15:E54-E58
13. R. Barnett, "Osteoarthritis," The Lancet, 2018:39:1985.
14. Huang Y, Deng Q, Yang L, Ma J, Wang Z, Huang D, Luo L, Zhou H.Efficacy and Safety of Ultrasound-Guided Radiofrequency Treatment for Chronic Pain in Patients with Knee Osteoarthritis: A Systematic Review and Meta-Analysis.Pain Res Manag. 2020 Sep 19;2020:2537075. doi: 10.1155/2020/2537075. eCollection 2020
15. T. Neogi, "The epidemiology and impact of pain in osteoarthritis," Osteoarthritis and Cartilage,2013:21(9):1145–1153.
16. Gunaratne R, Pratt DN, Banda J, Fick DP, Khan RJ, Robertson BW: Patient dissatisfaction following total knee arthroplasty: a systematic review of the literature. J Arthroplasty. 2017, 32:3854-60.10.1016/j.arth.2017.07.021
17. W.-J. Choi, S.-J. Hwang, J.-G. Song et al., "Radiofrequency treatment relieves chronic knee osteoarthritis pain: a double blind randomized controlled trial," Pain,2011: 152(3):481–487.
18. Kidd VD, Strum SR, Strum DS, Shah J.Genicular Nerve Radiofrequency Ablation

for Painful Knee Arthritis: The Why and the How. JBJS Essent Surg Tech. 2019 Mar 13;9(1):e10. doi: 10.2106/JBJS.ST.18.00016.
19. Conger A, Gililland J, Anderson L, Pelt CE, Peters C, McCormick ZL. Genicular Nerve Radiofrequency Ablation for the Treatment of Painful Knee Osteoarthritis: Current Evidence and Future Directions.Pain Med. 2021 Jul 25;22(Suppl 1):S20-S23. doi: 10.1093/pm/pnab129
20. Fonkoué L, Behets C, Kouassi JK, Coyette M, Detrembleur C, Thienpont E, Cornu O.Distribution of sensory nerves supplying the knee joint capsule and implications for genicular blockade and radiofrequency ablation: an anatomical study.Surg Radiol Anat. 2019 Dec;41(12):1461-1471. doi: 10.1007/s00276-019-02291-y. Epub 2019 Jul 23
21. Zhang H, Wang B, He J, Du Z.Efficacy and safety of radiofrequency ablation for treatment of knee osteoarthritis: a meta-analysis of randomized controlled trials. J Int Med Res. 2021 Apr;49(4):3000605211006647. doi: 10.1177/03000605211006647
22. McCormick ZL, Cohen SP, Walega DR, Kohan L.Technical considerations for genicular nerve radiofrequency ablation: optimizing outcomes.Reg Anesth Pain Med. 2021 Jun;46(6):518-523. doi: 10.1136/rapm-2020-102117. Epub 2021 Jan 22
23. Kim PY, Cohen SP.Genicular Nerve Blocks and Radiofrequency Ablation for Knee Osteoarthritis: More Nerves, More Questions.Pain Med. 2021 May 21;22(5):1019-1021. doi: 10.1093/pm/pnab022
24. Santana Pineda M. M., Vanlinthout L. E., Moreno Mart´ın A., van Zundert J., Rodriguez Huertas F., Novalbos Ruiz J. P.,"Analgesic effect and functional improvement caused by radiofrequency treatment of genicular nerves in patients with advanced osteoarthritis of the knee until 1 year following treatment," Regional Anesthesia and Pain Medicine, 2017:42(1): 62–68.
25. Ahmed A., Arora D., "Ultrasound-guided radiofrequency ablation of genicular nerves of knee for relief of intractable pain from knee osteoarthritis: a case series," Britis Journal of Pain,2018:12(3):145–154.
26. Sari S., Aydin O.N,Turan Y et al., "Which imaging method should be used for genicular nerve radio frequency thermocoagulation in chronic knee osteoarthritis?" Journal of Clinical Monitoring and Computing,2017:31:797–803.

12 Wound infiltration, when, where, how much /Infilitracija hirurške incizije, kada, gde, koliko

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Introduction

Wound infiltration (WI) with local anesthetics (LA) presents extensive LA injection in various tissue planes under direct visualization before surgical wound closure or preoperatively at the planned incision line[1] in the subdermal and musculofascial planes or instilled in a cavity (intra-articular intraperitoneal) [2-5]. The contraindications for WI are infection at the injection site and patient refusal for WI[6]. Still, WI demands from performer knowledge of anatomy and procedure specific sources of pain.

Wound infiltration (WI) with local anesthetics (LA) is used as anesthesia for minor surgeries, primarily by plastic surgeons to repair skin wounds, cosmetic surgery, oral surgery, and minor gynecological procedures. WI is added as part of postoperative analgesia regimen after general or regional anesthesia for different surgical procedures.

Wound infiltration in PROSPECT

In practice, procedure-specific WI techniques are proven safe and easy for learning and application[7,8]. Procedure-specific postoperative pain (PROSPECT) Working Group recommended WI for open abdominal surgeries, laparoscopic cholecystectomy, oncological breast surgeries, laminectomy, hallux valgus surgery, radical prostatectomy [1,9,10].

However, our literature search revealed the beneficial role of wound infiltration as part of multimodal analgesia in some other surgeries. [1] More clinical research is needed in the field regarding emergeny surgeries especially through laparotomy, open liver resection, videoasssissted thoracoscopic surgery, neurosurgery, cardiosurgery and total knee arthroplasty.

Wound infiltration technique

LA infiltration is usually in rhomboid shape around predicted incision place subcutaneously or intradermally following the imaginary surgical incision line[2]. Depending on the localization of infiltration, the WI of LA can be subdermal, intradermal, deep

subcutaneous, and subfascial[2]. Small needle diameter (27- to 30-gauge)[11,12]. decreases pain during the injection based on the speed of injection rate reduction[12,13]. LA's intradermal injection can induce anesthesia more rapidly than subcutaneous injection[14]. The specific anatomy of nerve endings in the dermis resembles a tree, so good injection technique leads to wide anesthesia with pain only on the initial puncture site. Initial perpendicular insertion of the needle and LA enables intradermal insertion of the needle[1]. Surgical incision infiltration under direct visualization is performed with a short 22-gauge needle through all tissue layers[15]. WI is usually done at the end of surgery[16].

Local anesthetics and adjuvants

The amount of LA depends on the site of WI, ranging from 3 ml for subdermal infiltration to 10 ml for the deep subcutaneous injection[2]. The calculation of LA maximal dosage is vital, reminding that it needs to be adjusted to kidney and hepatic function and obesity, age, and pregnancy. LA dosage is calculated using ideal body weight[1,17]. Caution is needed concerning local anesthetic systemic toxicity (LAST), which necessities the immediate use of intralipid and therapy recommended by LAST protocol, which is available in Serbian language (Figure 1)[2].

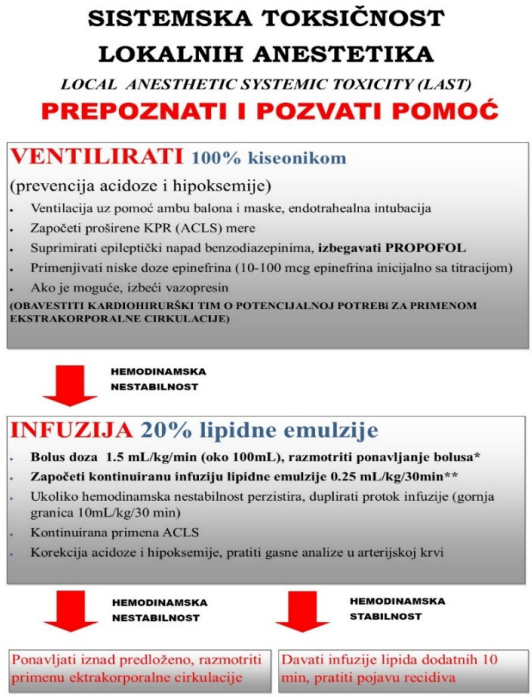

Figure 1. The guideline for local anesthetic systemic toxicity (LAST) therapy in the Serbian language. *a maximum number of boluses, including initial bolus; **maximum cumulative dose of lipid emulsion is 12 ml/kg. KPR-CPR cardiopulmonary resuscitation; ACLS-advanced cardiac life support. The copyrights SJAIT.

LA used for WI are combined with epinephrine, sodium bicarbonate, and different analgesics, including alpha-2-agonists, nonsteroid drugs (NSAIDs), and NMDA antagonists (Table 1)[1]. It is important to note that all named medications are used label off for WI since they can cause side effects on tissue including necrosis[1]. Studies rarely compare the effects of the addition of beforementioned medications for WI and after their systemic application.

Table 1. Medications used in combination with local anesthetics or alone for local wound infiltration or continuous wound infiltration.

Reference	Medication	Type of wound infiltration Single/continuous	Time of wound infiltration
Laminectomy[18]	Dexmedetomidine (2 μg/kg diluted in 20 mL 0.25% bupivacaine)	Single	At the end of surgery
Open cholecystectom[19]	Clonidine (3 μg/kg + 30 ml 0.25% bupivacaine)	Single	At the end of surgery
Inguinal herniorrhaphy[20]	Tramadol (1 mg/kg in 10 mL 0.9% normal saline	Single	Before wound closure
Inguinal herniorrhaphy[21]	Meloxicam	Single	Before skin closure
Thyroid surgery[22]	Lornoxicam (8 mg to 0.75% ropivacaine)	Single	Before skin closure
Thyroid surgery[23]	Diclofenac (50 mg)	Single	Before skin incision
Abdominal hysterectomy[24]	Ketamine (2 mg/kg) to bupivacaine 0.25%, 40 mL)	Single	
Laminectomy[25]	Ketorolac (30 mg added to levobupivacaine (200 mg) and adrenaline (0.5 mg)	Single	Before skin closure

Continuous wound infiltration

Continuous wound infiltration (CWI) is a mode of constant application of LA through specially designed multi-holed catheters. The technique is more expensive than single WI since it demands elastomeric pumps for continuous or intermittent LA delivery, and educated and skilled medical staff and postopertive follow-up [1,16,26]. The best CWI analgesia effects are in the skin regions with high-density subcutaneous and connective tissue. CWI is an alternative when other regional techniques are

contraindicated[26]. Continuous wound infiltration (CWI) enhances the effects of systemic postoperative analgesia, in some cases expressed an opioid-sparing result, shortened hospital stay, and increased patient satisfaction[4]. However, CWI is less present in the practice due to the relatively high price of wound catheters, need for additional education and established opinions about the technique[16].

Table 2. Study examples of local anesthetics type, dosage and time of application used for local wound infiltration or continuous wound infiltration for different surgical procedures.

Reference	Type of surgery	Local anesthetic	Mode of wound infiltration Single/continuous	Time of wound infiltration
Zhou et al. [28]	Craniotomy	Ropivacaine (0.5%,10ml)	Single	Prior incision
Batoz et al. [27]	Craniotomy	Ropivacaine (0.75%, 20 ml)	Single	Prior wound closure
Kang et al.[29]	Breast surgery	„Local mix“: lidocaine (1%, 10 ml) mixed 1:1 with bupivacaine (0.5%) "Local mix "was injected into the prior skin incision. Post-resection wound infiltration with "local mix "(7 ml in the breast site plus additional 3 ml in the sentinel node site)	Single	Prior incision Post-incisional
Lu et al. [30]	Breast surgery	Bupivacaine (0.5%, 5 ml diluted to 10 ml)	Single	Prior skin closure (into the dermis)
Kocabas et al.[31]	Sternotomy for cardiac surgery	Levobupivacaine (0.25%, 60 ml) a total of 30 ml of the sternum: 15 ml on each side, and a total of 30 ml of the study solution was infiltrated deeply around the mediastinal tubes: 15 ml on each side.	Single	Prior sternal wire placement: sternotomy and mediastinal tube sites were infiltrated
Koukis et al.[32]	Sternotomy for cardiac surgery	Ropivacaine (4 ml/h. 400 ml; mixture containing 300 ml ropivacaine (2 mg/ml) plus 100 ml ropivacaine (7,5 mg/ml))	Continuous	Precisely above the sternum and before closing the subcutaneous fascia, two specially designed catheters were placed on the sternum

Yang et al. [33]	VATS[a] lobectomy or anatomical segmentectomy	Bupivacaine (20 ml, 0.5%)	Single	Prior skin incision
Fiorelli et al.[34]	VATS[a] sympathectomy for palmar hyperhidrosis	Lidocaine (2%, 10 ml for three ports) and epinephrine	Single	Prior skin incision injection at each port site 5 min before incision
Silhoe et al.[35]	VATS[a] sympathectomy for palmar hyperhidrosis	Bupivacaine (0.5%, 10 ml for three ports)	Single	Prior skin incision to the port sites
Rao et al.[36]	Esophagectomy through thoracotomy	Ropivacaine (10 ml, 0.75%)	Single	Prior wound closure along each side of the intercostal wound edges were subcutaneously infiltrated
Zheng et al.[37]	Open gastrectomy	Ropivacaine (0.75%,10 ml) Ropivacaine (0.3%,5 ml/h)	Single and continuous	Prior wound closure
Sun et al.[38]	Open hepatectomy	Ropivacaine (7.5 mg/ml, 20 ml)	Single	Prior wound closure-infiltration of subcutaneous tissues, deep muscular fascia, and parietal peritoneum
Che et al.[39]	Open hepatectomy	Lidocaine (0.4%, 300 ml through elastomeric pump for 72 hours)	Continuous	Prior wound closure between the transversus abdominus and rectus abdominis
Beaussier et al. [40]	Open colorectal surgery	Ropivacaine (0.2%, 10 ml/h during 48 h)	Continuous	Prior wound closure-the catheter was positioned between the previously closed parietal peritoneum and the underside of the transversal fascia
Kim et al.[41]	Laparoscopic colorectal surgery	Ropivacaine (0.5%, 2ml/h per catheter during 48 hours)	Continuous	At the end of surgery-the catheters were positioned between subcutaneous fat and fascia and below the fascia
Lee et al.[42]	Laparoscopic colorectal surgery	Bupivacaine (0.5%, 5 ml)	Single	The end of surgery

Ball et al.[43]	Open abdominal aortic aneurysm repair	Levobupivacaine (0.5%, 10 ml) Levobupivacaine 0.25%, 4 ml/h (2 ml/h for each catheter) for 48 hours)	Single and continuous	The end of surgery pre-peritoneal catheters between the peritoneum and the fascia
Thompson et al.[44]	Open nephrectomy	Bupivacaine (0.25%, 29 ml) Bupivacaine (0.25%, 5 ml/hour for 96-hours)	Single and continuous	The end of surgery -after the closure of the peritoneum or transverse muscle, between the deep muscle layer and internal oblique
Ahn et al. [45]	Laparoscopic appendectomy	Bupivacaine (0.5%,10 ml)	Single	Prior skin incision
Alessandri et al. [46]	Laparoscopic hysterectomy	Levobupvacaine (0.5%,7 ml)	Single	Prior skin incision
Qureshi et al. [47]	Inguinal herniorrhaphy	Bupivacaine (0.25%,20 ml)	Single	Prior wound closure
LeBlanc et al. [48]	Inguinal herniorrhaphy	Bupivacaine (0.5% ,2 ml/h for 48 h)	Continuous	Prior wound closure
Li BL et al. [49]	Open reduction and internal fixation (ORIF)[b] for ankle fractures	0.5% ropivacaine, the total amount was between 15 ml and 30 ml depending on the length of the surgical incision	Single	Prior wound closure (dermis and subcutaneous infiltration)

[a]Video assisted thoracoscopic surgery=VATS; [b]Open reduction and internal fixation=ORIF; WI-wound infiltration; CWI-continues wound infiltration.

Complications of single and continuous wound infiltration

The main barrier for more comprehensive WI is fear of wound infection, which, in reality, does not exceed the incidence of WI after a particular type of surgery overall 1.2%[1,7,50]. CWI as specific complications connected with catheters including leakage, kinking, obstruction by blood or pump failure, which reaches the incidence typical for failed epidural[51].

Practical points

The performer (surgeon or anesthesiologist) must explain to the patient the persistence of feeling of touch and pull of tissue during surgery performed under single injection wound infiltration[52]. WI techniques are not always systematically planned and documented. Therefore, we recently proposed the list for follow-up planning after WI[1]. The more systematic approach to WI and better education of medical staff, particularly surgeons might lead to wider use of WI for postoperative analgesia. This can be beneficial for patients when nerve blocks are contraindicated or simply when motor block is

undesirable[1]. Here we should add newer findings that WI with levobupivacaine provided not just adequate analgesia after cesarean section, but also opioid sparing effect and significantly higher mechanical pain threshold[53].

We declare no conflicts of interest.

Reference

1.Stamenkovic, D.M.; Bezmarevic, M.; Bojic, S.; Unic-Stojanovic, D.; Stojkovic, D.; Slavkovic, D.Z.; Bancevic, V.;Maric,N.;Karanikolas,M.Updates on Wound Infiltration Use for Postoperative Pain Management: A Narrative Review. J. Clin. Med. 2021, 10.

2. Slavković D, Kostić Z, Milošević N, Rančić N, Dragojević-Simić V, Stamenković D, Miljković M. Surgical wound infiltration by local anesthetic (wound infiltration). SJAIT 2019; 41(7-8): 143-155.

3.Gasanova, I.; Alexander, J.; Ogunnaike, B.; Hamid, C.; Rogers, D.; Minhajuddin, A.; Joshi G.P. Transversus abdominis plane block versus surgical site infiltration for pain management after open total abdominal hysterectomy. Anesth. Analg. 2015; 121: 1383–1388.

4. Joshi, G.P.; Rawal, N.; Kehlet, H. Evidence-based management of postoperative pain in adults undergoing open inguinal hernia surgery. Br. J. Surg. 2012; 99: 168–185.

5. Barazanchi, A.W.H.; MacFater, W.S.; Rahiri, J.L.; Tutone, S.; Hill, A.G.; Joshi, G.P.; Kehlet, H.; Schug, S.; Van de Velde, M.; Vercauteren, M.; et al. Evidence-based management of pain after laparoscopic cholecystectomy: a PROSPECT review update. Br. J. Anaesth. 2018; 121: 787–803.

6. Saul, D.; Roch, J.; Lehmann, W.; Dresing, K. Infiltration anesthesia. Oper. Orthop. Traumatol. 2020;32: 4–12.

7.Scott, N.B. Wound infiltration for surgery. Anaesthesia 2010; 65 Suppl 1: 67–75.

8. Kehlet, H.; Liu, S.S. Continuous local anesthetic wound infusion to improve postoperative outcome: Back to the periphery? Anesthesiology 2007; 107: 369–371.

9.Better Postoperative Pain Management - ESRA Available online: https://esraeurope.org/prospect/ (accessed on Jan 26, 2021).

10. Jacobs, A.; Lemoine, A.; Joshi, G.P.; Van de Velde, M.; Bonnet, F.; Pogatzki-Zahn, E.; Schug, S.; Kehlet, H.; Rawal, N.; Delbos, A.; et al. PROSPECT guideline for oncological breast surgery: a systematic review and procedure-specific postoperative pain management recommendations. Anaesthesia 2020; 75: 664–673.

11. Gill, H.S.; Prausnitz, M.R. Does needle size matter? J. Diabetes Sci. Technol. 2007; 1: 725–729.

12.Arendt-Nielsen, L.; Egekvist, H.; Bjerring, P. Pain following controlled cutaneous insertion of needles with different diameters. Somatosens. Mot. Res. 2006; 23: 37–43,

13. Strazar, A.R.; Leynes, P.G.; Lalonde, D.H. Minimizing the pain of local anesthesia injection. Plast. Reconstr. Surg. 2013; 132: 675–684.

14.Zilinsky I; Bar-Meir E; Zaslansky R; Mendes D; Winkler E; Orenstein A Ten commandments for minimal pain during administration of local anesthetics. J. Drugs Dermatol. 2005; 4: 212-216.
15. Joshi, G.P.; Machi, A. Surgical site infiltration: A neuroanatomical approach. Best Pract. Res. Clin. Anaesthesiol. 2019; 33: 317–324.
16. Liu, S.S.; Richman, J.M.; Thirlby, R.C.; Wu, C.L. Efficacy of Continuous Wound Catheters Delivering Local Anesthetic for Postoperative Analgesia: A Quantitative and Qualitative Systematic Review of Randomized Controlled Trials. J. Am. Coll. Surg. 2006; 203: 914–932.
17. Hebbes CP,Thompson JP. Pharmacokinetics of anaesthetic drugs at extremes of body weight. BJA Educ. 2018; 18:364–370
18.Yadav U, Srivastava S, Srivastav D. Postoperative Analgesic Effect of Bupivacaine alone and with Dexmedetomidine in Wound Instillation for Lumbar Laminectomy: A Randomized Control Trial. Anesth Essays Res. 2020;14:149-153.
19.Bharti, N., S. Dontukurthy, I. Bala and G. Singh. Postoperative analgesic effect of intravenous (i.v.) clonidine compared with clonidine administration in wound infiltration for open cholecystectomy. Br J Anaesth 2013; 111: 656-661.
20.Kaki, A. M. and W. Al Marakbi. Post-herniorrhapy infiltration of tramadol versus bupivacaine for postoperative pain relief: a randomized study. Ann Saudi Med 2008; 28: 165-168.
21.Rømsing, J., S. Mysager, P. Vilmann, J. Sonne, N. E. Larsen, D. stergaard. "Postoperative analgesia is not different after local vs systemic administration of meloxicam in patients undergoing inguinal hernia repair." Can J Anaesth 2001; 48: 978-984.
22.Karamanlioglu B, Turan A, Memis D, Kaya G, Ozata S, Ture M. Infiltration with ropivacaine plus lornoxicam reduces postoperative pain and opioid consumption. Can J Anaesth. 2005;52:1047-53.
23. Loh, J.W.; Taib, N.A.; Cheong, Y.T.; Tin, T.S. A Double-Blind, Randomized Controlled Trial of Pre-incision Wound Infiltration Using Diclofenac Versus Bupivacaine for Post-operative Pain Relief in Open Thyroid and Parathyroid Surgery. World J. Surg. 2020, 44, 2656–2666.
24.Mohamed SA, Sayed DM, El Sherif FA, Abd El-Rahman AM. Effect of local wound infiltration with ketamine versus dexmedetomidine on postoperative pain and stress after abdominal hysterectomy, a randomized trial. Eur J Pain. 2018;22:951-960.
25.Pace V, Gul A, Prakash V, Park C, Placella G, Raine G. Wound Infiltration with Levobupivacaine, Ketorolac, and Adrenaline for Postoperative Pain Control after Spinal Fusion Surgery. Asian Spine J. 2020 Sep 3. doi: 10.31616/asj.2020.0107. Epub ahead of print. PMID: 32872752.
26. Paladini, G.; Carlo, S. Di; Musella, G.; Petrucci, E.; Scimia, P.; Ambrosoli, A.; Cofini, V.; Fusco, P. Continuous wound infiltration of local anesthetics in postoperative

pain management: Safety, efficacy and current perspectives. J. Pain Res. 2020; 13, 285–294.
27. Biswas, B.K.; Bithal, P.K. Preincision 0.25% Bupivacaine scalp infiltration and post-craniotomy pain: A randomized double-blind, placebo-controlled study. J. Neurosurg. Anesthesiol. 2003, 15, 234–239.
28. Zhou, H.; Ou, M.; Yang, Y.; Ruan, Q.; Pan, Y.; Li, Y. Effect of skin infiltration with ropivacaine on postoperative pain in patients undergoing craniotomy. Springerplus 2016, 5.
29. Kang, R.; Read, J.T.; Glaser, A.C.; Barth, R.J. Eliminating Opioids from Breast Conserving Surgery: Perioperative Pain Management Pathway. J. Am. Coll. Surg. 2020, 230, 975–982.
30. Lu, T.J.; Chen, J.H.; Hsu, H.M.; Wu, C.T.; Yu, J.C. Efficiency of infiltration with bupivacain after modified radical mastectomy. Acta Chir. Belg. 2011; 111:360–363.
31. Kocabas, S.; Yedicocuklu, D.; Yuksel, E.; Uysallar, E.; Askar, F. Infiltration of the sternotomy wound and the mediastinal tube sites with 0.25% levobupivacaine as adjunctive treatment for postoperative pain after cardiac surgery. Eur. J. Anaesthesiol. 2008; 25, 842–849.
32. Koukis, I.; Argiriou, M.; Dimakopoulou, A.; Panagiotakopoulos, V.; Theakos, N.; Charitos, C. Use of continuous subcutaneous anesthetic infusion in cardiac surgical patients after median sternotomy. J. Cardiothorac. Surg. 2008; 3, 2.
33. Yang, H.C.; Lee, J. young; Ahn, S.; Cho, S.; Kim, K.; Jheon, S.; Kim, J.S. Pain control of thoracoscopic major pulmonary resection: Is pre-emptive local bupivacaine injection able to replace the intravenous patient controlled analgesia? J. Thorac. Dis. 2015; 7, 1960–1969.
34. Fiorelli, A.; Vicidomini, G.; Laperuta, P.; Busiello, L.; Perrone, A.; Napolitano, F.; Messina, G.; Santini, M. Pre-emptive local analgesia in video-assisted thoracic surgery sympathectomy. Eur. J. Cardio-thoracic Surg. 2010; 37, 588–593.
35. Sihoe, A.D.L.; Manlulu, A. V.; Lee, T.W.; Thung, K.H.; Yim, A.P.C. Pre-emptive local anesthesia for needlescopic video-assisted thoracic surgery: a randomized controlled trial. Eur. J. Cardio-thoracic Surg. 2007; 31: 103–108.
36. Rao, Z.; Zhou, H.; Pan, X.; Chen, J.; Wang, Y.; Wang, Z.; Ding, Z. Ropivacaine wound infiltration: a fast-track approach in patients undergoing thoracotomy surgery. J. Surg. Res. 2017; 220, 379–384.
37. Zheng, X.; Feng, X.; Cai, X.J. Effectiveness and safety of continuous wound infiltration for postoperative pain management after open gastrectomy. World J. Gastroenterol. 2016; 22: 1902–1910.
38. Sun, J.X.; Bai, K.Y.; Liu, Y.F.; Du, G.; Fu, Z.H.; Zhang, H.; Yang, J.H.; Wang, B.; Wang, X.Y.; Jin, B. Effect of local wound infiltration with ropivacaine on postoperative pain relief and stress response reduction after open hepatectomy. World J. Gastroenterol. 2017; 23: 6733–6740.

39. Che, L.; Lu, X.; Pei, L. Efficacy and Safety of a Continuous Wound Catheter in Open Abdominal Partial Hepatectomy. Chinese Med. Sci. J. 2017; 32: 171–176.
40. Beaussier, M.; Parc, Y.; Guechot, J.; Cachanado, M.; Rousseau, A.; Lescot, T.; Rollin, M.; Aissou, M.; Lefevre, J.H.; Restoux, A.; et al. Ropivacaine preperitoneal wound infusion for pain relief and prevention of incisional hyperalgesia after laparoscopic colorectal surgery: a randomized, triple-arm, double-blind controlled evaluation vs intravenous lidocaine infusion, the CATCH study. Color. Dis. 2018; 20: 509–519.
41. Kim, S.E.; Kim, E. Local anesthesia with monitored anesthesia care for patients undergoing thyroidectomy - A case series. Korean J. Anesthesiol. 2016; 69: 635–639.
42. Lee, B.; Kim, K.; Ahn, S.; Shin, H.J.; Suh, D.H.; No, J.H.; Kim, Y.B. Continuous wound infiltration system for postoperative pain management in gynecologic oncology patients. Arch. Gynecol. Obstet. 2017; 295: 1219–1226.
43. Ball L; Pellerano G; Corsi L; Giudici N; Pellegrino A; Cannata D; Santori G; Palombo D; Pelosi P; Gratarola A Continuous epidural versus wound infusion plus single morphine bolus as postoperative analgesia in open abdominal aortic aneurysm repair: a randomized non-inferiority trial. Minerva Anestesiol. 2016; 82: 1296-305.
44. Thompson, E.; Green, A.; Hartsilver, E.; Stott, M.; Meikle, K.; Ormerod, V.; Lilaonitkul, M.; Powell, R. A Comparison of Continuous Wound Infiltration Plus Patient Controlled Analgesia Versus Epidural Analgesia after Open Renal Surgery. Urol. Androl. – Open J. 2020; 4, 20–26.
45. Ahn, S.R.; Kang, D.B.; Lee, C.; Park, W.C.; Lee, J.K. Postoperative pain relief using wound infiltration with 0.5% bupivacaine in single-incision laparoscopic surgery for an appendectomy. Ann. Coloproctol. 2013; 29: 238–242.
46. Alessandri, F.; Lijoi, D.; Mistrangelo, E.; Nicoletti, A.; Ragni, N. Effect of presurgical local infiltration of levobupivacaine in the surgical field on postsurgical wound pain in laparoscopic gynecological surgery. Acta Obstet. Gynecol. Scand. 2006; 85: 844–849.
47. Qureshi, R.; Khan, F. Effects of bupivacaine infiltration on postoperative tramadol consumption in elective day care unilateral inguinal hernia repair. J Pak Med Assoc. 2016; 66: 256-259.
48. LeBlanc, K.A.; Bellanger, D.; Rhynes, V.K.; Hausmann, M. Evaluation of continuous infusion of 0.5% bupivacaine by elastomeric pump for postoperative pain management after open inguinal hernia repair. J. Am. Coll. Surg. 2005; 200: 198–202.
49. Li, B.L.; Liu, X.; Cui, L.; Zhang, W.; Pang, H.; Wang, M.; Wang, H.Q. Local Infiltration Analgesia with Ropivacaine Improves Postoperative Pain Control in Ankle Fracture Patients: A Retrospective Cohort Study. Pain Res. Manag. 2020; 2020.
50. Claroni, C.; Marcelli, M.E.; Sofra, M.C.; Covotta, M.; Torregiani, G.; Giannarelli, D.; Forastiere, E. Preperitoneal continuous infusion of local anesthetics: What is the impact on surgical wound infections in humans? Pain Med 2016; 17:582–589.
51. Ventham, N.T.; Hughes, M.; O'Neill, S.; Johns, N.; Brady, R.R.; Wigmore, S.J. Systematic review and meta-analysis of continuous local anaesthetic wound infiltra-

tion versus epidural analgesia for postoperative pain following abdominal surgery. Br. J. Surg. 2013, 100, 1280–1289.
52. Thornton, P.C.; Buggy, D.J. Local anaesthetic wound infusion for acute postoperative pain: A viable option? Br. J. Anaesth. 2011; 107: 656–658.
53. Gómez-Ríos MÁ, Codesido-Barreiro P, Seco-Vilariño C, Calvín-Lamas M, Curt-Nuño F, Nieto-Serradilla L, Rabuñal-Álvarez MT, Fernández-Rodríguez F, Peteiro-Cartelle J, Pensado-Boo R, Bou G, Pensado-Castiñeiras A, Casans-Francés R. Wound Infusion of 0.35% Levobupivacaine Reduces Mechanical Secondary Hyperalgesia and Opioid Consumption After Cesarean Delivery. A Prospective, Randomized, Triple-Blind, Placebo-Controlled Trial. Anesth Analg. 2022 Jan 27. doi: 10.1213/ANE.0000000000005917. Epub ahead of print. PMID: 35086112.

13

Experience in the use of tapentadol in orthopedic patients in the perioperative period/Iskustva primene tapentadola u perioperativnom periodu kod ortopedskih pacijenata

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Abstract

Većina ortopedskih operacija praćena izuzetno jakim bolom. Perioperativna analgezija kod ovih pacijenta ima za cilj je da omogući ne samo kontrolu postoperativnog bola već i njihovu ranu aktivaciju. Jasne preporuke oko izbora terapijskog protokola još uvek ne postoje, već se primenjuju različiti terapijski modaliteti, farmakološki i/ili nefarmakološki kao deo multimodalnog koncepta analgezije. Opioidni analgetici zauzimaju centralno mesto u lečenju akutnog postoperativnog bola čiji izbor je u velikoj meri određen i njihovim neželjenim efektima. Tapentadol ima svoje mesto u okviru multimodalnog koncepta obezbeđujući adekvatan nivo analgezije u postoperativnom period, izborom prave doze kao i vremena davanja imajući u vidu metabolizam i vreme postizanja maksimalne koncentracije.

Keywords: postoperativna analgezija, tapentadol, ortopedska hirurgija, opioidi, multimodalna analgezija

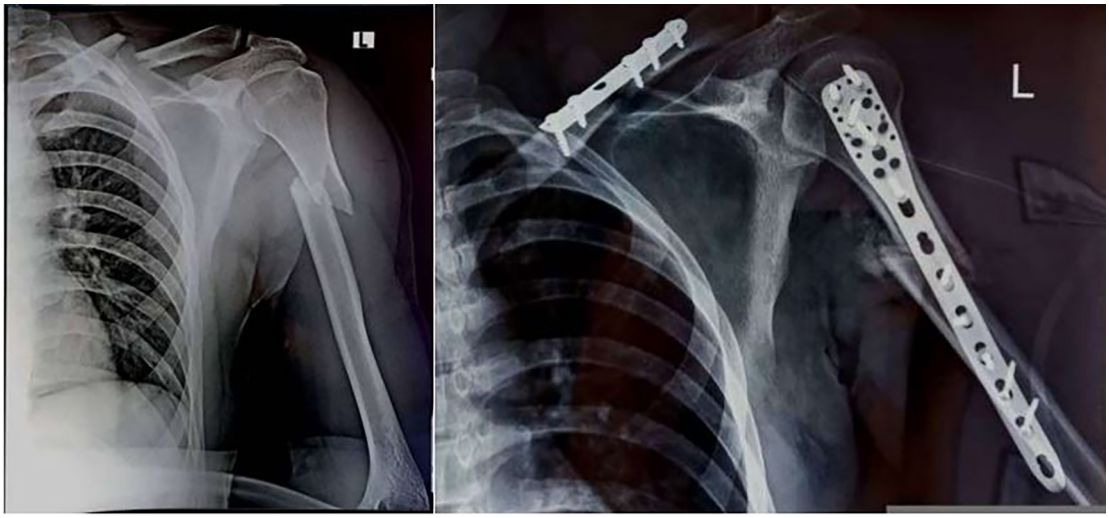
Uvod

Poslednjih godina beleži se znatno povećanje broja ortopedskih operacija u svetu, na račun starenja svetske populacije ali i povećanja saobraćajnog traumatizma (1,2). Većina ovih intervencija je praćena izuzetno jakim bolom (1,2). Cilj perioperativne analgezije kod ovih pacijenta je da omogući ne samo kontrolu postoperativnog bola već i njihovu ranu aktivaciju. Jasne preporuke oko izbora terapijskog protokola još uvek ne postoje, već se primenjuju različiti terapijski modaliteti, farmakološki i/ili nefarmakološki kao deo multimodalnog koncepta analgezije (1,2). Opioidni analgetici zauzimaju centralno mesto u lečenju akutnog postoperativnog bola čiji izbor je u velikoj meri određen i njihovim neželjenim efektima (1-4). Tapentadol je novi analgetik sa dvostrukim mehanizmom delovanja. Svoj efekat ostvaruje sinergičkim mehanizmom kao

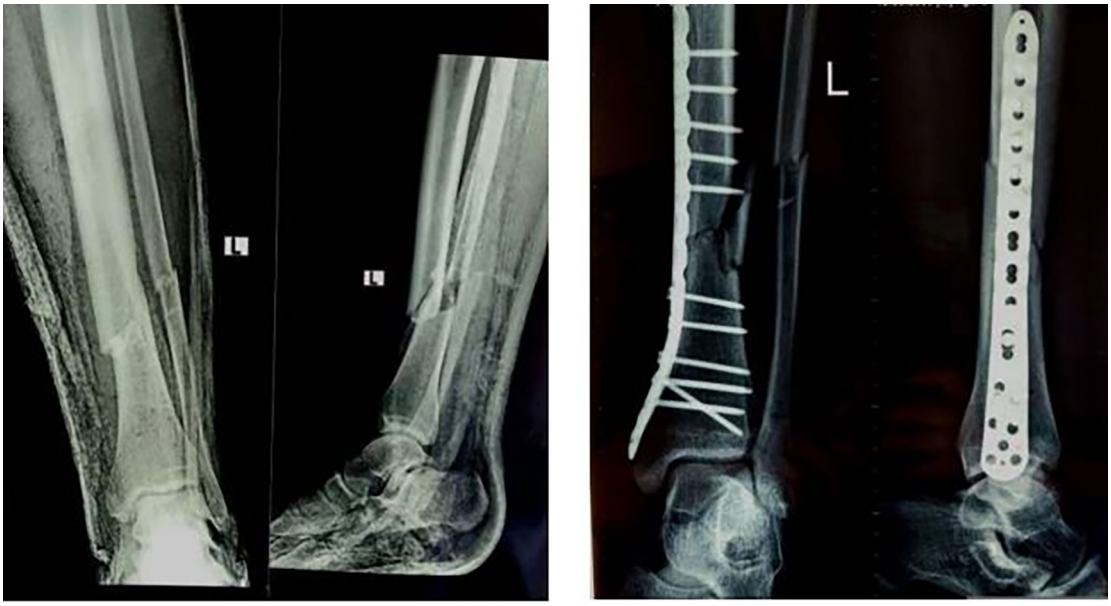
agonista μ-opioidnih receptora (MOR) i inhibitor ponovnog preuzimanja noradrenalina (NOR) (3-6). Međutim uzeti odvojeno, analgetički efekti svakog mehanizma pojedinačno su prilično mali ali zajedno su u stanju da proizvedu veći efekat koji se može uporediti sa efektom morfijuma ili oksikodona (6). Nasuprot tome, takav sinergistički efekat ne izaziva dublje ili češće neželjene efekte (mučnina, povraćanje, zatvor) (5,6,7,8). Tapentadol svoje analgetsko dejstvo vrši direktno, bez farmakološki aktivnog metabolita (2). Brzo i potpuno se resorbuje posle oralne primene, a zbog ekstenzivnog metabolizma tokom prvog prolaska srednja apsolutna biološka raspoloživost iznosi približno 32%. (2) Maksimalnu koncentraciju tapentadol u serumu postiže 1,25 sati posle unošenja film tablete (2). Adekvatna analgetska efikasnost tapentadola kod ortopedskih traumatoloških pacijenata, pokazana je smanjujući maksimalni bol u prva 24h kako u miru tako i tokom rane rehabilitacije (VAS<4) (9). Slične rezultate postigli su i D'Amato i sar., koristeći kombinaciju tapentadola i ketoprofa za lečenje umereno-jakih bolova nakon artroplastika kuka (10). Analilzirajući troškove, Wang i sar. su pokazali isplatljivost tapentadola u odnosu na oksikodon za lečenje akutnog postoperativnog bola nakon velikih operacija kuka (11). Rian i sar. su pokazali da analgetska efikasnost tapentadola sa sporim oslobađanjem, nakon ugradnje totalne proteze kolena, nije veća u odnosu na oksikodon ali da su značajno manji neželjeni efekti (12).

Case presentations

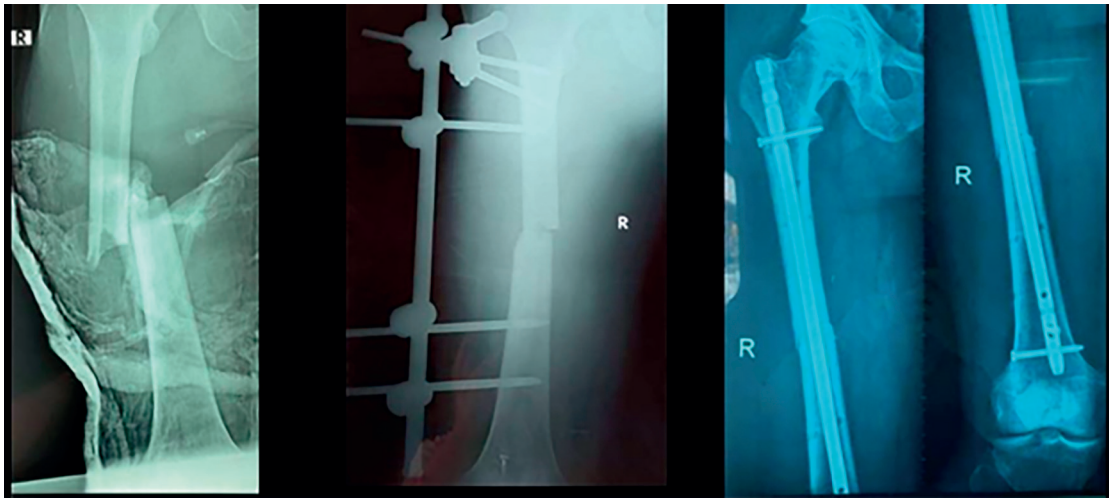
1. Pacijent (L.S. 2000god., TT 80 kg TV 185cm) povređen je u saobraćajnom udesu i tom prilikom zadobio prelom ključne kosti, dijafize humerusa i potkolenice (Dg: Fractura claviculae sin, Fr. dyaphisis humerii sin et fr. cruris l.sin). U istom operativnom aktu urađena je zatvorena osteosinteza klavikule, humerusa i potkolenice (Op. ORIF (claviculae - vibrio et plate, humerii – philos plate, tibiae –LCP) (Slika 1i 2).
   Pacijent 0 dana dobio Tapentadol a 100 mg/ 6h (16h, 22h, 04h) i Ketorolac a 30 mg/4-6h (15h, 19h, 01h). Prvog postoperativnog dana nastavljen i Tapentadol a 50 mg/8h (10h, 18h, 02h) i Ketorolac a 30 mg/ 8h (07h, 15h, 23h). Drugog postoperativnog dana tapentadol je dobijao u dozi od 50 mg/12h (10h, 22h) i Ketorolac a 30 mg/ 12h (07h, 19h). Intezitet bola na VAS 1-3 tokom sva tri dana.
2. Pacijent (B.P. 61god. TT 95 kg, TV 178cm), povređen tako što mu je pao tup predmet (drvo) na desnu nogu. DG: Fractura corporis femoris l.dex, Conquasatio cruris et pedis l dex.
   I Op: Fixatio externa femoris et amputatio transtibialis l.dex. U postoperativnom toku pacijent dobijao: 0 dana- Tapentadol a 100 mg/12h i Paracetamol 1 g/8h; 1. post dana uveden Tapentadol SR 50 mg/12h i Paracetamol a 1g/12h.
   II Op: Conversio, CRIF cum SUN. Postoperativna analgezija Tapentadol a 100 mg/12h i Paracetamol 1 g/8h a od 1 postoperativnog dana Tapentadol SR 50 mg/ 12h i Paracetamol a 1g/12h. (Slika 3 i 4).



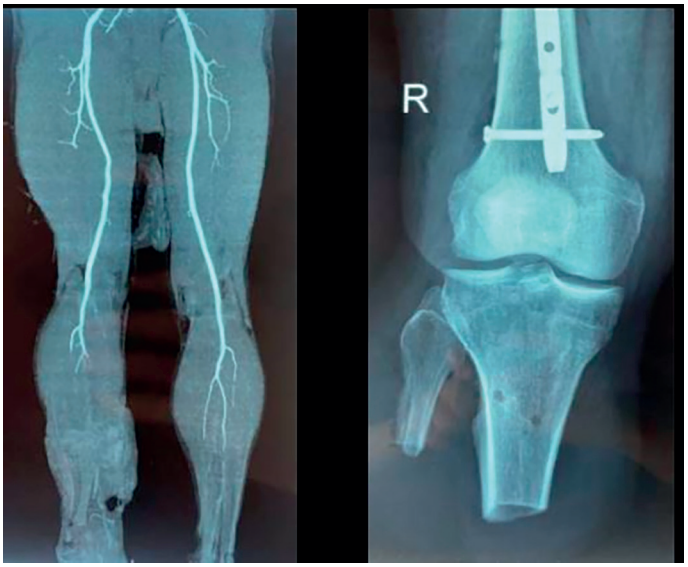
Slika 1. Prelom klavikule i humerusa pre i posle operativnog lečenja.



Slika 2. Prelom potkolenice pre i posle fiksacije.

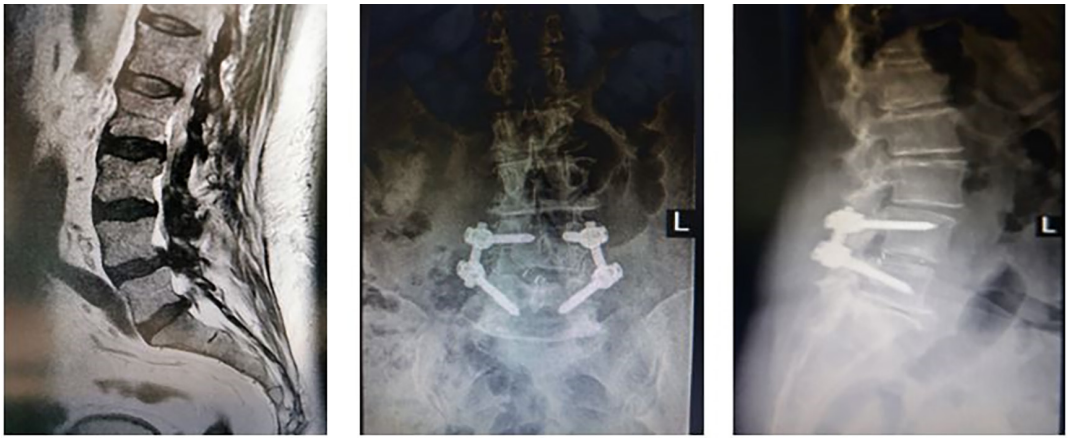


Slika 3. Prelom femura pre i posle fiksacije



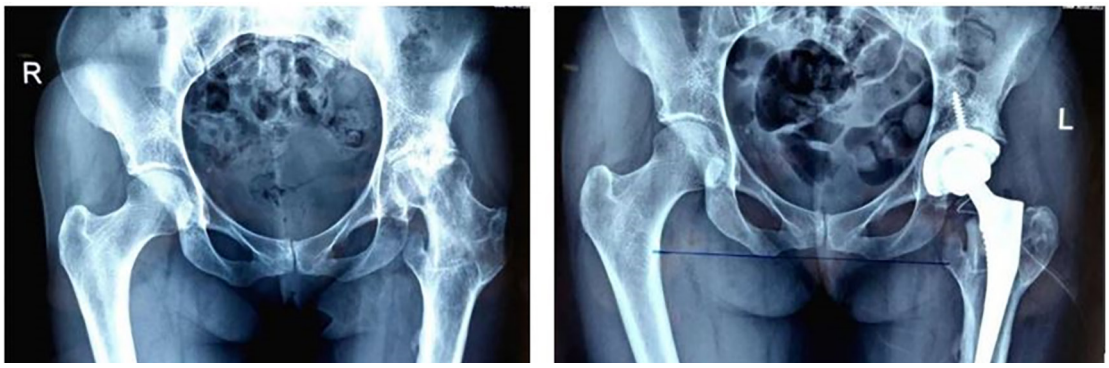
Slika 4. AngioCT i rtg nakon definitivne fiksacije

3. Pacijent (M. A., 58god., TT- 140 kg, TV- 185cm, BMI- 40,9 kg/m2) zbog bola u lumabalnom predelu (Dg: Instabilitas columnae vertebralis reg. L4-5 cum stenosis canalis spinalis) operativno lečen (OP: TLIF L4-L5). U toku operacije dobio lokalnu infiltrativnu analgeziju (LIA – 10 ml 2% Lidocain-a). Postoperativna analgezija: 0 dan- Ketorolak a 30 mg iv/4-6 h (16h,20h, 02h) i Tapentadol a 100 mg per os /6 sati (17h, 23h, 05h).
   1.postop dan: pacijent ustaje iz kreveta, kreće se, dobija: Ketorolac a 30 mg iv I amp i
   Tapentadol a 100 mg/ 12h. Maksimalan intezitet bola VAS 3 (Slika 5).



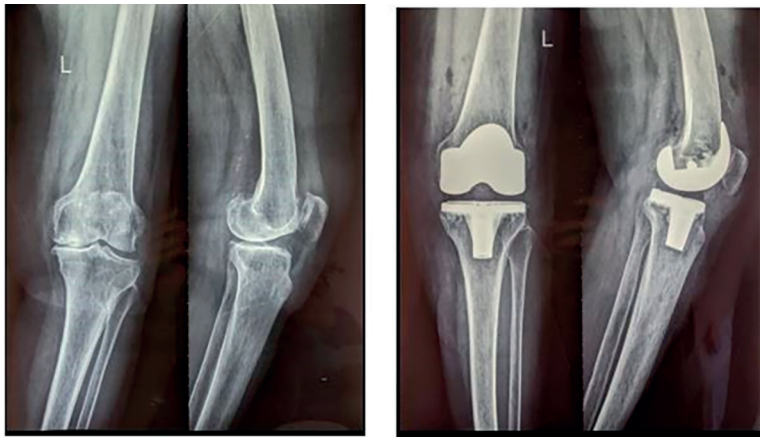
Slika 5. Lumbalni segment pre i nakon stabilizacije

4. Pacijent (P.K, 38 god., TT 65kg TV 173cm) dolazi zbog bolova u levom kuku, koji traju unazad dve godine (DG: Coxarthrosis l.sin). Urađena implantacija proteze kuka (OP: Implantatio PTC – Hybride). Pacijentkinja dobila lokalnu infiltrativnu analgeziju (LIA- 50 ml =10 ml 0,5% Levobupivacaina + Ketorolak a 30 mg+ 39 ml 0,9% NaCl). Postoperativna analgezija: 0. dan Tapentadol a 100 mg – prva doza a zatim na 6h po 50 mg, Ketorolak a 30 mg/ 6h; 1. post op dan: Tapentadol a 50 mg/12h (8h, 20h) i Ketorolak a 30 mg/12h; 2 post op dan: Ketorolak a 30 mg/ 12h. VAS mak 2 (Slika 6).



Slika 6. Stanje pre i posle ugradnje totalne proteze levog kuka

5. Pacijent (Lj. M. 91 god., TT 53kg, TV 159cm), žali se na bol u levom kolenu (Dg: Gonarthrosis l. sin. Pacijentkinji ugrađena leva proteza kolena (Op: Implantatio PTGl sin.). U postoperativnoj analgeziji dobijao: 0 dana- Tapentadol a 50 mg/ 6h (12h, 18h, 00h,06h) i Ketorolac a 30 mg/ 6h (15h, 21h, 03h);1 post op dan -Tapentadol a 50 mg/12h (6h, 18h) i Ketorolac a 30 mg / 12h; 2 post op dan- Ketorolac a 30 mg/ 12h (Slika 7).



Slika 7. Stanje pre i posle ugradnje totalne proteze levog kolena

Zaključak

Perioperativnom analgezijom kod ortopedskih pacijenta neophodno je postići adekvatnu kontrolu postoperativnog bola koja omogućava ranu aktivaciju ovih pacijenta. To se postiže primenom multimodalnog koncepta u okviru koga se primenjuju različiti terapijski modaliteti. Tapentadol ima svoje mesto u okviru ovog koncepta obezbeđujući adekvatan nivo analgezije u postoperativnom periodu, izborom prave doze kao i vremena davanja imajući u vidu metabolizam i vreme postizanja maksimalne koncentracije.

Reference

1. Miller R. Miller's anesthesia. 9th edition, Philadelphia, Elsevier; 2019.
2. Rehart S, Henniger M, Arndt M.[Acute pain therapy in orthopedics/trauma surgery]. Orthopade. 2018 Oct;47(10):883-896. doi: 10.1007/s00132-018-3618-4.PMID: 30132014
3. Polati E, Canonico PL, Schweiger V, Collino M.Tapentadol: an overview of the safety profile.J Pain Res. 2019 May 16;12:1569-1576. doi: 10.2147/JPR.S190154
4. Tzschentke T, Christoph T, Kogel B. The mu-opioid receptor agonist/noradrenaline reuptake inhibition (MOR-NRI) concept in analgesia: the case of tapentadol. CNS drugs. 2014;28(4):319–329. doi: 10.1007/s40263-014-0151-9.
5. Langford R. Is tapentadol different from classical opioids? A review of the evidence British Journal of Pain. 2016;104:217–221. doi: 10.1177/2049463716657363
6. Schroder W, Tzschentke T, Terlinden R, et al. Synergistic interaction between the two mechanisms of action of tapentadol in analgesia. J Pharmacol Exp Ther. 2011;337(1):312–320. doi: 10.1124/jpet.110.175042
7. Afilalo M, Etropolski MS, Kuperwasser B, et al. Efficacy and safety of tapentadol extended release compared with oxycodone controlled release for the management

of moderate to severe chronic pain related to osteoarthritis of the knee: a randomized, double-blind, placebo- and active-controlled phase III study. Clin Drug Investig. 2010;30(8):489–505. doi: 10.2165/11533440-000000000-00000
8. Coluzzi F, Ruggeri M. Clinical and release and oxycodone/naloxone extended release in comparison with controlled release oxycodone in musculoskeletal pain. Curr Med Res Opin. 2014;30(6):1139–1151. doi: 10.1185/03007995.2014.894501.
9. Haeseler G, Schaefers D, Prison N, Ahrens J, Liu X, Karch A.Combatting pain after orthopedic/trauma surgery- perioperative oral extended-release tapentadol vs. extended-release oxycodone/naloxone.BMC Anesthesiol. 2017 Jul 11;17(1):91. doi: 10.1186/s12871-017-0383-6
10. D'Amato T, Martorelli F, Fenocchio G, Simili V, Kon E, Di Matteo B, Scardino M. Tapentadol vs oxycodone/naloxone in the management of pain after total hip arthroplasty in the fast track setting: an observational study.J Exp Orthop. 2019 Jul 29;6(1):36. doi: 10.1186/s40634-019-0204-6
11. Wang X, Penm J, Patanwala AE.Cost-effectiveness of tapentadol immediate release versus oxycodone immediate release for acute post-operative pain after major hip surgeries. Curr Med Res Opin. 2022 Jan;38(1):115-121. doi: 10.1080/03007995.2021.1993161
12. Rian T, Skogvoll E, Hofstad J, Høvik L, Winther SB, Husby VS, Klaksvik J, Egeberg T, Sand K, Klepstad P, Wik TS.Tapentadol vs oxycodone for postoperative pain treatment the first 7 days after total knee arthroplasty: a randomized clinical trial. Pain. 2021 Feb 1;162(2):396-404. doi: 10.1097

14 Opioid induced hyperalgesia, how to overcome it

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Abstract

Opioid induced hyperalgesia (OIH) refers to a progressive decrease of nociceptive threshold after opioid exposure. Possible mechanisms in developing OIH are referred in μ opioid signalling, transcriptional mechanisms, pronociceptive jon channels and microglia. In clinical practice, diagnosis of OIH is very often difficult. The use of an adequate diagnostic test is very important, such as quantitative sensory testing (QST) to assess patient responses to defined physical stimuli (thermal and mechanical). Even with QST the demonstration of hyperalgesia around the surgical site is not necessarily diagnostic of OIH because the tissue response to surgical trauma, with release of inflammatory mediators, can cause peripheral and central sensitisation and can be manifested as hyperalgesia. In order to prevent OIH, some strategies have been overheard, such as opioid-free or low-dosing regimens, intravenous anaesthesia with propofol, addition of nitrous oxide, avoiding high infusion rates of remifentanil (less than 0.2 μg/kg/min), multimodal analgesia regimens including antidepressants, anticonvulsant agents, anti-inflammatory drugs, α2-Adrenoceptor agonists, NMDA antagonists and opioid switching.

Key words: Pain, hyperalgesia, multimodal analgesia.

Opioid induced hyperalgesia-introduction

Opioid induced hyperalgesia (OIH) refers to a progressive decrease of nociceptive threshold after opioid exposure. Despite evidence of OIH from both preclinical and clinical studies, absence of a powerful diagnostic test for OIH, has led some opinion leaders to conclude that OIH does not exist.

For 2 decades, a great number of preclinical studies have investigated the cellular mechanisms of OIH. We now know that a number of systems are involved in its

emergence including glutamatergic system, dynorphin, supraspinal descending facilitation, cytokines, and epigenetic regulation. The essence that emerges from preclinical trials is that opioid exposure may activate a pronociceptive process manifesting itself as OIH (1).

Possible mechanisms in developing OIH are referred in μ opioid signalling, transcriptional mechanisms, pronociceptive jon channels and microglia (table 1).

Table 1. Possible mechanisms in developing OIH

Possible mechanisms in developing OIH
μ opioid signalling
• Increased cyclic adenosine monophosphate and protein kinase A
• Protein kinase C
• C-Jun N-terminal kinase
• β-arrestin-2
• Src kinase
Transcriptional mechanisms
-cAMP response element-binding protein
• Mammalian target of rapamycin complex 1
Pronociceptive ion channels
• N-methyl-D-aspartate receptors
• Transient receptor potential vanilloid channels
Microglia
• Toll-like receptor 4
• P2X4 and P2X7 purinergic receptors
• Src kinase
• Brain-derived neurotrophic factor

Several facts obtained from clinical practice clearly indicate the undoubted existence of OIH. For example, 1) the opioid analgesic efficacy was reduced after intraoperative remifentanil infusion; 2) pain sensitivity was increased in subjects with opioid addiction in response to experimental pain (eg, cold pressor test); 3) opioid exposure diminished diffuse noxious inhibitory control in human subjects; and 4) painful response to a needle stick test was exacerbated in patients prescribed opioid therapy.

In clinical practice, diagnosis of OIH is very often difficult. In order to be able to diagnose OIH, we need an adequate diagnostic test. Quantitative sensory testing (QST) is one of the possible ways to assess OIH in human subjects. Differential diagnosis includes primarily tolerance, because both conditions are characterized by inadequate analgesia. The most important criteria for differential diagnosis are shown in the table 2.

Table 2. Differential Diagnosis of OIH

Findings	OIH Opioid	Tolerance
Exacerbated temporal pain summation (QST)	Yes	No
Decreased pain threshold (QST)	Yes	No
Decreased pain tolerance (QST)	Yes	No
Opioid dose regimen	Yes	No
Duration of opioid treatment	Yes	No
Pain quality	New onset of pain, such as burning, Diffuse and/or spontaneous pain	No change
Pain location	May be beyond the dermatome distribution	No change of preexisting pain
Pain intensity	Similar/greater than preexisting pain	Similar to preexisting pain
Opioid dose escalation	No change/worsening of pain	Improved pain relief
Opioid dose reduction	Improved opioid analgesia	Reduced opioid analgesia

Identifying hyperalgesia in patients

As mentioned earlier, there is still debate about the clinical manifestations of OIH. The most important reason is because some studies do not make an adequate distinction between increased pain severity and hyperalgesia. Many studies have used only pain scores and postoperative opioid consumption as surrogate markers of OIH. It is very important to say that many other potential factors can cause inadequate analgesia by changing underlying disease pathology. To make a clinical diagnosis of OIH a distinction needs to be made between high pain scores and altered sensory processing with allodynia and hyperalgesia.

The use of an adequate diagnostic test is very important, such as quantitative sensory testing (QST) to assess patient responses to defined physical stimuli (thermal and mechanical). Even with QST the demonstration of hyperalgesia around the surgical site is not necessarily diagnostic of OIH because the tissue response to surgical trauma, with release of inflammatory mediators, can cause peripheral and central sensitisation and can be manifested as hyperalgesia. But, if there is more widespread hyperalgesia, then there is an increased likelihood of OIH (table 2).

It is also very difficult to diagnose OIH in surgical patients. A systematic review of OIH after surgery identified 27 studies with approximately 1500 patients (2). Higher doses of intraoperative opioid (mainly remifentanil) were associated with an increase in postoperative pain scores, and a higher 24 h morphine consumption. A subsequent systematic review of acute OIH and tolerance showed similar finding (4). A large study using the PAIN OUT database found an association between worse pain-related outcomes and intraoperative use of remifentanil (5).

Can we prevent OIH?

In order to prevent OIH, some strategies have been overheard. It is opioid-free or low-dosing regimens. Anaesthetic technique should be considered: intravenous anaesthesia with propofol can have a lower risk of OIH when compared with anaesthesia with a volatile drug. Addition of nitrous oxide can reduce the incidence of hyperalgesia (6). Avoiding high infusion rates of remifentanil can reduce risk of OIH. Dose rates of more than 0.2 μg/kg/min can increase the risk of OIH, and for doses of more than 0.25 μg/kg/min acute tolerance can be problematic (7). Consideration of a gradual tapering of remifentanil at the end of surgery can also reduce OIH, possibly by reducing withdrawal-induced long-term potentiation at the first central synapse in the spinal cord (8).

Therapeutic strategies

Use of multimodal analgesia with low or no opioid component

Use of more than one type of non-opioid analgesic can have most effect on opioid consumption. Use of at least two non-opioid approaches can reduce adverse effects, such as respiratory depression, gastrointestinal dysfunction, as well as reducing opioid requirements (9). Others include simple analgesics such as paracetamol, non-steroidal anti-inflammatory drugs, dexmedetomidine, N-methyl-D-aspartate (NMDA) receptor antagonists (eg, ketamine), and opioid dose reduction (10).

It has been reported that the descending system is of paramount importance in OIH occurrence (11). Drugs that act by reinforcing the inhibitory descending system may be beneficial in such a context, such as antidepressants. Their efficacy has been established in many painful conditions, particularly in the presence of a prevalent neuropathic pain component (12). However, this group of drugs results in some common adverse effects, including antimuscarinic, antihistaminic and sympatholytic effects. Alternative tricyclics with a more noradrenergic activity, such as duloxetine, are often preferred in patients predisposed to sedative, anticholinergic, or hypotensive effects. Sodium channel-blocking agents may act both centrally and peripherally to reduce ectopic impulse generation and the activity of hyperactive wide dynamic range neurons in the dorsal horn.

Anticonvulsant agents (gabapentin, pregabalin, carbamazepine, phenytoin, valproate, and clonazepam), have been reported to relieve pain in peripheral and central

neuropathic pain conditions. They also inhibit NMDA receptors and also possess other activities, including sodium channel blockade. Anti-infammatory drugs, both steroidal and non-steroidal, may provide additional analgesia with different mechanisms and may reduce opioid dose.

α2-Adrenoceptor agonists (dexmedetomidine, clonidine) are analgesic drugs with synergistic effect when given together with opioids. One of the possible ways to reduce opioid dose is the use of agents that block the activity of NMDA receptors. NMDA antagonists may have direct analgesic effects or reverse opioid tolerance. Ketamine is a non-competitive NMDA receptor antagonist that exerts its primary effect when the NMDA receptor-controlled ion channel has been opened by a nociceptive barrage. Ketamine produces only a weak analgesic effect on acute pain but may significantly influence the central hyperexcitability and 'wind-up' phenomena in spinal cord neurons that presumably participate in the development of opioid tolerance and OIH (13). Opioid switching is one of the therapeutic strategies used in order to improve analgesia, especially in patients with chronic cancer pain (14). This observation is based on presence of incomplete cross-tolerance among opioids, as well as conclusion that the μ-opioid analgesics differ from one another (15).

Future research

Currently a large number of, primarily, preclinical studies are trying to find alternative mechanisms in pain therapy. They include agonists biased against β-arrestin-2, methylnaltrexone (TRPV1), c-Src (dasatinamb), inhibitors of the mammalian target of rapamycin (mTOR) and many others (2).

Conclusion

Opioid induced hyperalgesia is a state very difficult to diagnose and treat. It is necessary to make differential diagnosis with tolerance and acute neuropathic pain, by using specific test, but also looking hole clinical situation. Multimodal analgesia regimens are recommended in order to prevent high opioid dosage and development of OIH.

References

1. 1. Mao J. Clinical diagnosis of opioid-induced hyperalgesia. Reg Anesth Pain Med 2015; 40: 663–64
2. Fletcher D, Martinez V. Opioid-induced hyperalgesia in patients following surgery. A systematic review and meta-analysis. Br J Anaesth 2014; 112: 991–1004
3. Colvin LA, Bull F, Hales TG. Perioperative opioid analgesia-when is enough too much? A review of opioid-induced tolerance and hyperalgesia. Lancet 2019 Apr 13;393(10180):1558-1568.
4. Kim SH, Stoicea N, Soghomonyan S, Bergese SD. Remifentanil-acute opioid tolerance and opioid-induced hyperalgesia: a systematic review. Am J Ther 2015; 22: e62–74.

5. Sanfilippo F, Conticello C, Santonocito C, et al. Remifentanil and worse patient-reported outcomes regarding postoperative pain management after thyroidectomy. J Clin Anesth 2016; 31: 27–33
6. De Hoogd S, Ahlers SJGM, Van Dongen EPA, et al. Is intraoperative remifentanil associated with acute or chronic postoperative pain after prolonged surgery? An update of the literature. Clin J Pain 2016; 32: 726–35.
7. Yu EH, Tran DH, Lam SW, Irwin MG. Remifentanil tolerance and hyperalgesia: short-term gain, long-term pain? Anaesthesia 2016; 71: 1347–62.
8. Comelon M, Raeder J, Stubhaug A, Nielsen CS, Draegni T, Lenz H. Gradual withdrawal of remifentanil infusion may prevent opioid-induced hyperalgesia. Br J Anaesth 2016; 116: 524–30.
9. Memtsoudis SG, Poeran J, Zubizarreta N, et al. Association of multimodal pain management strategies with perioperative outcomes and resource utilization: a population-based study. Anesthesiology 2018; 128: 891–902
10. Mercieri M, Palmisani S, De Blasi RA, et al. Low-dose buprenorphine infusion to prevent postoperative hyperalgesia in patients undergoing major lung surgery and remifentanil infusion: a double-blind, randomized, active-controlled trial. Br J Anaesth 2017; 119: 792–802
11. Mercadante S, Arcuri E, Santoni A. Opioid-Induced Tolerance and Hyperalgesia. CNS Drugs 2019 Oct;33(10):943-955.
12. Edwards HL, Mulvey MR, Bennett MI. Cancer-related neuropathic pain. Cancers (Basel). 2019;11(3):373.
13. Mercadante S, Caruselli A, Casuccio A. The use of ketamine in a palliative-supportive care unit: a retrospective analysis. Ann Palliat Med. 2018;7:205–10.
14. Mercadante S, Arcuri E. Hyperalgesia and opioid switching. Am J Hosp Palliat Care. 2005;22:291–4
15. Mercadante S, Bruera E. Opioid switching in cancer pain: from the beginning to nowadays. Crit Rev Oncol Hematol. 2016;99:241–8

15 Barometric pressure and pain

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Abstract

There is a considerable body of evidence that barometric pressure (BMP) could affect patients with certain pain syndromes and cause several painful medical conditions. Changes in BMP occur either due to weather changes or environmental exposure to high altitude or diving. Here we discuss how weather influences headache, musculoskeletal and neuropathic pain. Also, pain syndromes related to exposure to high altitude and underwater pressure will be introduced.

Keywords: barometric pressure, diving, high altitude, pain.

Introduction

There is a considerable body of evidence that oscillations of barometric pressure (BMP) due to varying weather conditions could aggravate specific pain syndromes such as headache, musculoskeletal or neuropathic pain. Also, BMP changes resulting from exposure to high altitude or underwater pressure could have a causative relationship to several painful medical conditions.

Weather

Weather is a composite made of multiple variables such as BMP, temperature, humidity, wind speed etc.

Most studies suggested that headache is associated with low BMP, but some authors reported an association with high BMP or no association at all. (1) Interestingly, there is a discrepancy between the patients' beliefs and their factual susceptibility to weather variables. (2)

Lower BMP increases stress, and stress moderates the relationship between BMP and pain in patients with fibromyalgia. (3)

No association was observed between BMP and pain in patients with the hip (4) or knee osteoarthritis (OA) (5). However, the number of online searches for "knee pain" or "hip pain" increased dramatically with lower BMP. (6) In orthopedic trauma patients, low BMP was associated with increased pain across all patient visits during 1-year follow-up. (7)

Low back pain was not related to BMP regardless of self-reported weather sensitivity. (8)

Low BMP pressure aggravated neuropathic pain in guinea pigs with spinal nerve ligation (SNL) (9) as well as in rats with sciatic nerve chronic constriction injury (CCI) (10).

High altitude

Up to 8.3% of air travelers suffer from headache attributed to airplane travel (HAAT). (11) According to ICHD-3, HAAT is severe, unilateral or orbitofrontal with stabbing quality and temporally related to airplane ascent or descent. (12) It is most likely a result of barotrauma due to BMP changes on ascent or descent.

High-altitude headache (HAH), as defined by ICHD-3, HAH occurs above 2 500 meters above sea level in temporal relation to ascent, is bilateral and mild to moderate in intensity and can be aggravated by exertion, bending, coughing etc. (12) It is a cardinal sign of Acute and Chronic Mountain Sickness. Treatment includes NSAID and descent in severe cases.

Underwater

Decompression sickness (DCS) results from mechanical vascular obstruction or inflammation caused by gas bubbles formed during the rapid ascent of a diver. The most frequent and sometimes the only symptom of DCS is musculoskeletal pain. Patients complain of joint pain, most commonly shoulder and elbow pain, and myalgia of varying localization. (13) Therapy includes immediate 100% oxygen via a tight-fitting mask or hyperbaric chamber if needed.

According to ICHD-3, the diving headache could be diagnosed if the patient was diving to a depth greater than 10 m and had no evidence of DCS. It is often bifrontal, bitemporal, or bioccipital, throbbing in quality and can range from milder to more severe in intensity. (12) Prevention is critical, with special considerations regarding breathing technique and adherence to safety procedures.

Diving ascent headache is a less well-recognized entity that could be related to airplane headache. (14) A treatment similar to that for HAAT may be effective.

Barosinusistis

Prevalence of barosinusitis or “sinus squeeze” is estimated at 34% in divers, 25% in commercial pilots and 3% in hyperbaric chamber users (15). The most likely cause is BMP shift during flight or diving.

Barodontalgia

Barodontalgia is barometric pressure-induced dental pain. It affects divers more often than aircrew (8.2% vs. 5.8%, respectively) and more frequently civilian than military personnel (16).

Conclusion

Barometric pressure is becoming recognized as an important variable that can aggravate or alleviate numerous painful conditions such as headache, musculoskeletal and neuropathic pain. It also has a causative relationship with HAAT, HAH, DCS, diving headache, etc. Further research is needed in an attempt to understand and treat these conditions.

References

1. Maini K, Schuster NM. Headache and Barometric Pressure: a Narrative Review. Curr Pain Headache Rep. 2019 Nov 9;23(11):87. DOI: 10.1007/s11916 019-0826-5.
2. Hoffmann J, Hendra L, Neeb L, Martus P, Reuter U. Weather sensitivity in migraineurs. J Neurol. 2011;258:596–602.
3. Fagerlund AJ, Iversen M, Ekeland A, Malèn Moen C, Aslaksen PM. Blame it on the weather? The association between pain in fibromyalgia, relative humidity, temperature and barometric pressure. PLoS One. 2019 May 10;14(5):e0216902. DOI: 10.1371/journal.pone.0216902.
4. Fu K, Metcalf B, Bennell KL, Zhang Y, Deveza LA, Robbins SR, Ferreira ML, Hunter DJ. Association of weather factors with the risk of pain exacerbations in people with hip osteoarthritis. Scand J Rheumatol. 2021 Jan;50(1):68-73. DOI: 10.1080/03009742.2020.1760929.
5. Ferreira ML, Zhang Y, Metcalf B, Makovey J, Bennell KL, March L, Hunter DJ. The influence of weather on the risk of pain exacerbation in patients with knee osteoarthritis - a case-crossover study. Osteoarthritis Cartilage. 2016 Dec;24(12):2042-2047. DOI: 10.1016/j.joca.2016.07.016.
6. Telfer S, Obradovich N. Local weather is associated with rates of online searches for musculoskeletal pain symptoms. PLoS One. 2017 Aug 9;12(8):e0181266.
7. Shulman BS, Marcano AI, Davidovitch RI, Karia R, Egol KA.Injury. Nature's wrath-The effect of weather on pain following orthopaedic trauma. 2016 Aug;47(8):1841-6. DOI: 10.1016/j.injury.2016.05.043.
8. McGorry RW, Hsiang SH, Snook SH, Clancy EA, Young SL. Meteorological conditions and self-report of low back pain. Spine. 1998 Oct 1;23(19):2096-102; discussion 2103. DOI: 10.1097/00007632-199810010-00011.
9. Sato J, Itano Y, Funakubo M, Mizoguchi H, Itoh M, Mori R. Low barometric pressure aggravates neuropathic pain in guinea pigs. Neurosci Lett. 2011 Oct 3;503(2):152-6. DOI: 10.1016/j.neulet.2011.08.030.

10. Sato J, Takanari K, Omura S, Mizumura K. Effects of lowering barometric pressure on guarding behavior, heart rate and blood pressure in a rat model of neuropathic pain. Neurosci Lett. 2001. PMID: 11166927 Neurosci Lett. 2001 Feb 16;299(1-2):17-20. DOI: 10.1016/s0304-3940(00)01769-9.
11. Nierenberg H, Jackfert K. Headache Attributed to airplane travel: a review of literature. Current pain and headache reports. 2018;22:48.
12. The International Classification of Headache Disorders. 3rd edn. Cephalalgia. 2013;33(9):629–808.
13. Kirby JP. The Diagnosis of Decompression Sickness in Sport Divers. Mo Med. 2019 May-Jun;116(3):195-197.
14. Federico Mainardi F, Maggioni F, Zanchin G. Aeroplane headache, mountain descent headache, diving ascent headache. Three subtypes of headache attributed to imbalance between intrasinusal and external air pressure? Cephalalgia. 2018 May;38(6):1119-1127. DOI: 10.1177/0333102417724154.
15. Vaezeafshar R, Psaltis AJ, Rao VK, Zarabanda D, Patel ZM, Nayak JV. Barosinusitis: Comprehensive review and proposed new classification system. Allergy Rhinol (Providence). 2017 Oct 1;8(3):109-117. DOI: 10.2500/ar.2017.8.0221.
16. Nakdimon I, Zadik Y. Barodontalgia Among Aircrew and Divers. Aerosp Med Hum Perform. 2019 Feb 1;90(2):128-131. DOI: 10.3357/AMHP.5183.2019.

16 Specifics of pain processing in endurance sports

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Abstract

The unique characteristic of endurance athletes is their exceptional ability to tolerate pain which, as evidence suggests, may result from specific pain processing. Endurance athletes have enhanced conditioned pain modulation and reduced activation of brain regions typically activated by nociceptive stimulation compared to strength athletes and non-athletes. Pain tolerance is associated with personality traits such as contentiousness and grit and is inversely related to fear of pain. These findings imply a possible role of recreational endurance activities in patients suffering from chronic pain conditions.

Keywords: endurance, musculoskeletal, pain, sport.

Introduction

Endurance sports encompass a wide range of activities during which athletes perform a continuous intense exercise for prolonged periods of time. Musculoskeletal pain is almost ubiquitous among endurance athletes, with 99.8% of marathoners reporting moderate to severe pain during the race. (1) Unique characteristic of endurance athletes is their exceptional pain tolerance (2) which, as evidence suggests, may result from specific pain processing.

Transduction

Musculoskeletal pain can be divided into early-onset muscle soreness (EOMS) and delayed-onset muscle soreness (DOMS). Several theories regarding the possible cause of EOMS and DOMS were proposed, including lactate production (3), myofibril structural damage (4), fascia damage (5), inflammation (6), and oxidative stress (7).

Transmission

A current body of evidence suggests that central sensitization is not different in endurance athletes compared to strength athletes and non-athletes (8)

Modulation

Multiple studies report enhanced conditioned pain modulation in endurance athletes (9). Several mechanisms of exercise-induced hypoalgesia were explored, such as opioid (10), serotoninergic (11) and mesocorticolimbic (12) system activation, as well as muscle-brain communication via myokines (13).

Perception

Superior pain tolerance is most likely to be attributed to personality traits of endurance athletes, such as pronounced contentiousness and grit. Pain tolerance is inversely related to fear of pain. (2) Functional MRI shows reduced activation in several brain regions typically activated by nociceptive stimulation, such as the thalamus, primary and secondary somatosensory cortex, insula, anterior cingulate cortex, midcingulate cortex, dorsolateral prefrontal cortex, and brain stem. (14)

Conclusion

Exceptional pain tolerance observed in endurance athletes is likely a result of specific pain processing. Findings explored here provide a better understanding of pain modulation and perception and imply the possible role of recreational endurance activities in patients suffering from chronic pain.

References

1.O'Connor PJ. Pain During a Marathon Run: Prevalence and Correlates in a Cross-Sectional Study of 1,251 Recreational Runners in 251 Marathons. Front Sports Act Living. 2021 Feb 10;3:630584.

2.Susann Dahl Pettersen S, Aslaksen P, Pettersen A. Pain Processing in Elite and High-Level Athletes Compared to Non-athletes. Front Psychol. 2020; 11: 1908.

3.Jastrzębski Z, Żychowska M, Konieczna A, Ratkowski W, Radzimiński Ł. Changes in the acid-base balance and lactate concentration in the blood in amateur ultramarathon runners during a 100-km run. Biol Sport. 2015 Sep;32(3):261-5.

4.Tokinoya K, Ishikura K, Ra SG, Ebina K, Miyakawa S, Ohmorif H. Relationship between early-onset muscle soreness and indirect muscle damage markers and their dynamics after a full marathon. J Exerc Sci Fit. 2020 Sep; 18(3): 115–121.

5.Wilke J, Behringer M. Is "Delayed Onset Muscle Soreness" a False Friend? The Potential Implication of the Fascial Connective Tissue in Post-Exercise Discomfort. Int J Mol Sci. 2021 Aug 31;22(17):9482.

6.Mizumura K, Taguchi T. J Physiol Sci. Delayed onset muscle soreness: Involvement of neurotrophic factors. 2016 Jan;66(1):43-52.

7.Close, GL; Ashton, T.; Cable, T.; Doran, D.; MacLaren, D.P.M. Eccentric exercise, isokinetic muscle torque and delayed onset muscle soreness: The role of reactive oxygen species. Eur. J. Appl. Physiol. 2004, 91, 615–621.
8.Assa T, Geva N, Zarkh Y, Defrin R. The type of sports matters: Pain perception of endurance athletes versus strength athletes. Eur J Pain. 2019 Apr;23(4):686-696.
9.McDougall J, Jutzeler CR, Scott A, Crocker PRE, Kramer JLK. Conditioned pain modulation in elite athletes: a systematic review and meta-analysis. Scand J Pain. 2020 Jul 28;20(3):429-438.
10. Boecker H, Sprenger T, Spilker ME, Henriksen G, Koppenhoefer M, Wagner KJ, Valet M, Berthele A, Tolle TR. The runner's high: opioidergic mechanisms in the human brain. Cereb Cortex. 2008 Nov;18(11):2523-31.
11.Lopez-Alvarez VM, Puigdomenech M, Navarro X, Cobianchi S. Monoaminergic descending pathways contribute to modulation of neuropathic pain by increasing-intensity treadmill exercise after peripheral nerve injury. Exp Neurol. 2018 Jan;299(Pt A):42-55.
12.Kami K, Tajima F, Senba E. Brain Mechanisms of Exercise-Induced Hypoalgesia: To Find a Way Out from "Fear-Avoidance Belief". Int. J. Mol. Sci. 2022, 23(5), 2886.
13.Wang Y, Wu Z, Wang D, Huang C, Xu J, Liu C, Yang C. Muscle-brain communication in pain: The key role of myokines. Brain Research Bulletin, Volume 179, February 2022, Pages 25-35.
14.Geisler M, Ritter A, Herbsleb M, Bär K, Weiss T. Neural mechanisms of pain processing differ between endurance athletes and non-athletes: A functional connectivity magnetic resonance imaging study. Hum Brain Mapp. 2021 Dec 15;42(18):5927-5942.

17 Lumbar disc hernia - Indications for surgical treatment

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Abstract

Lumbar disc herniation (LDH) is one of the most common diseases in adults, and the most of these hernias are experienced in the third or fourth decade. Absolute indications for an urgent surgical treatment are progressive and significant lower limb weakness or cauda equina syndrome. Other indications for surgery include imaging confirmation of LDH, consistent with clinical findings, and failure to improve after six weeks of conservative care.

Key words: Lumbar disc herniation, indication, surgery

Introduction

Lumbar disc herniation (LDH) is one of the most common diseases in adults (1). The prevalence rate of LDH has increased yearly with lifestyle changes (aging population, heavy work pressure…). Most of them are under the 50 years (2).

Intervertebral disc herniation can be defined as the localized displacement of disc material (herniation of the nucleus pulposus through the fibrous bundles of the fibrous annulus) beyond the normal margins of the intervertebral disc space. In cases when the force acting on the nucleus pulposus is too strong, the fibers of the fibrous anus are ruptured and the nucleus tissue is herniated (3). Perforation of the fibrous annulus fibers usually occurs posteriorly. Dorsolateral protrusion is more common and affects one or possibly two nerve roots on the same side. Dorsomedial protrusion affects them bilaterally and can give cauda equina syndrome. There are three types of intervertebral disc prolapse:

- protrusion - the annulus is thinned at a certain point, but the fibers are not interrupted, and the prolapsed part of the nucleus is continuous with the rest

- extrusion - the annulus is interrupted and part of the disc that is prolapsed is free in the canal, but is continuous with that in iv space.
- sequestration - the prolapsed part of the disc is not continuous with the part which is in the intervertebral space.

The pain pathway originates in impingement of the nerve root by the herniated disc, which may in turn lead to nerve damage compression of the nerve likely leads to localized ischemia and nerve damage. At the same time, the chemical cascade is triggered by the nucleus pulposus on the nerve. A pro-inflammatory cascade mediated by tumour necrosis factor-alpha (TNF-α), interleukin factor-6 (IL-6), and matrix metalloproteinases (MMPs) leads to further sensitization and increased pain in the area. (4,5)

Signs and symptoms

Approximately 75% of lumbar flexion and extension occurs at the lumbosacral junction, 20% at the L4-L5 level, and the remaining 5% at the upper lumbar levels. Therefore, in about 90% of cases, lumbar disc herniations are localized in the lower two levels, with those in the L5-C1 level being twice as common as in the adjacent level.

LDH is the most common cause of sciatica, affecting 1-5% of the population annually (6). Signs and symptoms include radicular pain, sensory abnormalities, and weakness in the distribution of one or more lumbosacral nerve roots. Focal paresis, restricted trunk flexion, and increases in leg pain when sitting or with straining, coughing, and sneezing are also indicative (7-9). Cauda equina syvndrome from lumbar disc herniation accounts for up to 2-3% of all disc herniations (10).

Magnetic resonace imaging is the gold standard for radiological diagnosis. Also, computer tomography could be used.

Surgery

The first-line treatment for LDH is non-surgical (pharmacologic therapy, physical therapy, transforaminal or epidural steroid injections), and significant reduction in pain within 4 weeks is in 70% of patients (11). For symptoms that are resistant to initial conservative treatments, surgical treatment may be considered. If clinical signs and symptoms are correlated with radiological diagnosis, and the operation is performed within 2-3 months from the onset of the disease. Surgical treatment relieves the patient of radicular pain in 90 to 95% of cases. After 3 months, lumbar pain disappears in only 60% of cases. Overall, the results of surgical treatment are not satisfactory in 30 to 40% of patients. Surgical treatment enables faster relief from pain, but the therapeutic results after a long follow-up are similar to those in conservatively treated patients. In severe cauda equina syndrome, motor recovery lasts up to 18 months, and recovery of sphincter function, which is equally slow, is never complete (8-10, 12, 13).

The goal of the operation is to decompress the lumbar neural elements while preserving the normal anatomy and biomechanics. The absolute contraindication for

surgical treatment is difficult to define. Cardiac and pulmonary diseases carry a significant risk and great caution is required. Before the operation, it is necessary to assess the mental status of the patient.

Absolute indications for an urgent surgical treatment are progressive and significant lower limb weakness or cauda equina syndrome. In case of proven root compression with significant motor weakness, perform the operation as soon as possible (best within a week of weakness) (10, 12).

The relative indication for surgery is pain. Pain is individual for each patient, and if there is no positive effects of conservative therapy, surgical discectomy can be considered (10). Recurrent intense pain is a relative indication. The clinical indications for surgical treatment may be: patients with clinical signs and symptoms associated with LDH, with imaging confirmation of LDH consistent with clinicalfindings, and failure to improve after six weeks of conservative care (12, 14).

Few big studies showed that patients treated with discectomy reported greater improvement in back and leg pain, functional status, and overall satisfaction, compared to non-surgical care (15-18). Wilson and associates founded that severe leg pain, better mental health status, shorter duration of symptoms, and younger age are associated with positive outcome. Negative outcomes are associated with intact annulus fibrosus, longer duration of sick leave, workers' compensation, and greater severity of baseline symptoms. Preoperative factors including motor deficit, side and level of herniation, presence of Type 1 Modic changes and degeneration on MRI had non-significant associations with postoperative outcome (19).

Because possible complications, surgeons need to choose the most appropriate surgery according to the individual condition of the patient to achieve the best therapeutic effect (20).

Conclusion

Absolute indications for an urgent surgical treatment are progressive and significant lower limb weakness or cauda equina syndrome. Other indications for surgery include imaging confirmation of LDH, consistent with clinical findings, and failure to improve after six weeks of conservative care.

References

1. Lebow RL, Adogwa O, Parker SL, Sharma A, Cheng J, McGirt MJ. Asymptomatic same-site recurrent disc herniation after lumbar discectomy: Results of a prospective longitudinal study with 2-year serial imaging. Spine (Phila Pa 1976). 2011; 36:2147-2151.
2. Quinteros G, Yurac R, Zamorano JJ, Díez-Ulloa MA, Pudles E, Marré BA. Management of lumbar disc herniation with radiculopathy: Results of an Iberian-Latin American survey. Surg Neurol Int. 2021 Jul 19; 12:363.

3. Yoon WW, Koch J. Herniated discs: when is surgery necessary?. EFORT Open Rev. 2021; 6(6):526-530.
4. Kang JD, Stefanovic-Racic M, McIntyre LA, Georgescu HI, Evans CH. Toward a biochemical understanding of human intervertebral disc degeneration and herniation: contributions of nitric oxide, interleukins, prostaglandin E2, and matrix metalloproteinases. Spine (Phila Pa 1976) 1997; 22:1065–1073.
5. Van Boxem K, Huntoon M, Van Zundert J, Patijn J, van Kleef M, Joosten EA. Pulsed radiofrequency: a review of the basic science as applied to the pathophysiology of radicular pain: a call for clinical translation. Reg Anesth Pain Med 2014; 39:149–159
6. Frymoyer JW. Back pain and sciatica. N Engl J Med 1988;318:291–300 20
7. Vucetic N, Svensson O. Physical signs in lumbar disc hernia. Clin Orthop Relat Res 1996;333:192–201
8. Radulović D, Baščarević V. Acute interventions in cervical, thoracal and lumbar disc herniation. In: Samardžić M. (Ed.) Emergencies in neruosrugery. Diagnostical and therapeutical guidance. Obeležja. Belgrade. 2010; p193-215
9. Joković M. Degenerative diseases of lumbosacral spine. In: Samardžić M. (Ed.) Modern Neurosurgery. Selected chapters. Obeležja plus. Belgrade. 2013; p167-187
10. Radulović D, Tasić G, Joković M, Nikolić I. The role of surgical decompression of cauda equina in lumbar disc herniation and recovery of bladder function. Med Pregl. 2004; 57(7-8):327-30.
11. Weber H, Holme I, Amlie E. The natural course of acute sciatica with nerve root symptoms in a double-blind placebo-controlled trial evaluating the effect of piroxicam. Spine (Phila Pa 1976) 1993;18:1433–1438
12. Yoon WW, Koch J. Herniated discs: when is surgery necessary?. EFORT Open Rev. 2021;6(6):526-530.
13. Siccoli A, de Wispelaere MP, Schröder ML, Staartjes VE.Timing of Surgery in Tubular Microdiscectomy for Lumbar Disc Herniation and Its Effect on Functional Impairment Outcomes. Neurospine. 2020; 17(1):204-212.
14. Lorio M, Kim C, Araghi A, Inzana J, Yue JJ. International Society for the Advancement of Spine Surgery Policy 2019: surgical treatment of lumbar disc herniation with radiculopathy. Int J Spine Surg 2020;14:1–17.
15. Atlas SJ, Keller RB, Wu YA, Deyo RA, Singer DE. Long-term outcomes of surgical and nonsurgical management of lumbar spinal stenosis: 8 to 10 year results from the Maine Lumbar Spine Study. Spine (Phila Pa 1976) 2005;30:936–943.
16. Weinstein JN, Tosteson TD, Lurie JD, et al. Surgical vs nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT): a randomized trial. JAMA 2006;296:2441–2450.
17. Weinstein JN, Lurie JD, Tosteson TD, et al. Surgical vs nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT) ob-

servational cohort. JAMA 2006;296:2451–2459.
18. Arts MP, Kuršumović A, Miller LE, et al. Comparison of treatments for lumbar disc herniation: systematic review with network meta-analysis. Med (United States) 2019;98:1–9.
19. Wilson CA, Roffey DM, Chow D, Alkherayf F, Wai EK. A systematic review of preoperative predictors for postoperative clinical outcomes following lumbar discectomy. Spine J 2016;16:1413–1422)
20. Wei H, Shunli K, Zehua J, Tengfei Z, Yidong L, Rusen Z. Comparative Study of Three Minimally Invasive Surgical Approaches for the Treatment of L5/S1 Lumbar Intervertebral Disc Herniation. Turk Neurosurg. 2021;31(3):324-332.

Clinical effects of uridine monophosphate (Neuronal) in the treatment of peripheral compressive neuropathies and nerve injuries.

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Abstract

A large number of studies have shown that the use of drugs containing pyramidine nucleotides have an extremely positive effect on relieving pain intensity in patients with acute and chronic neuropathic pain. The use of these drugs in diabetic neuropathy, back and neck pain, as well as pain resulting from nerve injury leads to a significant reduction in pain. In addition, their beneficial effect on neuroregenerative processes has been established.

These drugs stimulate protein synthesis in nerve cells, myelin sheath synthesis and nerve growth in the process of P2Y receptor activation. Likewise, the use of uridine monophosphate (UMF), uridine triphosphate (UTF) and cytidine monophosphate (CMF) as a group of pyramidine nucleotides in combination with cobalamin (vitamin B12), niacin (vit B3), bedoxin (B6), thiamine (B6), thiamine (B1), and folic acid, can potentiate their analgesic effect by stimulating neuroregenerative processes.

The mechanisms of their action can be indirect through potentiation of protein synthesis in nerve cells, myelin synthesis and MBP (Myelin basic protein) synthesis, etc., as well as directly through stimulation of P2Y receptors which are responsible for the production of nucleotides (adenosine and uridine phosphates).(1)

Introduction

Neuropathic pain is defined as pain caused by a primary lesion or damage to the central or peripheral part of the nervous system. Damage can result from compression, rupture, ischemia or metabolic disorders, inflammatory processes or a combination of these.(2) Approximately 50-90% of people under the age of 45 experience back pain at some point in their lives. It can be short-term and disappear without treatment, but in many cases it becomes chronic lumbar pain syndrome.(3)

Research has shown that the use of drugs containing pyramidine nucleotides, from the group of uridine monophosphate (UMF), uridine triphosphate (UTF), and cytidine monophosphate (CMF), have a pronounced effect in relieving pain in patients with diabetic neuropathy, back and neck pain and in patients with compressive neuropathy.(4)The process leading to a reduction in pain perception is related to the activation of P2Y2 and P2Y4 receptors that are sensitive to nucleotides and their inhibitory role in the transmission of pain.(5)

Peripheral nervous system

Peripheral nervous system (PNS) consists of peripheral nerves, which are composed of a set of nerve fibers connected by connective tissue, and their motor and sensory endings. According to the type of nerve fibers located in the nerves, they can be divided into motor, sensory and mixed nerves. The nerve cell sends nerve impulses through the axon to the synaptic junction, and dendrites transmit synaptic information to the nerve cell body. Axons are lined with myelin sheath, which is produced by oligodendrocyte cells in the central nervous system and Schwann cells in the peripheral nervous system.(6)

The Schwann cell membrane surrounds the peripheral nerve fiber forming the myelin sheath, which is responsible for adequate conduction of the nerve impulse through the axon.(6)

The involvement of Schwan cells in the process of nerve myelination is under the direct influence of neurotrophrin (NF) and nerve growth factor (NGF). Myelination, which is influenced by Schwann cells, is directly related to the process of its differentiation and the synthesis of the basal lamina.(7)

Injuries of the peripheral nervous system

Peripheral nerve injuries can be divided into neuropraxia, axonotmesis, and neurotmesis. Neuropraxia involves nerve damage in which the axon is intact but there is damage to the myelin sheath. Neuropraxia is characterized by loss of motor functions with rare impairment of sensory functions. This type of nerve damage most often results from compression or circulatory disorders as part of transient ischemia.

Axonotmesis implies damage to the axon and myelin while preserving the epineurium and perineurium. This type of nerve damage is characterized by loss of its motor, sensitive and autonomic functions. It occurs after trauma and stretching of the nerves while the continuity of the epineurium is maintained.

Neurotmesis is the most severe nerve damage with a complete loss of nerve and perineural tissue continuity. Neurothemesis occurs after contusion, stretching, laceration or toxic damage after local application of anesthetics. In this case, the nerve and peyroneural tissue lose their continuity.

In relation to the mentioned types of nerve injuries, there is a clearly defined drug regimen, where the use of appropriate medications aimed at regeneration of nerve

function is justified. Nerve edema and partial demyelination are a clear indication for the use of drug therapy and subsequent physical therapy. Demyelination accompanied by axonal lesions is most often associated with the development of irreversible changes in the nerve and does not open up possibility for the useful application of neuroprotectors and neurostimulators. It should be noted that timely diagnosis of irreversibility of nerve damage in a number of cases greatly facilitates deciding on quality and promising surgery of reinnervation and transplantation.

Wallerian degeneration

The injury of a nerve fibre is followed by a separation of its proximal part, loss of innervation of the corresponding muscle group, and the consequent loss of the corresponding motor, sensory and autonomic function. Degeneration and fragmentation of the damaged part of the axon is called Wallerian degeneration. The degeneration process begins with an increase in the level of Ca2 + ions, which are in very low concentrations in a healthy axon. This leads to the activation of Ca2 + protease (calpain) resulting in the degradation of the axon cytoskeleton in the proximal parts.(8)

Alongside cytoskeletal degradation, macrophages are activated, thus helping to remove fragments by activating the process of phagocytosis. Schwann cells that begin to proliferate have the same function of removing axonal detritus, potentiating nerve tube formation.(9)

The process of axon degeneration is followed by a whole series of molecular changes and the beginning of the regeneration process. The level of NGF (messenger ribonucleic acid-mRNA) increases, which is directly related to the increase in macrophage migration and interleukin concentration. With the increasing mRNA levels, there is an increase in the concentration of brain-derived neurotrophic factor (BDNF), the expression of transmembrane receptors for neutrophil factors (p75NGFR) primarily in the distal parts of the injured axon and at the site of its repair. There is also a rapid regulation of neutrophil glial cell growth factors - GDNF (glial cell line-derived neutrophic factor).(10)

Regeneration of the peripheral nervous system

A characteristic of the peripheral nervous system is the ability to regenerate and recover its function after damage, unlike axons in the central nervous system which do not have such ability. Huebner EA, Strittmatter SM. Axon regeneration in the peripheral and central nervous systems. In: Cell Biology of the Axon. 2009. Springer Berlin Heidelberg:305–60.

However, despite the ability to regenerate, in a number of cases functional recovery is impossible and is related to the process of retrograde degeneration, complete lesions of nerve continuity, existing comorbidities and nonspecificity of reinnervation within organs with different functions.(11)

During the regeneration process, retrograde processes and metabolic changes occur as removing detritus of the damaged nerve during Wallerian degeneration by macrophages and Schwan cells. The relationship between axons and Schwan cells is intense and very important for the axon regeneration process.(12)

Schwan cells lose their myelinating phenotype and become responsible for tubular carrier formation in the process of nerve fiber regeneration. Axon proliferation is also associated with active enhancement of extracellular matrix function and increased synthesis of adhesive molecules (CAM), and extracellular proteins such as laminin (LM), fibro nectin (FN), heparin sulfate, proteoglycone (HSP), and tenascin in the basal membrane. The secretion of neurophilic factors such as NGF and BDNF leads to mutual attraction of nerve fibers during their regeneration and retention of the growth direction through the newly formed nerve fiber tube. Activation of cytokines such as interleukin (IL)-10 results in inhibition and termination of the inflammatory process, which began during Wallerian degeneration.(10). The neural tube and the axon growth band that form Schwann cells is called the Büngner belt.(13)

It should be noted, however, that if the distance between the site of axon injury and the muscle is short, reinnervation of the muscle may occur. However, if reinnervation is delayed, then Schwan cells degrade and do not stimulate axon growth which, in addition to the development of muscle atrophy, reduces the ability to form the necessary synapses. All this points to the extremely important role of Schwan cells in the regeneration process and opens up possibility of further research aimed at treating damage to the peripheral nervous system.

Nucleotides and their therapeutic effect

Nucleotides are very important in the regulation of a large number of cellular and pathological mechanisms, which are important in the process of homeostasis.(14) Nucleotides are monomers composed of parts of sugar, which are bound to one or more phosphate groups, such as cytosine, adenine, guanine, and participate in energy production and cell signaling processes, as well as the programmed cell death-apoptosis.(15)

Nucleotide function is related to the type of receptor to which it binds. Purin receptors are divided into two types P1 (adenine selective receptors) and P2 receptors, which are divided into P2y and G proteins and are susceptible to nucleotides containing adenine and uracil.(15) These nucleotides modulate the processes related to endocrine and exocrine function, platelet aggregation, cell proliferation, their differentiation; they regulate inflammatory processes and the processes of healing and reparation. Several types of nucleotides, such as ATP, UTP, UMP and adenosine, are signal modules in the processes of nerve cell function, maintenance of synaptic processes, neuromodulation and regeneration.(16)

Functioning as neuromodulators, nucleotides control microglial stimulation under normal and pathological conditions. The action of nucleotides on P2y receptors

affects the regulation of spinal cord microglial cells after damage to peripheral nerves, leading to the relief of neuropathic pain. In addition, extracellular nucleotides have the ability to interact with proximal cells, promoting neurite differentiation and growth.(17)

Another important role of nucleotides is the regulation of macrophage activity, and the production of interleukins (IL-6, IL-9, IL-13) by activating P2y and mRNA receptors. Control of macrophage activity is necessary in the processes of nerve tissue regeneration and the production of myelin and glycoproteins.(18) Nucleotide-containing drugs have proven through controlled clinical studies to have a beneficial effect in patients with neuromuscular diseases, diabetic neuropathies, as well as in patients with spinal nerve lesions.

Studies analyzing the application of UTP and UMP have indicated a beneficial effect in terms of potentiating axon growth, their association, and myelination.(19) Cytidine preparations, for their part, indicated to their positive effect on the functional recovery of damaged nerves and their peripheral regeneration.(20) The use of uridine and cytidine nucleotides associated with the use of hydroxycobalamin (B12) have shown a beneficial effect in the treatment of resistant anemia. Likewise, they showed a better effect in reducing neuropathic pain in combination with vitamin B complex than when used alone.(21)

The combination of uridine nucleotides, vitamin B12 and folic acid has shown a good effect in reducing neuropathic pain associated with peripheral diabetic neuropathy, with a significant reduction in nonsteroidal anti-inflammatory drugs.(22) Vitamin B12 plays a very important role in DNA synthesis and neurological functions, and its deficiency can lead to unsuccessful methylation of basic myelin proteins which can be a cause of peripheral neuropathy. In addition, B vitamins have an analgesic effect in neuropathies and nociceptive sensations.(23)

Discussion

A large number of studies have confirmed the beneficial effect of nucleotides and B vitamins in the treatment of diseases of the peripheral nervous system. A study analyzing the use of cytidine-uridine-hydroxycobalmin in the treatment of chronic neuropathic back pain in 48 patients aged between 21 and 80 years, in whom the previous therapeutic approach had no effect, indicated that the group in which the said complex was added to the therapy, had statistically significant improvement in the clinical picture and reduction in pain perception.(24

The use of nucleotides in combination with B vitamins and folic acid had a beneficial effect on patients with alcoholic polyneuropathy. The study included 120 patients aged between 28 and 65 years.(21) The study, which included 212 patients with peripheral neuropathy and neuropathic pain, used two-month oral therapy consisting of uridine monophosphate (UMP)-folic acid-hydroxycobalamin.(22) In this group, patients had an average age of 59 years. In most of the patients, a reduction in neuropathic pain

and its intensity was achieved. In all of them, the additional use of analgesics was reduced by more than 70%. The increase in malignant diseases and their long-term treatment is increasingly connected with the long-term appearance of neuropathic pain. The use of nucleotides and vitamin B12 in a large number of these patients led to a reduction in the intensity of neuropathic pain.(25)

Conclusion

The therapy of nerve damage requires an approach that would promote its regenerative potentials, primarily using the ability of Schwan cells to provide direction for the growth of the axon itself and later enable the process of its myelination.

Potentiation of regenerative processes of damaged axons is possible by using uridine and cytidine nucleotides in combination with B vitamins.

References

1. Abbracchio MP, Burnstock G, Boeynaems JM, Barnard EA, Boyer JL, Kennedy C, Knight GE, Fumagalli M, Gachet C, Jacobson KA, Weisman GA (September 2006). "International Union of Pharmacology LVIII: update on the P2Y G protein-coupled nucleotide receptors: from molecular mechanisms and pathophysiology to therapy". Pharmacological Reviews. 58 (3): 281–341. doi:10.1124/pr.58.3.3
2. Woolf CJ. Neuropathic pain. In: Pain. Philadelphia: Lippincott Williams Wilkins, 2004: 765–95.
3. Silva GNS, Monteiro PB, Virgínio NA, Souto CGV, Oliveira MVAV. Systematization of nursing care for patients with Herniated Disc. Health Science Magazine New Hope. 2013;11(2):55–71
4. Muller D. Treatment of neuropathic pain syndrome. Results of an open study on the efficacy of a pyrimidine nucleotide preparation. Fortschritte der Medizin Originalien. 2002;120:131–3.
5. Okada K, Tanaka H, Temporin K, Okamoto M, Kuroda Y, Moritomo H, et al.Methylcobalamin increases Erk1/2 and Akt activities through the methylation cycle and promotes nerve regeneration in a rat sciatic nerve injury model. Experimental Neurology. 2010;222(2):191–203.
6. Bhatheja K, Field J. Schwann cells: origins and role in axonal maintenance and regeneration. The International Journal of Biochemistry & Cell Biology. 2006;38(12):1995–9.
7. Garbay B, Heapec AM, Sargueila F, Cassagne C. Myelin synthesis in the peripheral nervous system. Progress in Neurobiology. 2000;61(3):267–304
8. Gaudet AD, Popovich PG, Ramer MS. Wallerian degeneration: gaining perspective on inflammatory events after peripheral nerve injury. Journal of Neuroinflammation. 2011;8(1):110.
9. Campana WM. Schwann cells: activated peripheral glia and their role in neuropathic pain. Brain, Behavior, and Immunity. 2007;21(5):522–7.

10. Frostick, SP, Qi Yin, Kemp GJ. Schwann cells, neurotrophic factors, and peripheral nerve regeneration. Microsurgery. 1998;18(7):397–405
11. Navarro X. Neural plasticity after nerve injury and regeneration. International Review of Neurobiology. 2009;87:483–505.
12. Webber C, Zochodne D. The nerve regenerative microenvironment: early behavior and partnership of axons and Schwann cells. Experimental Neurology. 2010;223(1):51–9.
13. Ngeow WC. Scar less: a review of methods of scar reduction at sites of peripheral nerve repair. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology. 2010;109(3):357–66.
14. Fausther M, Sévigny J. Nucleosides and extracellular nucleotides regulate hepatic functions through a complex system of membrane proteins. Biological Complications. 2011;334(2):100–17.
15. Burnstock G. Pathophysiology and therapeutic potential of purinergic signaling. Pharmacological Reviews. 2006;58(1):58–86.
16. Ulrich H, Abbracchio MP, Burnstock G. Extrinsic purinergic regulation of neural stem/ progenitor cells: implications for CNS development and repair. Stem Cell Reviews and Reports. 2012;8(3):755–67.
17. Menéndez-Méndez A, Díaz-Hernández JI, Miras-Portugal MT. The vesicular nucleotide transporter (VNUT) is involved in the extracellular ATP effect on neuronal differentiation. Purinergic Signalling. 2015;11(2):239–49.
18. Stoll G, Jander S, Myers RR. Degenerarion and regeneration os the peripheral nervous system: from Augustus Waller's observations to neuroinflammation. Journal of the Pheripheral Nervous System. 2002;7(1):13–27.
19. Martiáñez T, Carrascal M, Lamarca A, Segura M, Durany N, Masgrau R, Abian J, Gella A. UTP affects the Schwannoma cell line proteome through P2Y receptors leading to cytoskeletal reorganisation. Proteomics. 2012;12(1):145–56
20. Parisi V, Coppola G, Ziccardi L, Gallinaro G, Falsini B. Cytidine-5′-diphosphocholine (Citicoline): a pilot study in patients with non-arteritic ischaemic optic neuropathy. European Journal of Neurology. 2008;15(5):465–74.
21. Nunes CP, Higashi R, Ribeiro MG, de Souza Fonseca A, Leite A, Krymchantowski AV, et al. Efficacy and tolerability of a combination of uridine, cytidine, and vitamin B12.Brasileira de Medicina. 2008;65(1/2):15.
22. Negrão L, Almeida P, Alcino S, Duro H, Libório T, Melo SU, Figueira R, Gonçalves S, Neto PL. Effect of the combination of uridine nucleotides, folic acid and vitamin B12 on the clinical expression of peripheral neuropathies. Pain management. 2014;4(3):191–6.
23. Gazoni FM, Malezan WR, Santos FC. B complex vitamins for analgesic therapy. Revista Dor. 2016;17(1):52–6.
24. Lauretti GC, Omals M, Pereira AC, et al. Clinical evaluation of the analgesic effect of

the cytidine-uridine-hydroxocobalamin complex as a coadjuvant in the treatment of chronic neuropathic low back pain. Column. 2004;3(2):73–6.
25. Solomon LR. Functional vitamin B12 deficiency in advanced malignancy: implications for the management of neuropathy and neuropathic pain. Supportive Care in Cancer. 2016;24(8):3489–94.

Analgesics in sports - what is allowed and what is forbidden

19

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The use of analgetic in sports is regulated by Prohibited list issued every year by World Antidoping Agency (WADA). Analgesics (morphine, oxycodone, fentanyl, buprenorphine) are prohibited in sport as narcotics that are prohibited in competition. Certain restrictions exist for substances that can have analgesics effects in sport although they are not classified like that (cannabinoids and glucocorticoids).

Tetrahydrocannabinol (THC) is prohibited in sport and is the only cannabinoid for which there is a urinary threshold and it is set at 150 ng/mL. If the level of THC in athlete urine goes above the threshold, then the labs report it as a positive test. There are no threshold limits for any other cannabinoid (natural or synthetic). All other cannabinoids (except cannabidiol) are prohibited in-competition in any amount, including natural cannabinoids (e.g., cannabigerol, cannabichromene, cannabinol, and others) and synthetic cannabinoids (e.g., cannabinoid compounds denoted by the initials "JWH" and a number, HU-210, K2/Spice, AB-PINACA, and many others). This put CBD oil in risky position since it is allowed but since the concentration of THC is variable there are no antidoping authority who recommended usage. All glucocorticoids are prohibited when administered by any injectable, oral [including oromucosal (e.g. buccal, gingival, sublingual)] or rectal route. Due to high rate of prescribing drugs from this group athletes and sprot entourage should be cautious.

Except Prohibited list WADA has regular Monitoring list where the group of narcotics: codeine, hydrocodone and tramadol is monitored only in competition samples. There are exceptions that, for example, tramadol is forbidden only in cycling, as one of the most used and abused analgetic in sport. Finally, there are special consideration for combination of analgesics with stimulants, mainly pseudoephedrine, which could be a doping trap for athletes. All other combination will be discussed. As conclusion analgesics are allowed in sport except those who are restricted by WADA Prohibited list.

Reference

1.Prohibited list - https://www.wada-ama.org/en/prohibited-list (retrieved 16.04.2022)
2.Monitoring list-https://www.wada-ama.org/sites/ default/files/ resources/files/ 2022 list_ monitoring_program_final_en.pdf (retrieved 16.04.2022)

The treatment of pain during the COVID-19 pandemic – problems and solutions

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Abstract

Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors. The main goal of pain therapy should be to reduce pain and increase functioning with maximum safety of the applied therapy in patients suffering from pain.

Nowadays, in time of pandemic the Coronavirus Disease 2019 (COVID-19), healthcare pain therapy professionals face two problems: first, patients who have pain as a part of the COVID-19 infection, and second, patients who have already had some kind of chronic pain syndrome. Although treatment of pain is a basic human right, the COVID-19 pandemic has forced the health care system around the world to reallocate health resources to units and facilities to treat COVID-19 positive patients. Chronic pain is widespread in society and almost all adults have experienced at least one episode of musculoskeletal pain associated with injury or disease. Up to 88% of patients with chronic pain have other comorbidities such as depression, cardiovascular and pulmonary diseases, diabetes mellitus, and cancer. Untreated chronic pain can seriously affect the quality of life of patients. During the pandemic risk factors for pain morbidity and mortality have been amplified. There is evidence that COVID-pain is associated with myalgias, referred pain, and widespread hyperalgesia.

It is important for the treatment of chronic pain to ensure continuity of care and pain drugs application and modifying multimodal pain therapy to avoid the risk of COVID-19 infection. Telemedicine can be a good way to help patients suffering from various painful conditions during a pandemic.

Key words: COVID-pain, chronic pain, pain therapy, telemedicine

Introduction

The pain has a multidimensional, complex dimension: it is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors. The pain therapy is globally very important due to fact that the pain is a major health, economic and social problem, as it impairs the quality of life (QoL) of patients with frequent development of chronic pain syndrome (40%) (1).

Since the end of 2019, the Coronavirus Disease 2019 (COVID-19) was declared a pandemic by the World Health Organization (WHO) and has become a global health threat. The COVID-19 pandemic forced healthcare systems worldwide to redistribute healthcare resources toward intensive care units and other Covid-19 dedicated sites (2).

In the time of the COVID-19 pandemic, healthcare pain therapy professionals face two problems: first, patients who have pain as part of the COVID-19 infection, and second, patients who have already had some kind of chronic pain syndrome. Treatment of pain is a basic human right, but the COVID-19 pandemic has forced the health care systems around the world to reallocate health resources to treat COVID-19 positive patients (1).

The COVID-19 pandemic has changed people's lifestyles, affected the lives of people worldwide and reduced person-to-person contact. Patients tend to stay away from hospitals due to fear of infection, so that untreated acute pain can progress to chronic pain, increasing the risk of disability, negative ideas and depressive status. The isolation of the patient due to the COVID-19 pandemic leads to greater stress and anxiety, which may lead to exacerbation of symptoms not only related to COVID-19, but also worsen pain symptoms and general clinical condition (2).

COVID-pain

Available the WHO reports suggest that pain is a common symptom during infection with the new Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2). These COVID-pain-related symptoms primarily include: muscle pain (myalgia) and/or joint pain (arthralgia) -14.8%, sore throat -13.9% and headache -13.6% (4). Pain can be an early symptom of COVID-19 infection including myalgia/arthralgia, back pain, and headache. If the pain begins earlier, it can be more severe and widespread and become chronic. Intensity of the pain and widespread pain are related to the presence of pain at clinical presentation. The pain that accompanies COVID-19 may be due to the neurotropic action of the virus, the activation of nociceptive sensory neurons by cytokines and chemokines, direct affections of peripheral nerves and muscles, and autoimmune reactions having the potential to increase the incidence of chronic pain syndromes (5).

According to the recent research, potential mechanisms of COVID-pain (SARS-CoV-2/COVID-19-induced pain) occur due to activation of ACE2/RAS (angiotensin-converting enzyme 2/ renin–angiotensin system) pathway and the direct virus-induced damage. SARS-CoV-2 causes a strong inflammatory response with elevated

cytokine levels (IL-6, IL-10 and TNF α) are present, especially in patients with moderate or severe disease. Inflammasomes are a crucial part of the inflammatory cascade [37,38]. They are engaged in the production of proinflammatory cytokines (6). Calcitonin generelated peptide (CGRP) has a crucial role in the pathogenesis of neuropathic pain and possibly to direct a nociceptive transmission (5).

Pain in intensive care unit (ICU) patients can be associated with viral disease itself (myalgia, arthralgia, peripheral neuropathies), may be caused by continuous pain and discomfort associated with ICU treatment, intermittent procedural pain and chronic pain present before the admission to the ICU. Undertreatment of pain in ICU patients may trigger delirium and cause peripheral neuropathies (5). It is recommended that, in patients in ICU who are unable to self-report pain, behavioral pain assessment scales should be used: the Behavioral Pain Scale (BPS) and the Critical Care Pain Observation Tool (CPOT). Optimal analgo-sedation strategy in the critically ill should achieve effective analgesia, targeted sedation and reduced risk of delirium and agitation (6).

Chronic pain

Chronic pain is a prevalent condition worldwide and causes suffering, limitation of daily activities and reduced quality of life (QoL) of affected patients. Between 13 and 47% of the population is affected by chronic pain. With the aging of our population, the prevalence of chronic pain in older patients is increasing (7). Chronic pain is a real "disease" associated with multiple adaptations in the nervous, endocrine, and immune systems. According to the 11th International Classification of Diseases (ICD-11), chronic pain can be classified into seven categories: primary, cancer related, post-traumatic and postsurgical, neuropathic, visceral, musculoskeletal, and headache/orofacial (8). Multi-morbidity is independently associated with chronic pain. Pain is also associated with arthritis, bone and joint disorders, myofascial disorders, cancers, neurological disorders, depression and other chronic disorders (7).

Adequate chronic pain management has a moral and ethical imperative, but also mitigates against further physical and psychological complications. Untreated chronic pain can cause cognitive, affective, and emotional disorders in chronic pain patients and can induce immunosuppression in some patients (9).

Healthcare systems across the world are engaged in limiting the spread of COVID -19 infection. The social and economic consequences of the COVID pandemic may have negative impact on pain and the care of chronic pain patients. As a result of that, all pain management services have been postponed or cancelled, including outpatient procedures and patient visits, and all elective surgical procedures. Many technical solutions have been utilized for remote assessment and treatment of chronic pain. Telephone consultation is the first and low-cost example of telemedicine for remote treatment of pain (7).

Pain therapy

During the COVID 19, multimodal analgesia, or the concurrent use of multiple medications employing different mechanisms of action, has been associated with improved analgesia with fewer side effects. It is important for the pain treatment to ensure continuity of care and pain drugs application and modifying pain therapie to avoid the risk of COVID-19 infection. The pain treatments often differ according to the personal experiences and preferences of the practitioners (10).

Nonopioids

Non-steroidal anti-inflammatory drugs (NSAID) perform their analgesic effect primarily through peripheral inhibition of prostaglandin synthesis by acting on the cyclo-oxygenase enzyme (COX-1 and COX-2). There are some physicians that advise against the use of ibuprofen or other NSAIDs, based on the assumption that its use may increase the severity of COVID-19 disease (11). This was based on the assumption that NSAIDs could increase the levels of ACE and mask early symptoms of the disease such as fever and myalgias. Discontinuation of prescribed NSAIDs for chronic pain conditions is not recommended at this time. Acetaminophen (paracetamol) has been proposed as an alternative to NSAID use, but there are also issues with acetaminophen toxicity in high doses. It can also be synergistically combined with other analgesic drugs (10).

Opioids

Opioids are cough suppressants, and may mask or delay the initial presenting symptoms of COVID-19 infection. Lethargy, nausea, and gastrointestinal symptoms that are associated with COVID-19 infection could be worsened by prescribed opioids. Chronic opioid therapy may lead to opioid induced immune-suppression in some patients. The effects of opioids on the immune system depend on the type of opioid, dose, nature of immunity, and the patient's situation. Opioids with minimal immunosuppressive characteristics should be used. Buprenorphine is highly recommended, tramadol and oxycodone can be used as the second option, while morphine and fentanyl are not recommended due to side effects and addiction potential (9).

Gabapentinoids

Peripheral nervous system involvement, including painful neuropathies, was reported in many patients with SARS-CoV-2 infection. Gabapentin and pregabalin are calcium channel α2-δ ligands commonly used in the treatment neuropathic pain. Peripheral neuropathies are prevalent in COVID-19 patients and may require an addition of gabapentinoids to the pain treatment regime. Calcium channel ligands reduce respiratory drive and combined therapy with opioids might be potentially hazardous (10).

Interventional pain procedures

Interventional pain procedures are typically minimally invasive procedures that, when appropriately indicated, relieve acute and chronic pain as well as minimize the

use of analgesics and are often performed on an outpatient basis. In order to minimize the number of people attending hospitals, many hospitals have limited or stopped the number of elective interventional procedures being performed (11).

Telemedicine

Telemedicine is defined as telecommunications and electronic exchange information through various platforms and different communication methods (12). Many colleagues in pain clinics are starting with telephone or telemedicine consultations instead of routine outpatient-based consultations. The patient should be present at the first examination, while the telemedicine method could be used for subsequent consultations or control examinations. Telemedicine has become an effective way of providing necessary medical services to patients with chronic pain during the COVID-19 epidemic that provides ongoing services to patients: assessments, treatment, and follow-up. Tele-consultation in patients with rural background may not be practical due to issues pertaining to education, network, etc. (13).

Conclusion

The COVID-19 pandemic situation has changed people's lifestyles. At the pandemic time, it is important for the multimodal treatment of chronic pain to ensure continuity of care and pain drugs application; use of telemedicine; and modifying therapy to avoid the risk of COVID-19 infection. For the treatment of pain, each patient requires an individual approach based on available knowledge, the patient's condition and comorbidities.

References

1. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. 2020;161(9):1976-1982.
2. Puntillo F, Giglio M, Brienza N, Viswanath O, Urits I, Kaye AD, et al. Impact of COVID-19 pandemic on chronic pain management: Looking for the best way to deliver care. Best Practice & Research Clinical Anaesthesiology. 2020; (34): 529-537.
3. Cascella M, Del Gaudio A, Vittori A, Bimonte S, Del Prete P, Forte CA, et al. COVID-Pain: Acute and Late-Onset Painful Clinical Manifestations in COVID-19 – Molecular Mechanisms and Research Perspectives. Journal of Pain Research 2021;14: 2403–2412.
4. Murat S, Karatekin BD, Icagasioglu A, Ulasoglu C, Icten S, Incealtin O. Clinical presentations of pain in patients with COVID-19 infection. Ir J Med Sci. 2021;190(3):913-917. doi:10.1007/s11845-020-02433-x.
5. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Miao X, Li Y, Hu B. Neurologic Manifestations of Hospitalized Patients With Coronavi-

rus Disease 2019 in Wuhan, China. JAMA Neurol. 2020;77(6):683-690.
6. Mangalmurti N, Hunter CA. Cytokine storms: understanding COVID-19. Immunity 2020;53(1):19-25.
7. Piraccini E, Byrne H, Taddei S. Chronic pain management in COVID-19 era. J Clin Anesth. 2020;65:109852. doi: 10.1016/j.jclinane.2020.109852.
8. Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. A classification of chronic pain for ICD-11. Pain. 2015;156(6):1003-1007.
9. El-Tallawy SN, Nalamasu R, Pergolizzi JV, Gharibo C. Pain Management During the COVID-19 Pandemic. Pain Ther. https://doi.org/10.1007/s40122-020-00190-4.
10. Eccleston C, Blyth FM, Dear BF, Fisher EA, Keefe FJ, Lynch ME, Palermo TM, Reid MC, Williams ACC. Managing patients with chronic pain during the COVID-19 outbreak: considerations for the rapid introduction of remotely supported (eHealth) pain management services. Pain. 2020;161(5):889-893.
11. Lo Bianco G, Papa A, Schatman ME, Tinnirello A, Terranova G, Leoni MLG, Shapiro H, Mercadante S. Practical Advices for Treating Chronic Pain in the Time of COVID-19: A Narrative Review Focusing on Interventional Techniques. J J. Clin. Med. 2021; 25;10(11):2303. doi: 10.3390/jcm10112303.
12. Ghai B, Malhotra N, Singh Bajwa SJ. Telemedicine for chronic pain management during COVID-19 pandemic. Indian J Anaesth. 2020; 64(6): 456-462.
13. Zachrison KS, Boggs KM, Hayden EM, Espinola JA, Camargo CA Jr. Understanding barriers to telemedicine implementation in rural emergency departments. Ann Emerg Med. 2020;75:392–9.

Novi pristupi u lečenju hroničnog kancerskog bola

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Apstrakt

Bol je peti vitalni znak u kliničkoj medicini, time je značaj terapije istog nesporan. Hronični kancerski bol predstavlja poseban entitet, time je i terapija istog za sve one stručnajke koje se svakodnevno susreću sa ovom vrstom pacijenata, kompleksna i izazovna kako u godinama iza, tako i u budućnosti. Koncept "kancer preživelih" iako po definiciji robustan, predstavlja onkološku stvarnost. Zahvaljujući nepretku u svim onkološkim terapijskim modalitetima, broj ovih pacijenata će i dalje biti u porastu što nam daje obavezu da terapiju hroničnog kancerskog bola svakodnevno unapređujemo. Opioidi su i dalje osnovni terapijski izbor za lečenje jakog hroničnog kancerskog bola. U Republici Srbiji izbor "novih" opioidnih analgetika je dobar. Međutim upotreba istih je još uvek na niskom nivou, najviše zbog i dalje prisutnog fenomena opiofobije. Razumevanje patofiziološkog mehanizma hroničnog kancerskog bola je kompleksno ali izvodljivo. Uz razumevanje istog, izbor terapije opioidima je lakši, a posebno ukoliko se stručnjaci iz ove oblasti opredele za neki od najnovijih vodiča terapije hroničnog kancerskog bola. Savremeni princip 5 As koji je predložila NCCN 2019.g. put je ka pravilnom terapijskom izboru. Primena četvorostepene skale u oceni i terapiji bola u odnosu na raniju trostepenu koju je dala SZO, je takođe put ka efikasnijoj analgeziji. Kontraverze u savremenom pristupu lečenju kancerskog bola postoje u vezi primene kanabinoida, pri čemu su poslednje preporuke protiv primene istih. Dokazano je da morfin i drugi opioidi imaju različite efekte na imuni system i to uglavnom negativan. Bol sa druge strane takođe ima negativan uticaj na imunološki sistem čoveka pa time i njegovo prisustvo uslovno rečeno može dovesti do progresije karcinoma. U uslovima kada nemamo drugih izbora za lečenje jakog kancerskog bola, opioidi ostaju osnov istog. S tim u vezi nada u prevazilaženje ove vrste problema stoji u danas prisutnom razvijanju novih neopioidnih molekula.

Ključne reči: hroničan kancerski bol, opioidi, analgezija

Uvod

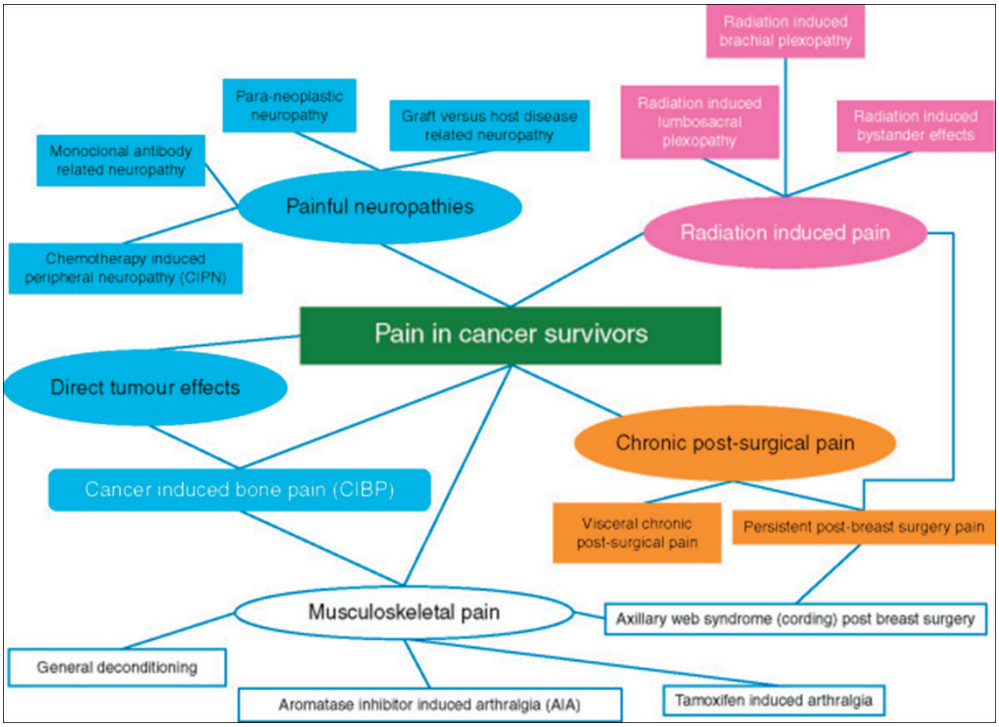
Uprkos poboljšanjima u razumevanju i lečenju hroničnog kancerskog bola, mnoge međunarodne i lokalno razvijene smernice i dalje navode da kod značajnog procenta onkoloških pacijenata bol nije adekvatno lečen. Poslednji objavljeni epidemiološki podaci od strane Svetske zdravstvene organizacije iz februara 2019.g pokazuju da su maligni tumori i dalje među vodećim uzrocima morbiditeta i mortaliteta širom sveta i bili su odgovorni za 18,1 milion novih slučajeva i 9,6 miliona smrtnih slučajeva godišnje. Bol oseća 55% pacijenata koji imaju dijagnostikivano neko od malignih oboljenja i 66% pacijenata koji imaju uznapredovalu, metastatsku ili terminalnu bolest. Hronični kancerski bol može izazvati psihološku patnju u obliku anksioznosti, depresije, straha ili osećaja beznađa, a anksioznost i depresija mogu zauzvrat da pogoršaju bol. Cilj upravljanja bolom je ublažiti bol do nivoa koji omogućava prihvatljiv kvalitet života (1-4). Pristup lečenju hroničnog kancerskog bola je veoma različit među lekarima, različitim nivoima zdravstvenih ustanova kao i na globalnom nivou između različitih. država. Međunarodna Komisija „Lancet“ čiji okvir delovanja je globalni pristup palijativnoj nezi sa posebnim osvrtom na terapiju hroničnog kancerskog bola, pozvala je zdravstvene sisteme i njihove lidere, uključujući akademike, da se pozabave takozvanom podelom u borbi protiv bolova od 10 do 90 – ako se zna da 10% najbogatijih zemalja poseduje 90% distribuiranog morfina -ekvivalentnih opioida (5).

Koncept „kancer preživeli“

Rano otkrivanje i napredak u onkološkom lečenju su izrazito poboljšani tokom poslednje četiri decenije. U tom vremenskom okviru i broj preživelih od karcinoma se povećao, te se procenjuje da u svetu živi preko 10 miliona “preživelih od karcinoma”. Transformacija u preživljavanju onkoloških bolesnika je upečatljiva; pacijenti sa dijagnostikovanim svim tipovima karcinoma 1971-72. imali su preživljavanje od 50% godinu dana nakon postavljanja dijagnoze, 2014. godine, jednogodišnje preživljavanje nakon postavljanja dijagnoze za sve tipove karcinoma se povećalo na 70,4%, a 10-godišnje preživljavanje nakon postavljanja dijagnoze iznosilo je 50 %. Iz perspektive definicije kancer preživeli i prisustva bola, definicija preživelih obuhvata period stadijum bolesti od postavljanja dijagnoze (kada je samo prisustvo tumora uzrok bola) preko stadijuma lečenja (koji takođe može da rezultira bolom), do stanja mirovanja ili izlečenja od bolesti (gde se često susreću uporni i na terapiju refraktorni oblici hroničnog kancerskog bola, najčešće neuropatskog porekla) (6). Kako se populacija preživelih od karcinoma širi, svim kliničarima, uključujući onkologe, lekare kućnog lečenja, specijaliste palijativne medicine i lekare primarne zdravstvene zaštite koji najčešće komuniciraju sa ovim pacijentima, biće potrebno novo znanje i veštine za implementaciju najboljih terapijskih rešenja za hronični kancerski bol. Pregled različitih uzroka bola kod „kancer preživelih“ pacijenata odnose na samu bolest i onkološki tretman. Patofiziologija

nastanka kancerskog bola je slabo shvaćena; međutim, nova laboratorijska istraživanja ukazuju na unakrsnu povezanost između aktivnosti kancerskih ćelija, imunološkog i nervnog sistema domaćina, kao važni potencijalni mehanizmi koji mogu biti široko relevantni za mnoge sindrome kancerskog bola (7). Uzroci kancerskog bola u „cancer survivors" su označeni na Slici 1.

Slika 1. Uzroci hroničnog kancerskog bola. (6)



Hroničan kancerski bol ne predstavlja jedan entitet. Obuhvata čitav niz etioloških, patofizioloških i anatomskih podtipova, a svi zahtevaju jedinstvenu deskriptivnu terminologiju, tehnike procene i modalitete lečenja. Reis-Pina sa saradnicima je prospektivno procenio adekvatnost terapije hroničnog kancerskog bola pomoću Pain Management Indeksa (PMI) kod 1802 pacijenata sa uznapredovalim/metastatskim solidnim tumorima u 110 onkoloških centara i odeljenja palijativnog zbrinjavanja ili hospisa, posebno posvećenih karcinomima i/ili lečenju hroničnog kancerskog bola. Studija je pokazala da su pacijenti i dalje klasifikovani kao potencijalno nedovoljno lečeni u 25,3% slučajeva (raspon 9,8% –55,3%) (8). Opioidi su osnovni lekovi za lečenje umereno jakog i jakog bola. Ostvaruju svoja dejstva vezivanjem za opioidne receptore (μ-mu, δ-delta i κ-kappa,) koji se nalaze u više regija mozga, kičmenoj moždini, ali i na perifernom nervnom sistemu. Zbog potencijalnih neželjenih dejstava ali i nepoznavanja osnovnih principa lečenja umerenog i jakog hroničnog kancerskog bola opiofobija je nažalost i

dalje visoko prisutna u svetu, posebno u zemljama u razvoju gde pripada i Republika Srbija. Upotreba opioida ili neupotreba predstavlja problem epidemioloških razmera i u SAD (9). Srbija se tradicionalno nalazi na niskom stepenu upotrebe opioida kao i većina zemalja u razvoju u odnosu na SAD, Centralnu Evropu, Englesku i Kanadu (10-12). Podaci globalne, nacionalne i regionalne upotrebe opioida data je studiji Chengsheng Ju sa saradnicima (Slika 2) (13).

Nemačka je na vrhu lestvice po upotrebi opijata, dok je procenat umrlih od eventualnih ozbiljnih neželjenih efekata najniži, postavlja se pitanje šta Nemačka radi bolje u odnosu na druge zemlje? U Nemačkoj postoji paradoks u povećanoj upotrebi opioida i smanjenju smrtnosti od predoziranja u odnosu na druge razvijene zemlje. To je postigla pažljivim odabirom i praćenjem pacijenata, boljim sistemom zdravstvene i socijalne zaštite, restriktivnijim merama zloupotrebe i pravilnom farmakološkom modulacijom bola (14).

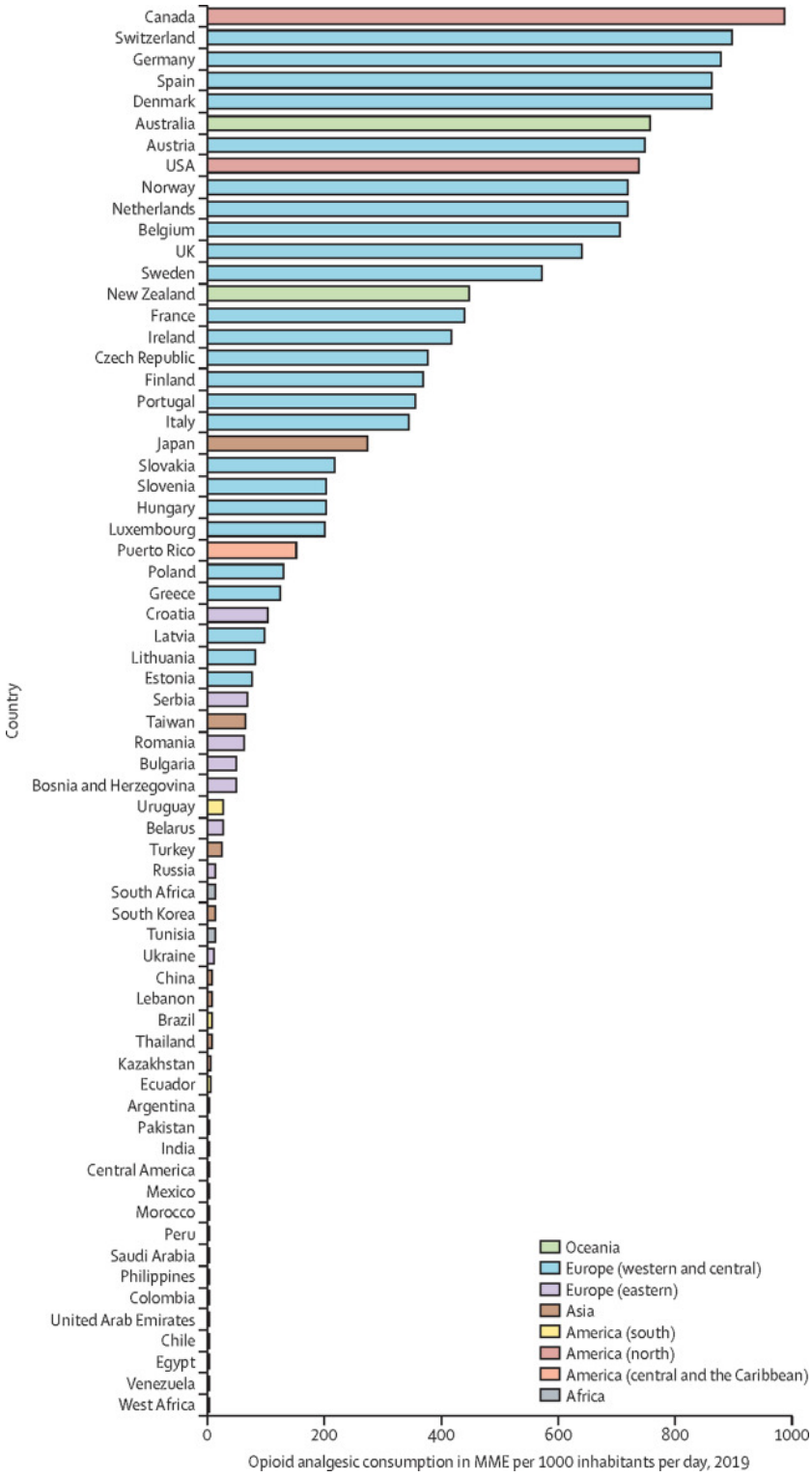
U svetu, prepreke u adekvatnom lečenju hroničnog kancerskog bola odnose se na nejednaku primenu vodiča i preporuka lečenja koje su predložile različite onkološke i anesteziološke međunarodne organizacije. Ovakve takozvane „barijere“ za pravilno lečenje kancerskog bola sveobuhvatno su predstavljene u Evropskom žurnalu (European Journal of Pain) 2019. godine (15). Navodi se da je kod najmanje trećine onkoloških pacijenata neadekvatna primena terapije kancerskog bola u toku primene specifičnog onkološkog lečenja ili je neadekvatna i odložena neophodna primena opioida. Preporuka 4 koju je izdala NCCN (National Comprehensive Cancer Network) 2020. godine u svojim vodičima za tretman hroničnog kancerskog bola, iako uopštena, ona je osnova svih ostalih preporuka sa stepenom preporuke IA, a ona glasi: Pacijenti treba da dobiju prilagođen multimodalni tretman koji smanjuje bol i njegov uticaj na svakodnevni život i koji može uključivati kombinaciju lekova, nefarmakoloških tretmana, onkoloških intervencija, fizičke rehabilitacije i psihosocijalne ili duhovne podrške (16). NCCN je još 2019. dao sledeću preporuku – Cilj upravljanja bolom je da se optimizuje ishod lečenja bola u 5 dimenzija, koje se često nazivaju „5 As“: Analgezija: optimizuje analgeziju (ublažavanje bola); Aktivnost: optimizuje aktivnosti svakodnevnog života (psihosocijalno funkcionisanje), Neželjeni efekti (Adverse effect): minimizirati neželjene događaje, Aberantno uzimanje lekova: izbegavati aberantno uzimanje lekova (ishodi povezani sa zavisnošću), Uticaj (Affect): odnos između bola i raspoloženja (17).

Da li je morfin još uvek „zlatni standard“ u lečenju jakog hroničnog kancerskog bola?

Opioidni receptori se nalaze u celom telu čoveka, zato su neželjeni efekti opioida u suštini samo opioidni efekti. Šta čini „idealnim“ opioidom za upotrebu?

- Pouzdana efikasnost – bioraspoloživost i farmakodinamika
- Minimalni neželjeni efekti – manji i ozbiljni
- Bezbedan metabolizam i eliminacija

Slika 2. Poređenje upotrebe opioidnih analgetika individualno po zemljama i regionima u 2019. MME - milligram morphine equivalent (13)



• Širok spektar puteva primene i dostupnih formulacija

Morfin međutim ne ispunjava sve ove kriterijume!(18)

Sa tim u vezi neophodno je napomenutu da se u savremenom pristupu lečenju kancerskog bola u Republici Srbiji nekoliko godina unazad koriste dva nova oblika opioidnih analgetika. Tapentadol koji je nov centralni analgetik sa dvostrukim mehanizmom dejstva: μ opioid receptor agonist i inhibitor ponovnog preuzimanja noradrenalina -NRI- ima opioid sparing efekat, smanjuje broj neželjenih dejstava (GI), obezbeđuje uravnoteženu analgeziju, lako je prilagodljiv i prihvatljiv pacijentima, efikasan je u različitim bolnim stanjima: akutni, hronični, postoperativni, maligni, nemaligni, neuropatski i nociceptivni bol. Niža stopa gastrointestinalnih neželjenih efekata i ukupni povoljan bezbednosni profil tapentadola u poređenju sa drugim opioidnim analgeticima mogu biti od prednosti kod pacijenata sa karcinomom koji često pate od mučnine, povraćanja, zatvora ili drugih događaja koji dodatno smanjuju kvalitet njihovog života (19). Potraga za odgovarajućim lekom, zasnovanim na mehanizmima razvoja opioid indukovanom disfunkcijom creva (opioid-induced bowel dysfunction – OIBD), dovela je do upotrebe kombinacije jakog opioida sa antagonistom opioidnih receptora u lečenju pacijenata sa hroničnim kancerskim bolom i konstipacijom. Nalokson pokazuje mnogo jači afinitet prema opioidnim receptorima u crevnom zidu nego oksikodon. Njegovo periferno delovanje dovodi do poboljšanja funkcije creva i smanjenja problema opstipacije. Pored toga, nalokson se skoro u potpunosti eliminiše u jetri, dok se aktivni oblik oksikodona apsorbuje u krvotok i njegovo centralno analgetičko dejstvo je neometano. Klinička istraživanja potvrđuju da nalokson ne smanjuje efikasnost oksikodona protiv bolova u lečenju kancerskog bola, kao i nekancerskog bola. Kombinacija oksikodona sa naloksonom ostaje efikasan analgetik u ovom mehanizmu, istovremeno pokazujući značajan povoljan uticaj na profilaksu i lečenje OIBD-a (20–22). Osnovne kontraindikacije za upotrebu oksikodona/naloksona su disfunkcija jetre, nefrolitijaza, paralitički ileus, druga opstruktivna i inflamatorna stanja creva, pankreatitis, dijareja i preosetljivost na sastojke preparata. Važno je napomenuti da je maksimalna dnevna doza oksikodona/naloksona 160/80 mg dnevno.

Da li su WHO analgetske stepenice još uvek važeće?

Uprkos debati i ažuriranjima „dijagrama" terapije bola „princip stepenica ili merdevina" iz 1986, njegova obrazovnu vrednost i prednosti koje proizilaze iz njegovog korišćenja širom sveta su nesporne. Međutim, proširenje njegove upotrebe na druge vrste terapije bola je naišao na neke prepreke. Mnogi stručnjaci iz oblasti terapije bola smatrali su da je početak korak po korak nedovoljan i neefikasan za kontrolu intenzivnog bola i stoga je predložen brzi dijagram koji počinje direktno od koraka 3. Adaptacija analgetičkih merdevina za akutni i hronični bol maligne i nemaligne etiologije koji je ponuđen zasniva se na istim principima kao i original korišćenja „merdevina"

u pristupu terapiji bola. Ova revizija integriše u princip „merdevina“ i četvrti korak te uključuje u razmatranje primenu neurohirurških procedura kao što su moždani simulatori, invazivne tehnike, kao npr. nervne blokade i neurolize (npr. fenolizacija, alkoholizacija, termokoagulacija i radiofrekvencija). Ovaj prilagođeni model takođe ima primenu u pedijatriji kao i primenu u urgentnim stanjima akutnih bolnih stanja (23).

Lečenje hroničnog kancerskog bola u eri moderne onkologije

Postoji nekoliko potencijalnih novih „targeta“ za lečenje kancerskog bola. TRV130 je novi ligand koji proizvodi analgeziju bez ozbiljnih nuspojava i podnošljivosti sličnu onoj morfinu. IBNTxA je još jedno jedinjenje koje može da posreduje u snažnoj analgeziji sa značajno manjim rizikom od respiratorne depresije i gastrointestinalnih efekata ili efekata sličnih lekovima. Intenzitet osećaja bola pokazuje dnevne varijacije, sa najmanjom percipiranom varijacijom tokom noćnih sati. Ovo otkriće je dovelo do studija koje su ispitivale upotrebu melatonina za lečenje bola, za koji se čini da ispoljava analgetička svojstva delujući na MT2 receptor koji se nalazi u dorzalnom rogu kičmene moždine i u više oblasti centralnog nervnog sistema. Kvetiapin je atipični antipsihotik koji se koristi za lečenje nekih psihijatrijskih stanja koji je takođe pokazao potencijalna analgetička svojstva na životinjskim modelima i koštanim metastazama. Densosumab (Prolia®) je prvi odobreni lek za lečenje kancerskog bola kod koštanih metastaza. Antitelo tanezumab potencijalni je novi analgetik za lečenje kancerskog bola porekla koštanih metastaza, on blokira aktivnost molekula koji signaliziraju bol a koji se zove neuralni faktor rasta (Nerve growth factor - NFG) (24).

Da li kanabis-bazirani medikamenti imaju ulogu u terapiji kancerskog bola?

Uprkos rastućem interesovanju, potencijalnim koristima, ograničeno istraživanje o efikasnosti medicinske marihuana (medical Marijuana – MMJ) za lečenje hroničnih simptoma povezanih sa karcinomom i dalje postoji. U SAD, pojedine države imaju Medicinski program kanabisa (Medical Cannabis Program - MCP) upućen delimično za pacijente sa hroničnim, iscrpljujućim bolom koji se ne mogu adekvatno ili bezbedno lečiti konvencionalnim farmaceutskim lekovima. MCP su jedinstveni, ne samo zato što omogućavaju pacijentima da sami upravljaju svojim tretmanom kanabisa, već zato što deluju u suprotnosti sa saveznim zakonom SAD, što ga čini izazovnim za istraživače da koriste konvencionalne istraživačke dizajne za merenje njihove efikasnosti. Do danas nijedna studija nije koristila randomizovano kontrolisano ispitivanje za merenje efekata MMJ (25). NCCN vodiči za kanabis medicinske proizvode i njihovu upotrebu, objavljeni su 2019. godine i revidirani poslednji put u martu 2021. godine. Prema tim vodičima predlaže se: Nemojte nuditi sledeće, za lečenje hroničnog bola kod odraslih: nabilon, dronabinol, THC (delta-9-tetrahidrokanabinol) i kombinaciju kanabidiola (CBD) sa THC-om. Nemojte nuditi CBD za lečenje hroničnog bola kod odraslih osim u okviru kliničkog ispitivanja (26).

Opioidni analgetici i imunologija karcinoma – prijatelji ili neprijatelji?

Dokazano je da morfin i drugi opioidi imaju različite efekte na imuni sistem. Da bismo razumeli njihov uticaj na biologiju karcinoma, moramo razumeti normalne interakcije između imunih i tumorskih ćelija. Privučene i aktivirane citokinima i hemokinima, citotoksične T ćelije (CD4, CD8) i NK ćelije „ubijaju" tumorske ćelije. Neke maligne ćelije mogu preživeti, ali sam rast tumora je inhibiran kontinuiranom imunološkom aktivnošću. Imunoselekcija („uređivanje") ili genetska nestabilnost dovodi do selekcije manje imunogenih tumorskih ćelija, koje mogu „pobeći". Citokini oslobođeni iz tumorskih ćelija i uključivanje inhibitornih imunih ćelija (kao što su Tregs ćelije) olakšava ćelijama tumora izbegavanje imunološke kontrole što dovodi do rasta tumora. Morfin (i drugi opioidi) mogu uticati na broj i funkciju imunih ćelija sa posledičnim inhibicijskim ili stimulativnim efektom na rast tumora i metastaziranje. Duža upotreba morfina povećava TGFb što dovodi do smanjenja IL-2 i IFNg posredovanog MOR. IL-2 je posebno važan u sazrevanju i diferencijaciji CD4þCD8þ ćelija i NK ćelijske aktivnosti, a samim tim i ovaj antiinflamatorni odgovor može dovesti do „promocije" ćelija tumora. Međutim, uporedni studije su sugerisale da određeni opioidi mogu biti manje imunoaktivni sa manje potencijalnih „štetnih efekata" koji utiču na imunološki nadzor tumorskih ćelija. Visoke stope prevalencije bola kod pacijenata sa karcinomom i odsustvo efikasnog alternativnog nonopioidnog režima, u mnogim slučajevima ostavljaju nas u dilemi. Napuštanje visoko efikasnih analgetika bez bilo kakve zamene je nehumano i time onemogućeno s obzirom na veoma značajan drugi dokazani mehanizam, odnosno negativan uticaj prisustva bola i stresa na imunološki sistem čoveka i time uticaj na progresiju karcinoma (27).

Zaključak

Hronični kancerski bol ostaje preovlađujući i jak za mnoge pacijente, posebno kod onih sa uznapredovalom bolešću. Efikasnost lečenja kancerskog bola u rutinskoj praksi malo se promenio u poslednjih 30 godina od objavljivanja pristupu terapiji bola od strane SZO. Postoji niz potencijalnih objašnjenja za ovo razočaravajuće stanje koje uključuje slabu procenu i klasifikaciju bola kod pacijenata sa karcinomom, sporo prevođenje osnovnih naučnih istraživanja u delotvorne kliničke intervencije, i posebno iz globalne perspektive, stanje gde zemlje u razvoju nemaju pristup jakim opioidima. Međutim, takođe je verovatno da će strategije za upravljanje kancerskim bolom koje se fokusiraju na promovisanje efikasnog ponašanja zdravstvenih radnika i pacijenata biti primenjivane i sprovođene sa istim prioritetom kao druge fiziološki zasnovane strategije. Davanje prioriteta povećanju samoefikasnosti i smanjenje interferencije kao primarni ishod u vidu numeričke ocene intenziteta bola, mogu omogućiti preciznije „upravljanje" bolom kod onkoloških pacijenata.

Konflikt interesa: Autori odbacuju mogućnost postojanja konflikta interesa.

Literatura

1. Fallon M, Giusti R, Aielli F, Hoskin P, Rolke R, Sharma M et al. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines. Ann Oncol 2018 Oct 1;29(Suppl 4):iv166-iv191.
2. Swarm RA, Paice JA, Anghelescu DL, Are M, Bruce JY, Buga S et al. Adult Cancer Pain, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2019 Aug 1;17(8):977-1007.
3. WHO Guidelines for the Pharmacological and Radio therapeutic Management of Cancer Pain in Adults and Adolescents [Internet]. [cited 26 December 2021]. Available from: www.who.int/publications/i/item/978924155039
4. Italian Association of Oncologistsd (AIOM). Lineguida sulla Terapia del Dolore in Oncologia [Guidelines on Cancer Pain Management] [Internet]. [cited 15 January 2022]. Available from: https://www.aiom.it/linee-guida-aiom-terapia-del-dolore-in-oncologia-2019
5. Knaul FM, Farmer PE, Krakauer EL, De Lima L, Bhadelia A, Jiang Kwete X et al. Alleviating the access abyss in palliative care and pain relief-an imperative of universal health coverage: the *Lancet* Commission report. Lancet 2018 Apr 7; 391(10128):1391-1454.
6. Brown M, Farquhar-Smith P. Pain in cancer survivors; filling in the gaps. Br J Anaesth 2017 Oct 1;119(4):723-736.
7. Cox-Martin E, Anderson-Mellies A, Borges V, Bradley C. Chronic pain, health-related quality of life, and employment in working-age cancer survivors. J Cancer Surviv 2020 Apr;14(2):179-187.
8. Reis-Pina P, Acharya A, Barbosa A, Lawlor PG. Episodic Cancer Pain: Patient Reporting, Prevalence, and Clinicodemographic Associations at Initial Cancer Pain Clinic Assessment. Pain Res Manag 2020 May 22;2020:6190862.
9. Han B, Compton WM, Blanco C, Crane E, Lee J, Jones CM. Prescription Opioid Use, Misuse, and Use Disorders in U.S. Adults: 2015 National Survey on Drug Use and Health. Ann Intern Med 2017 Sep 5;167(5):293-301.
10. Schubert I, Ihle P, Sabatowski R. Increase in opiate prescription in Germany between 2000 and 2010: a study based on insurance data. Dtsch Arztebl Int 2013 Jan;110(4):45-51.
11. Cooper AJM, Willis J, Fuller J, Benecke H, Leighton-Scott J, Andersohn F et al. Prevalence and Incidence Trends for Diagnosed Prescription Opioid Use Disorders in the United Kingdom. Pain Ther 2017 Jun;6(1):73-84.
12. Fischer B, Varatharajan T, Shield K, Rehm J, Jones W. Crude estimates of prescription opioid-related misuse and use disorder populations towards informing intervention system need in Canada. Drug Alcohol Depend 2018 Aug 1;189:76-79.
13. Ju C, Wei L, Man KKC, Wang Z, Ma TT, Chan AYL et al. Global, regional, and national trends in opioid analgesic consumption from 2015 to 2019: a longitudinal study. Lancet Public Health 2022 Apr;7(4):e335-e346.

14. Bosetti C, Santucci C, Radrezza S, Erthal J, Berterame S, Corli O. Trends in the consumption of opioids for the treatment of severe pain in Europe, 1990-2016. Eur J Pain 2019 Apr;23(4):697-707.
15. Bennett MI, Eisenberg E, Ahmedzai SH, Bhaskar A, O'Brien T, Mercadante S et al. Standards for the management of cancer-related pain across Europe-A position paper from the EFIC Task Force on Cancer Pain. Eur J Pain 2019 Apr;23(4):660-668.
16. Schatz AA, Oliver TK, Swarm RA, Paice JA, Darbari DS, Dowell D et al. Bridging the Gap Among Clinical Practice Guidelines for Pain Management in Cancer and Sickle Cell Disease. J Natl Compr Canc Netw 2020 Apr;18(4):392-399.
17. Swarm RA, Paice JA, Anghelescu DL, Are M, Bruce JY, Buga S et al. Adult Cancer Pain, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2019 Aug 1;17(8):977-1007.
18. Ahmedzai SH. Improving pain experience in cancer patients. J Pain Palliat Care Pharmacother 2014 Mar;28(1):49-50.
19. Galiè E, Villani V, Terrenato I, Pace A. Tapentadol in neuropathic pain cancer patients: a prospective open label study. Neurol Sci 2017 Oct;38(10):1747-1752.
20. Ahmedzai SH, Leppert W, Janecki M, Pakosz A, Lomax M, Duerr H et al. Long-term safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate-to-severe chronic cancer pain. Support Care Cancer 2015 Mar;23(3):823-30.
21. Sandner-Kiesling A, Leyendecker P, Hopp M, Tarau L, Lejcko J, Meissner W et al. Long-term efficacy and safety of combined prolonged-release oxycodone and naloxone in the management of non-cancer chronic pain. Int J Clin Pract 2010 May;64(6):763-74.
22. Löwenstein O, Leyendecker P, Lux EA, Blagden M, Simpson KH, Hopp M et al. Efficacy and safety of combined prolonged-release oxycodone and naloxone in the management of moderate/severe chronic non-malignant pain: results of a prospectively designed pooled analysis of two randomised, double-blind clinical trials. BMC Clin Pharmacol 2010 Sep 29;10:12
23. Ballantyne JC, Kalso E, Stannard C. WHO analgesic ladder: a good concept gone astray. BMJ 2016 Jan 6;352:i20.
24. Chwistek M. Managing Cancer Pain in an Era of Modern Oncology. Pract Pain Manag 2018;18(2).
25. Vigil JM, Stith SS, Adams IM, Reeve AP. Associations between medical cannabis and prescription opioid use in chronic pain patients: A preliminary cohort study. PLoS One 2017 Nov 16;12(11):e0187795.
26. Cannabis-based medicinal products. NICE guideline [NG144] [Internet]. [cited 25 January 2022]. Available from: https://www.nice.org.uk/guidance/ng144
27. Wigmore T, Farquhar-Smith P. Opioids and cancer: friend or foe? Curr Opin Support Palliat Care 2016 Jun;10(2):109-18.

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Regenerative medicine: Ushering in a new era in pain therapy

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Abstract

The concept of "regenerative medicine" was first used as a concept of musculoskeletal injuries in 1930. The term regenerative medicine encompasses several therapies including viscosupplementation, prolotherapy, platelet-rich plasma therapy (PRP), and stem cell therapy. The concept of treatments is similar. Still, mechanisms of reparative properties largely differ. Prolotherapy was one of the first methods used, mainly for tendon and ligament injuries treatment. With the technology advancement, regenerative medicine expanded to PRP and stem cell therapy. The number of indications for regenerative medicine treatments significantly increased and apart from musculoskeletal injuries, it is used for treatment of degenerative diseases, degenerative discs disease as well as other problems regarding spinal pathology. Ultrasound provides injection to the exact site of injury.

Key words: regenerative medicine; regeneration; viscosupplementation; platelet-rich plasma; stem cells

Introduction

Regenerative medicine is defined by the National Institutes of Health as "the process of creating living functional tissues to repair or replace tissue or organ function lost due to age, disease, damage, or congenital defects."(1) Regenerative medicine is a field that applies biological science principles to promote regeneration by delivering or replacing organs, cells, or tissues in an attempt to restore diseased and damaged tissues and whole organs. There are various methods such as viscosupplementation, stem cells, platelet-rich plasma, and prolotherapy in the treatment and management of chronic pain. As increasing evidence on regenerative medicine is generated, more interventional pain physicians are looking to use this field for pain-mediated peripheral sources via percutaneous means. (2)

Viscosupplementation

This includes the injection of hyaluronic acid (HA) into intra-articular space which restores the viscosity and elasticity of osteoarthritic synovial fluid. (3,4) HA plays an essential role in shock absorption, lubrication, and the viscoelastic nature of the synovial fluid.

Prolotherapy

The term „prolotherapy" first appeared in the medical literature during the mid-1950s and was described as a form of treatment for an „incompetent structures through the generation of new cellular tissue".(5,6) The idea of introducing an irritating substance to induce healing has been used since the time of Hippocrates.(7) The modern use of prolotherapy can be traced back to 1930.(8) Prolotherapy is the injection of a solution to rehabilitate an incomponent structure and promote sclerosis at the injection site.(9,10) Prolotherapy differs from other regenerative medicine techniques because injectate lacks a biological component. Proliferant solutions used in this form of treatment are hypothesized to induce collagen deposition through chemomodulation, as well as the „temporary neurolysis" of peripheral nociceptors through chemoneuromodulation. The possible mechanism is that modulation in this setting is mediated by multiple growth factors and cytokines.(11-13)

Although the exact proliferant used in prolotherapy often varies, all solutions, excluding chemotactic agents, have the universal effect of inciting local tissue irritation, which leads to an influx of inflammatory cells. Inflammation, being the first step in the wound-healing cascade, results in the end-product of fibroblast proliferation with the subsequent deposition of collagen. (14) The most commonly used injectate for prolotherapy is hypertonic dextrose which causes a stimulation of the body's inflammatory cascade. Osmotic agents act by dehydrating local cells to become antigenic.(15)

Platelet-rich plasma therapy

Platelet-rich plasma (PRP) releases bioactive proteins and stimulates the body's ability to heal due to its regenerative, analgesic, and anti-inflammatory properties. Initially used clinically in the fields of cardiothoracic and maxillofacial surgery in the late 1980s and early 1990s. PRP has since been adopted into the field of musculoskeletal medicine. (16) The concept behind its use as a nonsurgical treatment modality is to place it directly into areas of soft tissue pathology, via percutaneous injection, to facilitate tissue regeneration. Healing occurs secondary based on PRP's ability to augment the recruitment, proliferation, and differentiation of cells involved in the regeneration of injured tissue.(17,18) These actions are mediated by numerous growth factors and bioactive proteins secreted by PRP's platelets following activation, in a degranulation process. (19)

PRP by its strictest definition is an autologous sample of blood with a concentration of platelets above the physiological baseline.(16, 20). Due to variability in methods

of PRP preparations, there is no universal classification system. However, PRP is mainly categorized into two categories: leukocyte-rich PRP (LR-PRP) and leukocyte-poor PRP (LP-PRP). LR-PRP has neutrophil counts above baseline and thus is associated with proinflammatory effects.(21) Data suggests that LR-PRP is superior for tendinopathy, and LP-PRP is more effective for OA.(22,23)

Platelets are nuclear, cytoplasmatic fragments of megakaryocytes. The initial steps in the process of wound healing involve platelet activation, adhesion, and aggregation. After the activation phase, alpha granules in the platelets degranulate and release multiple growth factors and cytokines. PRP contains more than 300 growth factors and cytokines which are involved in cell proliferation, tissue remodeling, enhancement of mitogenesis, extracellular matrix synthesis, mesenchymal differentiation, and suppressing inflammation which play an important role in wound healing. (24) Some of the growth factors and cytokines include PGDF-AA, TGF-B1, IGF-1, VEGF, EGF, IL-1, and many more. PRP delivers supraphysiologic concentrations of these molecules to an injury site to promote tissue remodeling, repair, and regeneration.(25)

Mesenchymal stem cells (MSCs)

Adult tissues often can repair and regenerate the following injury. To date, the exact mechanism of repair is poorly understood; however, it is hypothesized that it occurs through the proliferation and differentiation of cells that ultimately restore tissue functionality. One possible explanation is found within nonhematopoietic progenitor cells found in pathological tissue, as well as cell reservoirs at other locations, which may help to provide this reparative capability. (26) These regenerative-capable cells are commonly referred to as mesenchymal stem cells (MSCs), or bone marrow stromal cells. (27) MSCs are purported to be multipotent cells, with the capability of replicating as an undifferentiated cell (28) and also multilineage differentiation in response to local cell signaling pathways. (29-32)

Bone marrow was the first location from which stem cells were isolated. Since that time stem cells have been found in a variety of tissue types including adipose (33-35) and synovium, among others. (36) Differences in marker gene expression between marrow-derived MSCs and MSCs from other sources have been demonstrated. However, the effects of these differences have not been fully delineated. (37) Conflicting evidence currently exists regarding the differentiation efficacy of MSCs obtained from different stem cells reservoirs, such as marrow and adipose tissue. (37,38) In addition, there is controversy surrounding the quality of stem cells derived from bone marrow or adipose MSCs concerning growth kinetics, cell senescence, and multilineage differentiation potential. These differences in MSCs and mesenchymal-like cells prompted the International Society for Cellular Therapy to create criteria for MSCs based on surface marker expression, activity in culture, as well as differentiation potential. (39)

Evidence suggests that in response to injury, MSCs are first mobilized from perivascular niches into the peripheral circulation. (40-42) with subsequent migration

into damaged tissues. Although the exact reparative mechanism of MSCs is uncertain, early evidence suggested that these cells may differentiate into naïve cells of the injured tissue. More recent evidence suggests MSCs may also induce healing through a paracrine-like effect. This includes the mobilization of MSCs to specific injured tissues, followed by the ability for these reparative cells to secrete bioactive factors that induce a regenerative microenvironment known as "trophic activity." (43)

The indications for MSCs vary depending on the harvest site. Sources of MSCs include bone marrow, adipose tissue, umbilical cord, skeletal, muscle, peripheral blood, and amniotic fluid. (44) Specific indications for bone-marrow-derived MSCs include treatment of osteonecrosis of the femoral head and OA of the shoulder. It can also be used for rotator cuff and patellar tendinopathy. Adipose-derived MSCs can be used for lateral epicondylitis and Achilles tendinopathy. Amniotic-derived MSCs can be used in the treatment of plantar fasciitis.

Contraindications

Contraindications differ depending on the regenerative medicine method that is employed. General contraindications include active infection, either systematic or at the injection site, and coagulopathy.(45) Therapy-specific contraindications include venous stasis, Hylan allergy, and allergy to eggs for viscosupplementation, as some of the products are derived from rooster combs.(17) Stem cell therapy should be avoided in patients with bone marrow-derived cancers or immunocompromised states.(46)

Absolute contraindications of PRP administration are critical thrombocytopenia, platelet dysfunction syndrome, and hemodynamic instability. Relative contraindications include bone or blood cancer, anemia, regular nonsteroidal anti-inflammatory drugs use within 48 hours of the procedure, corticosteroid injection of the knee within one month, or systemic steroid use within two weeks. Absolute contraindications for prolotherapy include active rheumatological disorders, corn allergy, or immunosuppressive therapy. (10)

Complications

Regenerative therapy is generally well tolerated. The most common side effects are injection site swelling, pain or soreness, or stiffness. (47,48) Therapy-specific complications include haemarthrosis, septic arthritis, seizures, pulmonary embolism, and anaphylactic reaction. However, these more severe side effects are extremely rare. Stem cell therapy is well tolerated, with most patients reporting satisfaction with the procedure. Other reported side effects include low-grade fevers. (49,50)

Complications of PRP injections are extremely rare. Since it is an autologous product, the chance of having an allergic or immune reaction is non-existent. The most common side effect includes local site infection and pain at the injection site. Historically, bovine thrombin serves as an activator in some commercially available PRP kits. It

carries a potential risk of coagulopathy. When bovine thrombin is used as an activator, patients develop antibodies to bovine factor V and bovine thrombin itself. When factor V level decreases below 30%, the risk of hemorrhage increases in patients; for this reason, autologous thrombin or recombinant human thrombin is available as an activator.

Rare adverse effects of prolotherapy include sleep disturbance, radicular pain, irregular menstruation, and lumbar puncture headache. Other even rarer effects include meningitis, adhesive arachnoiditis, and encephalomyelitis. (51,52)

Conclusion

Regenerative medicine is a intriguing concept in the field of pain medicine. Focused research is needed to better understand the indications for regenerative technologies in the treatment of painful conditions. In vitro and animal studies are needed to explain cellular mechanisms by which regenerative agents lead to improvement in pain states. There is also a need for ongoing clinical trials including randomized sham or placebo-controlled trials, comparative effectiveness studies, and assessments of the influence of regenerative treatments on health service utilization.

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References

1. National Institutes of Health. Fact sheet: Regenerative medicine. 2010. Available at: https://report.nih.gov/nihfactsheets/Pdfs/RegenerativeMedicine(NIBIB).pdf
2. Centeno CJ, Busse D, Kisiday J, et al: Increased knee cartilage volume in degenerative joint disease using percutaneously implanted, autologous mesenchymal stem cells. Pain Physician 2008; 11:343-353.
3. Henrotin Y, Raman R, Richette P, Bard H, Jerosch J, Conrozier T, Chevalier X, Migliore A. Consensus statement on viscosupplementation with hyaluronic acid for the management of osteoarthritis. Semin Arthritis Rheum. 2015;45:140-9.
4. Balazs EA, Denlinger JL. Viscosupplementation: a new concept in the treatment of osteoarthritis. J Rheumatol Suppl. 1993; 39:3-9.
5. Hackett GS: Ligament and Tendon Relaxation Treated by Prolotherapy (Ed5). Springfield, IL, Charles C. Thomas Publisher, 1991.
6. Linetsky F, Trescot A, Manchikanti L: Interventional Techniques in Chronic Non-Spinal Pain: Regenerative Injection Therapy. ASIPP Publishing Group, 2009, pp 87-98.
7. Mooney V: Prolotherapy at the fringe of medical care, or is it the frontier? Spine J 2003; 3:253-254.
8. Linetsky S-H: Prolotherapy, in Wallace M, Staats P (eds): Pain Medicine and Management: Just the Facts. New York, McGraw-Hill Companies, 2004, pp 318-324.
9. Dagenais S, Yelland MJ, Del Mar C, Schoene ML. Prolotherapy Injections for chronic low-back pain. Cochrane Database Syst Rev. 2007; CD004059.

10. Siadat AH, Isseroff RR. Prolotherapy: Potential for the Treatment of Chronic Wounds? Adv Wound Care (New Rochelle). 2019; 8: 160-167.
11. Linetsky F, Botwin K, Torres F, et al: Position paper of the Florida Academy of Pain Medicine on regenerative injection therapy: effectiveness and appropriate usage. Pain Clin 2002; 4:38-45.
12. Reeves KD, Hassanein K: Randomized, prospective, placebo-controlled double-blind study of dextrose prolotherapy for osteoarthritic thumb and finger (DIP, PIP, and trapeziometacarpal) joints: evidence of clinical efficacy. J Altern Complement Med 2000; 6:311-320.
13. Wilkinson HA: Injection therapy for enthesopathies causing axial spine pain and the "failed back syndrome": A single blinded, randomized and cross-over study. Pain Physician 2005; 8:167-173.
14. Banks AR: A rationale for prolotherapy. J Orthop Med 1991; 13:54-59.
15. Yelland MJ, Del Mar C, Pirozzo S, et al: Prolotherapy injections for chronic low back pain: a systematic review. Spine 2004; 29:2126-2133.
16. Engerbretsen L, Steffen K, Alsousou J, et al: IOC consensus paper on the use of platelet-rich plasma in sports medicine. Br J Sports Med 2010; 44:1072-1081.
17. Foster TE, Puskas BL, Mandelbaum BR, et al: Platelet-rich plasma: from basic science to clinical applications. Am J Sports Med 2009; 37: 2259-2272.
18. Anitua E, Andia I, Ardanza B, et al: Autologous platelets as a source of proteins for healing and tissue regeneration. Thromb Haemost 2004; 91:4-15.
19. Marx RE: Platelet-rich plasma: evidence to support its use. J Oral Maxillofac Surg 2004; 62:489-496.
20. Hall MP, Band PA, Meislin RJ, et al: Platelet-rich plasma: current concepts and applications in sports medicine. J Am Acad Orthop Surg 2009; 17:602-608.
21. Dragoo JL, Braun HJ, Durham JL, Ridley BA, Odegaard JI, Luong R, Arnoczky SP. Comparison of the acute inflammatory response of two commercial platelet-rich plasma systems in healthy rabbit tendons. Am J Sports Med. 2012; 40:1274-81.
22. Fitzpatrick J, Bulsara M, Zheng MH. The Effectiveness of Platelet-Rich Plasma in the Treatment of Tendinopathy: A Meta-analysis of Randomized Controlled Clinical Trials. Am J Sports Med. 2017;45:226-233.
23. Braun HJ, Kim HJ, Chu CR, Dragoo JL. The effect of platelet-rich plasma formulations and blood products on human synoviocytes: implications for intra-articular injury and therapy. Am J Sports Med. 2014;42:1204-10.
24. Coppinger JA, Cagney G, Toomey S, Kislinger T, Belton O, McRedmond JP, Cahill DJ, Emili A, Fitzgerald DJ, Maguire PB. Characterization of the proteins released from activated platelets leads to localization of novel platelet proteins in human atherosclerotic lesions. Blood. 2004;103:2096-104.
25. El-Sharkawy H, Kantarci A, Deady J, Hasturk H, Liu H, Alshahat M, Van Dyke TE. Platelet-rich plasma: growth factors and pro- and anti-inflammatory properties. J Periodontol. 2007;78:661-9.

26. Pittenger MF, Mackay AM, Beck SC, et al: Multilineage potential of adult human mesenchymal stem cells. Science 1999; 284:143-147.
27. Fong EL, Chan CK, Goodman SB: Stem cell homing in musculoskeletal injury. Biomaterials 2011; 32:395-409.
28. Grigolo B, Lisignoli G, Desando G, et al: Osteoarthritis treated with mesenchymal stem cells on hyaluronan-based scaffold in rabbit. Tissue Eng C Methods 2009; 15:647-658.
29. Prockop DJ, Gregory CA, Spees JL: One strategy for cell and gene therapy: harnessing the power of adult stem cells to repair tissues. Proc Natl Acad Sci USA 2003 (suppl11); 100:11917-11923.
30. Woodbury D, Schwarz EJ, Prockop DJ, et al: Adult rat and human bone marrow stromal cells differentiate into neurons. J Neurosci Res 2000; 61:364-370.
31. Meliga E, Strem BM, Duckers HJ, et al: Adipose-derived cells. Cell Transplant 2007;16:963-970.
32. Minguell JJ, Conget P, Erices A: Biology and clinical utilization of mesenchymal progenitor cells. Braz J Med Biol Res 2000; 33:881-887.
33. Nelson L, Fairclough J, Archer CW: Use of stem cells in the biological repair of articular cartilage. Expert Opin Biol Ther 2010; 10:43-55.
34. Lee RH, Kim B, Choi I, et al: Characterization and expression analysis of mesenchymal stem cells from human bone marrow and adipose tissue. Cell Physiol Biochem 2004; 14:311-324.
35. Gimble JM, Katz AJ, Bunnell BA: Adipose-derived stem cells for regenerative medicine. Circ Res 2007; 100:1249-1260.
36. Barry FP, Murphy JM: Mesenchymal stem cells: clinical applications and biological characterization. Int J Biochem Cell Biol 2004; 36:568-584.
37. Im GI, Shin YW, Lee KB: Do adipose tissue-derived mesenchymal stem cells have the same osteogenic and chondrogenic potential as bone marrow-derived cells? Osteoarthritis Cartilage 2005; 13:845-853.
38. De Ugarte DA, Morizono K, Elbarbary A, et al: Comparison of multi-lineage cells from human adipose tissue and bone marrow. Cells Tissues Organs 2003; 74:101-109.
39. Dominici M, Le Blanc K, Mueller I, et al: Minimal criteria for defining multipotent mesenchymal stromal cells. The international society for cellular therapy position statement. Cryotherapy 2006; 8:315-317.
40. Mansilla E, Marín GH, Drago H, et al: Bloodstream cells phenotypically identical to human mesenchymal bone marrow stem cells circulate in large amounts under the influence of acute large skin damage: New evidence for their use in regenerative medicine. Transplant Proc 2006; 38:967-969.
41. Ramírez M, Lucia A, Gómez-Gallego F, et al: Mobilisation of mesenchymal cells into blood in response to skeletal muscle injury. Br J Sports Med 2006; 40:719-722.

42. Zannettino AC, Paton S, Arthur A, et al: Multipotential human adipose-derived stromal stem cells exhibit a perivascular phenotype in vitro and in vivo. J Cell Physiol 2008; 214:413-421.
43. Caplan AI: Adult mesenchymal stem cells for tissue engineering versus regenerative medicine. J Cell Physiol 2007; 213:341-347.
44. Medical Advisory Secretariat. Intra-articular viscosupplementation with hylan g-f 20 to treat osteoarthritis of the knee: an evidence-based analysis. Ont Health Technol Assess Ser. 2005;5:1-66.
45. Chahla J, Mannava S, Cinque ME, Geeslin AG, Codina D, LaPrade RF. Bone Marrow Aspirate Concentrate Harvesting and Processing Technique. Arthrosc Tech. 2017;6:e441-e445.
46. Jain NK, Gulati M. Platelet-rich plasma: a healing virtuoso. Blood Res. 2016;51:3-5.
47. Buchanan BK, DeLuca JP, Lammlein KP. Technical Innovation Case Report: Ultrasound-Guided Prolotherapy Injection for Insertional Achilles Calcific Tendinosis. Case Rep Orthop. 2016; 1560161.
48. Vangsness CT, Farr J, Boyd J, Dellaero DT, Mills CR, LeRoux-Williams M. Adult human mesenchymal stem cells delivered via intra-articular injection to the knee following partial medial meniscectomy: a randomized, double-blind, controlled study. J Bone Joint Surg Am. 2014;96:90-8.
49. Poulos J. The limited application of stem cells in medicine: a review. Stem Cell Res Ther. 2018;9:1.
50. Zehnder JL, Leung LL. Development of antibodies to thrombin and factor V with recurrent bleeding in a patient exposed to topical bovine thrombin. Blood. 1990;76:2011-6.
51. Hunt WE, Baird WC. Complications following injection of sclerosing agent to precipitate fibro-osseous proliferation. J Neurosurg 1961;18:461-5.
52. Schneider RC, Williams JJ, Liss L. Fatality after injection of sclerosing agent to precipitate fibro-osseous proliferation. J Am Med Assoc. 1959;170:1768-72.

Analgesics and endurance sports – painful dilema

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Abstract

Endurance sports are characterized by repeated isotonic contractions of sizeable skeletal muscle groups, the main factor for muscle damage and soreness. Muscle soreness and pain are among the least welcome side effects of exercise. Removing that pain can significantly facilitate exercise, allow sports activity to last longer and affect recovery after exercise. In addition to the use of analgesics in the treatment of pain, analgesics are increasingly common to improve sports performance. This paper points out the dilemmas of using analgesics in endurance sports. Most NSAIDs, especially Ibuprofen, are "over the counter" drugs and can be bought without a prescription. Ergogenic effects of all analgesics used in endurance sports are controversial because some studies show different results. Besides the potential ergogenic effect, the most significant advantage of using aspirin in endurance sports is that aspirin significantly reduces the risk of adverse cardiac events. When applied in recommended doses, acetaminophen does not induce typical NSAID gastrointestinal side effects but can induce severe liver damage in higher doses. Studies demonstrate that the ergogenic effect of acetaminophen depends on the timing of ingestion and dosage. Tramadol is a potent drug, but recent evidence suggests a high risk of abuse and dependence abuse among athletes. By consuming a mixture of these analgesics, athletes might be seeking a possibly dangerous ergogenic advantage, which may compromise their health and other competitors' safety, so special attention is needed.

Key words: muscle soreness, ergogenic, analgetics, endurance

Introduction

Endurance sports are characterised by repeated isotonic contractions of sizeable skeletal muscle groups. Typical examples include running, swimming and cycling

among summer sports, and cross-country skiing or speed skating among winter sports. From a physiological point of view, endurance exercise is typically performed at a submaximal intensity to move the anaerobic threshold progressively. (1) Repeated isotonic contractions are the main factor for muscle damage and muscle soreness, which is an entity of ultrastructural muscle damage. (2) Clinical signs include impaired muscular force capacities, painful restriction of movement, stiffness, swelling, and altered biomechanics in adjacent joints. (3) Early-onset muscle soreness is one of the least welcome side effects of exercise, but the pain signals that some tissue irritation or damage has occurred. Masking that pain can lead to a more severe injury. On the other hand, removing pain can significantly facilitate exercise, allow sports activity to last longer and affect recovery after exercise. In sports, the prescription of analgesics by a trained sports physician is a common clinical practice aimed at attenuating the pain derived from sport-related injuries. However, growing evidence points toward the intended use of analgesics to increase exercise performance. (4) In this regard, some athletes use over-the-counter pain killers and other analgesic drugs without injury to increase their physical capacity via increased pain tolerance. (5)

Previous studies have shown that the use and abuse of analgesics in sports are frequent and possibly dangerous (6, 7) and that the incidence and severity of electrolyte disturbances (8,9), gastrointestinal (10) and renal adverse events (11) during and after racing double after taking analgesics. This paper points out the dilemmas of using analgesics in endurance sports.

Ibuprofen, Aspirin and NSAIDs

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID), which non-selectively inhibits cyclooxygenase isozymes 1 and 2 (COX-1 and COX-2), resulting in the inhibition of prostaglandins and related compounds at peripheral sites (12). Prostaglandin is essential for synthesizing collagen, the primary structural material of all muscles, bones and tendons. Ibuprofen reduces how much collagen a person forms in response to exercise. However, NSAIDs reduce pain and muscle soreness. The big problem is that most NSAIDs, especially Ibuprofen, are "over the counter" drugs and can be bought without a prescription (13).

NSAIDs are consistently the most declared medication on doping control forms at the Olympics, Paralympics and FIFA World Cup tournaments because the World Anti-Doping Agency does not prohibit the use of NSAIDs. (14). Also, there is a big dilemma about the ergogenic effects of NSAIDs. *Ergogenic effects* are intended to enhance physical performance, stamina, or recovery. It is controversial because some studies show that NSAIDs have an ergogenic effect (15), but some show quite the opposite. (16) A recent study showed the prevalence of use and awareness of the risk of an oral non-steroidal anti-inflammatory drug in recreational runners. Among the others, the most interesting results show that Twenty-four percent (n = 171) of NSAID users used oral NSAIDs on prescription for a non-exercise-related medical condition. Twenty-four

(3.4%) of NSAID users reported exceeding the recommended daily dose of NSAIDs, 75% of whom were male. Also Thirty-two per cent (n = 234) of respondents experienced a suspected adverse drug reaction (ADR) a result of NSAID use, including gastrointestinal discomfort (n = 99), heartburn (n = 67), nausea and vomiting (n = 34), diarrhoea (n = 11) and gastrointestinal bleeding (n = 11). (17)

Aspirin blocks prostaglandin synthesis. It is non-selective for COX-1 and COX-2 enzymes (18). The ergogenic effect of aspirin is also a controversial issue because there are studies that show that aspirin has an ergogenic effect and those that show the opposite. (19) However, the most significant advantage of using aspirin in endurance sports is that aspirin significantly reduces the risk of adverse cardiac events. (20)

Acetaminophen\Paracetamol

Acetaminophen has analgesic and antipyretic properties similar to NSAIDs, but contrary to them, it does not possess any anti-inflammatory activity. It does not induce typical NSAID gastrointestinal side effects when applied in recommended doses. However, it suppresses prostaglandin production, likewise NSAIDs. The mechanism of action is complex and includes the effects of both the peripheral (COX inhibition) and central (COX, serotonergic descending neuronal pathway, L-arginine/NO pathway, cannabinoid system) antinociception processes and ìredoxî mechanism. (21). For example, a study conducted among 141 young sub-elite athletes reported that 9.5% of all participants (22). Similar to these findings, in a cohort of 98 young regional-to-national-level athletes, Garcin et al.reported that paracetamol was detected during urinary screening for doping substances in 9.2% of the participants. The most commonly reported reason for consuming paracetamol among athletes is to decrease pain from previous athletic exertion (23). The acute ergogenic effect of acetaminophen is not well known. Therefore paracetamol use is not prohibited by the World Anti-Doping Agency. (24) In a recent large meta-analysis involving ten studies, the effect of ingestion time on the ergogenic effect of acetaminophen was demonstrated. The effects of paracetamol are moderated by the timing of ingestion and the performance test. Specifically, paracetamol was ergogenic for endurance performance when ingested from 45 to 60 min before exercise. Furthermore, we also found that paracetamol enhances performance in cycling or running time-to-exhaustion tests but not in time trials. Still, it should be mentioned that these effects were in the range of a trivial to small magnitude. (25)It should be mentioned that the included studies varied in the dose of paracetamol provided to their participants. Specifically, some studies provided paracetamol in doses relative to body mass (e.g., 20 mg/kg of body mass), whereas others used absolute doses from 500 to 1500 mg of paracetamol. The last dose is likely to be more ergogenic given that paracetamol systemic bioavailability is dose-dependent. Particular attention should be paid to acetaminophen overdose because it is often found as a combination in the composition of other products. It can lead to severe liver damage. (26)

Opioids

Tramadol is a synthetic drug used to treat moderate to the severe nerve, muscle, spinal column and arthritis pain. It is not banned by the World Anti-Doping Agency, although numerous studies show that it significantly improves sports performance in endurance sports, especially in cycling. (27) Very recent evidence suggests that the risk of abuse and dependence abuse induced by the chronic intake of tramadol might have been underestimated. (28) Some reports suggest that tramadol is chronically ingested by cyclists not to treat injuries but to reduce pain between stages. Some have linked this use of tramadol with the increasing number of crashes in the peloton. (29)

Conclusion

Early-onset muscle soreness is a significant problem for endurance athletes. Therefore, they often resort to various analgesics, ignoring the potential harmful effects. By consuming a mixture of these analgetics, athletes might be seeking a possibly dangerous ergogenic advantage, which may compromise their health and other competitors' safety. Nevertheless, as this is a reasonably novel topic, future research is needed, mainly related to different doses of analgesics, the timing of ingestion, and various endurance tests.

References

1. Morici G, Gruttad'Auria CI, Baiamonte P, Mazzuca E, Castrogiovanni A, Bonsignore MR. Endurance training: is it bad for you?. Breathe (Sheff). 2016;12(2):140-147.
2. Tokinoya K, Ishikura K, Ra SG, Ebina K, Miyakawa S, Ohmori H. Relationship between early-onset muscle soreness and indirect muscle damage markers and their dynamics after a full marathon. Journal of Exercise Science & Fitness, 2020;18(3):115-121.
3. Heiss R, Lutter C, Freiwald J, Hoppe MW, Grim C, Poettgen K, et al. Advances in Delayed-Onset Muscle Soreness (DOMS) - Part II: Treatment and Prevention. Sportverletz Sportschaden. 2019; 33(1):21-29.
4. Tscholl P, Alonso JM, Dolle G, Junge A, Dvorak J. The Use of Drugs and Nutritional Supplements in Top-Level Track and Field Athletes. Am J.Sports Med. 2009; 38:133-140.
5. Lundberg TR, Howatson G. Analgesic and anti-inflammatory drugs in sports: Implications for exercise performance and training adaptations. Scand. J.Med.Sci. Sports. 2018; 28: 2252-2262.
6. Alaranta A, Alaranta H, Heliovaara M, et al. Ample use of physician-prescribed medications in Finnish elite athletes. Int J Sports Med. 2006;27: 919–25.
7. Da Silva ER,De Rose EH,Ribeiro JP, et al. Non-steroidal anti-inflammatory use in the XV Pan-American Games (2007). Br J Sports Med. 2011;45: 91–4 .
8. Wharam PC, Speedy DB, Noakes TD, et al. NSAID use increases the risk of developing hyponatremia during an Ironman triathlon. Med Sci Sports Exerc. 2006;38: 618–22.

9. Scheer V, Hoffman MD. Exercise-associated hyponatremia: practical guide to its recognition, treatment and avoidance during prolonged exercise. Deutsche Zeitschrift für Sportmedizin. 2018; 69: 311–318.
10. Halvorsen FA, Lyng J, Ritland S. Gastrointestinal bleeding in marathon runners. Scand J Gastroenterol. 1986;21: 493–7.
11. Le Meur Y, Paraf F, Szelag JC, et al. Acute renal failure in a marathon runner: role of glomerular bleeding in tubular injury. Am J Med. 1998;105: 251–2.
12. Malmberg AB, Yaksh TL. Cyclooxygenase inhibition and the spinal release of prostglandin E2 and amino acids evoked by paw formalin injection: a microdialysis study in unanesthetized rats. J Neurosci. 1995;15:2768–2778.
13. Warden SJ. Prophylactic use of NSAIDs by athletes: a risk/benefit assessment. Physician Sportsmed. 2010; 38: 132–138.
14. CorriganB, Kazlauskas R. Medication use in athletes selected for doping control at the Sydney Olympics (2000). Clin J Sport Med. 2003; 13: 33–40.
15. Holgado D, Hopker J, Sanabria D, Zabala M. Analgesics and Sport Performance:Beyond the Pain-Modulating Effects. PM R. 2018;10(1):72–82.
16. Cornu, C, Grange, C, Regalin A, et al. Effect of Non-Steroidal Anti-Inflammatory Drugs on Sport Performance Indices in Healthy People: a Meta-Analysis of Randomized Controlled Trials. Sports Med – Open. 2020;6 (1):20.
17. Rosenbloom CJ, Morley FL, Ahmed I, Cox AR. Oral non-steroidal anti-inflammatory drug use in recreational runners participating in Parkrun UK: Prevalence of use and awareness of risk. International Journal of Pharmacy Practice. 2020; 28,(6): 561–568.
18. Vane JR, Botting RM: The mechanism of action of aspirin. Thromb Res. 2003;110(5-6):255-8.
19. Roi GS, Garagiola U, Verza P, Spadari G, Radice D, Zecca L, et al. Aspirin does not affect exercise performance. Int J Sports Med. 1994;15(5):224-7.
20. Siegel AJ. Prerace aspirin to protect susceptible runners from cardiac arrest during marathons: is opportunity knocking?. Open Heart. 2015;2(1):e000102.
21. Jóźwiak-Bebenista M, Nowak JZ. Paracetamol: mechanism of action, applications and safety concern. Acta Pol Pharm. 2014;71(1):11-23.
22. Garcin M, Mille-Hamard L, Billat V, Imbenotte M, Humbert L, Lhermitte Z. Use of acetaminophen in young subelite athletes. *J.* Sports Med. Phys. Fitness. 2005: 45: 604–607.
23. Garcin M, Mille-Hamard L, Billat V, Humbert L, Lhermitte M. Influence of acetaminophen consumption on perceived exertion at the lactate concentration threshold. Percept. Mot. Skills. 2005; 101: 675–683.
24. Pagotto FD, Paradisis G, Maridaki M, Papavassiliou T, Zacharogiannis E. Effect of acute acetaminophen injestion on running endurance performance. J. Exerc. Physiol. Online. 2018; 21: 106–118.

25. Grgic J, Mikulic P. Effects of Paracetamol (Acetaminophen) Ingestion on Endurance Performance: A Systematic Review and Meta-Analysis. Sports. 2021; 9(9):126.
26. Forrest JA, Clements JA, Prescott LF. Clinical pharmacokinetics of paracetamol. Clin. Pharmacokinet. 1982; *7*: 93–107.
27. Hernandez E, Sanabria D. Tramadol effects on physical performance and sustained attention during a 20-min indoor cycling time-trial: A randomised controlled trial. J Sci Med Sport. 2018;21(7):654-660.
28. Stannard C. Tramadol is not "opioid-lite." BMJ. 2019; 365: 12095.
29. Baltazar-Martins G, Muñoz G, Carreras D, Plata M, Jesus MG, Del Coso J. The use of tramadol in combination with pseudoephedrine and caffeine in sports. Drug Testing and Analysis. 2020;12 (8):1203-1205.

Radiofrequency Ablation for Painful Knee Osteoarthritis

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Abstract

Knee pain has a lifetime prevalence rate of ~45%,1, and represents a source of significant disability and reduced quality of life. The most common cause of chronic knee pain is osteoarthritis (OA), characterized by the progressive loss of articular cartilage, with other etiologies including rheumatoid arthritis, trauma, crystal arthropathies, and persistent postsurgical pain. The pulse generator of RFA creates an electromagnetic field surrounding the electrode tip that activates adjacent molecules, thus generating frictional heat. After reaching the temperature threshold, the sensory nerve is partially denervated, relieving the refractory pain. The people who are most likely to be candidates for the radiofrequency ablation in the knee are those who: had a total or partial knee replacement, and the pain continued after the surgery, want knee surgery as a last resort option, have health issues that make knee replacement surgery too risky, have chronic knee pain due to degenerative joint disease (osteoarthritis), have a knee injury marked by chronic painful inflammation, need pain relief before or after knee surgery. There is no reason to live with chronic knee pain when minimally invasive procedures, like the geniculate block knee treatment, are available

Keywords: knee osteoarthritis, chronic knee pain, radiofrequency ablation,

Introduction

Knee pain has a lifetime prevalence rate of ~45 %, and represents a source of significant disability and reduced quality of life (1,2). Risk factors for the development of knee pain include a history of prior injury or surgery, obesity, and advancing age (3). The most common cause of chronic knee pain is osteoarthritis (OA), characterized by the progressive loss of articular cartilage, with other etiologies including rheumatoid arthritis, trauma, crystal arthropathies, and persistent postsurgical pain (4,5).

It is most frequently found in the elderly, with a relatively high prevalence of about 40% among 70 to 74 years.2 The number of patients with knee OA has increased in tandem with the aging of the general population (6). It is predicted that 67 million people in the United States will have been diagnosed with OA by 2030.22 The weight-bearing joints, such as the knees and hips, are the most frequently affected (7). Total knee arthroplasty is considered the treatment of choice for end-stage knee OA and can provide excellent postoperative pain relief, excellent deformity correction, and satisfactory functional recovery (8,9). However, not all patients are appropriate candidates for this treatment because of age, comorbidities, or other factors.

Knee innervation

The innervation of the knee joint is complex given that genicular nerves arise from branches of three significant nerves: the sciatic, femoral, and obturator, all of which are themselves derived from the lumbar plexus (10,11). In the popliteal fossa, the sciatic nerve bifurcates into the tibial and common peroneal nerves. The tibial nerve remains in the posterior compartment of the lower leg. It gives off the superomedial (SM) and inferomedial (IM) genicular nerves to the rear aspect of the knee joint. The common peroneal nerve passes into the anterior compartment of the lower leg and contributes the superior lateral (SL) genicular nerve to the anterior portion of the knee. These genicular branches of the sciatic nerve reliably course in approximation to the periosteum at the medial and lateral junctions of the distal femoral shaft and epicondyles and at the medial corner of the proximal tibia and epicondyle. The saphenous nerve is a cutaneous sensory branch of the femoral nerve and gives off suprapatellar and infrapatellar (IP) genicular nerves to the anterior portion of the knee. The contribution of the obturator nerve is more variable, but its posterior branch can provide an articular branch to the posterior knee. The complexity of the knee joint's innervation has resulted in a disparity in procedural techniques among the available controlled and observational studies. Studies report on a range of procedural targets, including the SM, IM, and SL genicular nerves in combination, the saphenous nerve, the sciatic nerve, the IP genicular nerve, the IP and SM genicular nerves in a variety, the femoral, tibial, saphenous nerves, and peripatellar plexus in combination, and the intra-articular joint space (12-18).

Treatment

Effective pain management plays a vital role in treating OA and improving the prognosis. Conservative treatment is the first choice for early-stage OA. It may involve physical therapy, intra-articular injections (platelet-rich plasma, glucocorticoids, glucosamine, and hyaluronic acid), and oral anti-inflammatory drugs.

Radiofrequency ablation (RFA) was first described in 1891 (19). The pulse generator of RFA creates an electromagnetic field surrounding the electrode tip that activates adjacent molecules, thus generating frictional heat (20). After reaching the temperature

threshold, the sensory nerve is partially denervated, relieving the refractory pain. In short-term follow-ups, Leggett et al. found that RFA significantly reduced chronic low back pain associated with the lumbar facet joints and sacroiliac joints, discogenic low back pain, and coccygeal pain (21). Amr et al. reported that RFA intervention acted faster, provided a longer duration of analgesia, worked in a higher proportion of patients, and had a better safety profile in the management of refractory cancer pain (22). However, few studies have determined whether RFA can relieve knee OA pain. It is currently used to improve joint function and relieve pain by destroying nerves that innervate painful tissue or by disturbing the transmission of pain signals.

RFA is reportedly a reliable method for managing chronic knee pain related to knee OA. Its noninvasive nature and low complication rate make it a more advantageous technique than other conservative treatments (23). The present meta-analysis indicated that the use of RFA is associated with improved pain relief within 24 weeks (24). During this genicular nerve block treatment, patients that responded well to the diagnostic nerve block undergo the ablation procedure, usually done with a local anesthetic on an outpatient basis. Once again, fluoroscopic or ultrasound guidance is used (25).

The people who are most likely to be candidates for the radiofrequency ablation in the knee are those who:

- had a total or partial knee replacement, and the pain continued after the surgery,
- want knee surgery as a last resort option,
- have health issues that make knee replacement surgery too risky,
- have chronic knee pain due to degenerative joint disease (osteoarthritis),
- have a knee injury marked by chronic painful inflammation,
- need pain relief before or after knee surgery (25).

The patient lies on a procedure table during the procedure, and the body, except for the knee being treated, is covered with a sheet. The physician sterilizes the injection sites and numbs them with an anesthetic. Using a fluoroscope (or some technology) as a guidance system, a cannula (needle with a thin tube) is inserted into the correct position near a genicular nerve. While inserted, a local anesthetic is administered to numb (block) the nerve to stop pain signaling. This procedure is repeated until several (usually three) genicular nerves are blocked. In some cases, people are sedated so they do not feel any pain from the injection. Once discharged, strenuous activity is recommended to avoid at least 24 hours. However, it is also important to resume normal moderate activities that previously caused knee pain. This helps determine whether the genicular nerve block for knee pain is working.

The pain relief from the genicular nerve ablation procedure can last from six months to one year or even longer. It is a low-risk procedure that is done on an outpatient basis.

Though both procedures are considered low-risk pain treatments, any medical practice can lead to complications. Though rare, potential genicular nerve block complications include:

- septic arthritis (joint inflammation caused by infection),
- allergic reactions to the anesthetics,
- severe pain or infection at the needle sites or elsewhere,
- pain that becomes severe or progressive,
- leg muscle numbness or weakness that lasts longer than 8 hours,
- fever,
- bladder or bowel dysfunction.

Conclusion

There is no reason to live with chronic knee pain when minimally invasive procedures, like the geniculate block knee treatment, are available (26).

References

1. Mannoni A, Briganti MP, di Bari M, et al. Epidemiological profile of symptomatic osteoarthritis in older adults: a population-based study in Dicomano, Italy. Ann Rheum Dis. 2003;62(6):576–578.
2. Michael JW, Schlüter-Brust KU, Eysel P. The epidemiology, etiology, diagnosis, and treatment of osteoarthritis of the knee. Dtsch Arztebl Int. 2010;107(9):152–162.
3. Garstang SV, Stitik TP. Osteoarthritis: epidemiology, risk factors, and pathophysiology. Am J Phys Med Rehabil. 2006;85(11 Suppl): S2–S14.
4. Zhang W, Doherty M, Peat G, et al. EULAR evidence-based recommendations for the diagnosis of knee osteoarthritis. Ann Rheum Dis. 2010;69(3):483–489.
5. Karaman H, Tüfek A, Kavak GÖ, et al. Intra-articularly applied pulsed radiofrequency can reduce chronic knee pain in patients with osteoarthritis. J Chin Med Assoc. 2011;74(8):336–340.
6. Pai YC, Rymer WZ, Chang RW, et al. Effect of age and osteoarthritis on knee proprioception. Arthritis Rheum 1997; 40: 2260–2265.
7. Hootman JM and Helmick CG. Projections of US prevalence of arthritis and associated activity limitations. Arthritis Rheum 2006; 54: 226–229.
8. Paredes-Carnero X, Escobar J, Galdo JM, et al. Total knee arthroplasty for treating osteoarthritis associated with the extraarticular deformity. J Clin Orthop Trauma 2018; 9: 125–132.
9. Tani I, Nakano N, Takayama K, et al. Navigated total knee arthroplasty for osteoarthritis with extra-articular deformity. Acta Ortop Bras 2018; 26: 170–174.

10. Hirasawa Y, Okajima S, Ohta M, Tokioka T. Nerve distribution to the human knee joint:
11. an anatomical and immunohistochemical study. Int Orthop. 2000;24(1):1–4.
12. Kennedy JC, Alexander IJ, Hayes KC. Nerve supply of the human knee and its functional importance. Am J Sports Med. 1982;10(6):329–335.
13. Choi WJ, Hwang SJ, Song JG, et al. Radiofrequency treatment relieves chronic knee osteoarthritis pain: a double-blind, randomized controlled trial. Pain. 2011;152(3):481–487.
14. Sarı S, Aydın ON, Turan Y, et al. Which one is more effective for treating chronic pain in knee osteoarthritis: radiofrequency neurotomy of the genicular nerves or intra-articular injection? Int J Rheum Dis. Epub 2016 Aug 12.
15. Qudsi-Sinclair S, Borrás-Rubio E, Abellan-Guillén JF, Padilla del Rey ML, Ruiz-Merino G. A comparison of genicular nerve treatment using either radiofrequency or analgesic block with corticosteroid for pain after total knee arthroplasty: a double-blind, randomized clinical study. Pain Pract. 2017;17(5):578–588.
16. Davis T, Loudermilk E, Depalma M, et al. Prospective, multicenter, randomized, crossover clinical trial comparing the safety and effectiveness of cooled radiofrequency ablation with corticosteroid injection in the management of knee pain from osteoarthritis. Reg Anesth Pain Med. 2018;43(1):84–91.
17. El-Hakeim EH, Elawamy A, Kamel EZ, et al. Fluoroscopic guided radiofrequency of genicular nerves for pain alleviation in chronic knee osteoarthritis: a single-blind randomized controlled trial. Pain Physician. 2018;21(2):169–177.
18. McCormick ZL, Reddy R, Korn M, et al. A prospective randomized trial of prognostic genicular nerve blocks to determine the predictive value for the outcome of cooled radiofrequency ablation for chronic knee pain due to osteoarthritis. Pain Med. Epub 2017 Dec 28.
19. Akbas M, Luleci N, Dere K, Luleci E, Ozdemir U, Toman H. Efficacy of pulsed radiofrequency treatment on the saphenous nerve in patients with chronic knee pain. J Back Musculoskelet Rehabil. 2011;24(2): 77–82.
20. Hong K and Georgiades C. Radiofrequency ablation: mechanism of action and devices. J Vasc Interv Radiol 2010; 21: S179–S186.
21. Connors JC, Boike AM, Rao N, et al. Radiofrequency ablation for treating painful neuroma. J Foot Ankle Surg 2020; 59: 457–461.
22. Hootman JM and Helmick CG. Projections of US prevalence of arthritis and associated activity limitations. Arthritis Rheum 2006; 54: 226–229.
23. Chung SR, Baek JH, Choi YJ, et al. Longer-term outcomes of radiofrequency ablation for locally recurrent papillary thyroid cancer. Eur Radiol 2019; 29: 4897–4903.
24. Hlavsa J, Prochazka V, Andrasina T, et al. Radiofrequency ablation in pancreatic cancer. Rozhl Chir 2019; 98: 441–449.
25. Leggett LE, Sorel LJ, Lorenzetti DL, et al. Radiofrequency ablation for chronic low

back pain: a systematic review of randomized controlled trials. Pain Res Manag 2014; 19: e146–e153.
26. Amr SA, Reyad RM, Othman AH, et al. Comparison between radiofrequency ablation and chemical neurolysis of thoracic splanchnic nerves for managing abdominal cancer pain, randomized trial. Eur J Pain 2018; 22: 1782–1790.
27. https://www.sapnamed.com/pain-treatment/genicular-nerve-block-and-radiofrequency-ablation-gnrfa/

Trigeminal Neuralgia - Suicide Disease

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Abstract

Trigeminal Neuralgia is the worst pain in the world. It is often unbearable pain, which is why patients, unable to reduce the pain, resort to suicide. This is why this pain is also called suicidal pain. Trigeminal neuralgia is defined by the International Association for the Study of Pain (IASP) as a sudden, usually unilateral, severe, brief, stabbing, recurrent episode of pain in the distribution of one or more branches of the trigeminal nerve. Based on clinical observations, compression of the nervus trigeminus near the origin of the brain stem, the so-called root entry zone, by blood vessels or tumors, may cause trigeminal neuralgia. Local pressure causes demyelination that leads to abnormal depolarization resulting in ectopic impulses. The description of the pain is fundamental; it must be sharp, shooting, lancinating, and "electric shock." The pain can be brought on by ordinary stimuli, such as eating, washing, shaving, cold, warmth, and draught. When the diagnosis of trigeminal neuralgia is made, the patient needs to undergo a magnetic resonance imaging (MRI) scan to exclude specific pathologies such as a tumor or multiple sclerosis, which could cause secondary trigeminal neuralgia. The medication of choice in pain management is carbamazepine. From an observational study, carbamazepine can reduce pain symptoms in about 70% of the cases. If the medical treatment is unsuccessful or has too many side effects, an invasive treatment can be carried out. This is currently five clinically reasonable possibilities surgical microvascular decompression (MVD), stereotactic radiation therapy, Gamma knife, percutaneous balloon micro compression, percutaneous glycerol rhizolysis, and percutaneous radiofrequency (RF) treatment of the Gasserian ganglion, Gasserian ganglion stimulation/neuromodulation.

Key words: trigeminal neuralgia, unilateral facial pain, suicidal pain

Introduction

Trigeminal neuralgia, or "Tic Doloureux," is a painful condition of the face (1)., declared Peter J.Jannetta, MD, in Striking Back!, a Layman's Guide for Facial Pain Patients (2). It is often unbearable pain, which is why patients, unable to reduce the pain, resort to suicide. This is why this pain is also called suicidal pain. Trigeminal neuralgia is defined by the International Association for the Study of Pain (IASP) as a sudden, usually unilateral, severe, brief, stabbing, recurrent episode of pain in the distribution of one or more branches of the trigeminal nerve (3). Trigeminal neuralgia is the most common form of facial pain in people older than 50 years of age. Various epidemiological studies have shown the annual incidence to be about 4-5 new patients per 100,000. The highest incidence occurs in the ages of 50 and 70 years; in 90% of the cases, the symptoms begin after 40 years. Trigeminal neuralgia is more prevalent in women than men, with a ratio of 1.5:1 (4).

Pathophysiology

The pathophysiology is unclear. Based on clinical observations, compression of the nervus trigeminus near the origin of the brain stem, the so-called root entry zone, by blood vessels or tumors, may cause trigeminal neuralgia. Local pressure causes demyelination that leads to abnormal depolarization resulting in ectopic impulses. The most commonly accepted theory as to the pathophysiology of trigeminal neuralgia is the "ignition" hypothesis put forward by Devor et al. [6]. There is some recent evidence suggesting that patients with more atypical forms of trigeminal neuralgia may, in fact, have more major changes, as they have been shown to have overactivation of central facilitation of trigeminal nociceptive processing rather than only peripheral changes (5). Trigeminal neuralgia is further divided into idiopathic and symptomatic types. Symptomatic trigeminal neuralgias are those much rarer where a primary cause is identified, such as a benign or malignant tumor, demyelisation such as that which occurs in multiple sclerosis, or the rarer arterial or vascular malformation (IASP 2010) (6).

Diagnosis

Trigeminal neuralgia is recognized by unilateral short-lived, intense, sharp, shooting pains in 1 or more branches of the fifth cranial nerve. The description of the pain is fundamental; it must be sharp, shooting, lancinating, and "electric shock." The pain can be brought on by ordinary stimuli, such as eating, washing, shaving, cold, warmth, and draught (7).

The International Headache Society described the following criteria for essential trigeminal neuralgia:

1. Paroxysmal pain that lasts from a fraction of a second to 2 minutes, occurring in 1 or more branches of the nervus trigeminus, and fulfilling criteria 2 and 3.

2. The pain has at least one of the following characteristics: 1 intense, sharp, superficial, or stabbing. 2 precipitated from trigger areas or by trigger factors.
3. The patient stereotypically describes the patient's attacks.
4. There are no signs of neurological disorders.
5. The attacks are not caused by other disorders (8).

The most frequent location of the pain is in the second and third divisions of the trigeminal nerve. It is rare to see the pain in only the first trigeminal division. If patients report pain in only the first division, then it is important to establish whether they truly have trigeminal neuralgia or whether it could be a trigeminal autonomic cephalalgia (9).

Severe pain will often induce depression, and patients become extremely fearful of when they will get their next attack of pain and whether it will be more severe than previous episodes (10).

Differential Diagnosis

Any unilateral, episodic pain needs to be assessed as potential symptomatic neuralgia, as not all such pain will be neuropathic initially. The other major class of conditions to consider is the trigeminal autonomic cephalalgias. The major differentiating factor is that these pains tend to occur in the first division rather than in the second and third divisions of the trigeminal nerve. In patients with one of these conditions, each pain attack might be of longer duration (11). Attacks may not exhibit a refractory period and can be more numerous. Patients with these conditions are often restless and agitated, whereas patients with trigeminal neuralgia want to keep very still. Patients will report autonomic features including tearing, redness of the eye, meiosis, edema of the upper eyelids, stuffy nose or rhinorrhea, redness of the face, and a feeling of fullness in the ear. These patients should not undergo surgical treatments (12). Less frequently, trigeminal neuralgia is seen in younger patients. It is essential that multiple sclerosis always be considered in the differential diagnosis, especially in bilateral cases (13).

Additional test

When the diagnosis of trigeminal neuralgia is made, the patient needs to undergo magnetic resonance imaging (MRI) scan to exclude specific pathologies such as a tumor or multiple sclerosis, which could cause secondary trigeminal neuralgia (14). The MRI scan can also be used if a suspected compression of the nervus trigeminus in the fossa cranial posterior. Sometimes the MRI scan is sensitive enough to detect blood vessels that have come in contact with the nervus trigeminus (15). The role of venous compression in the pathogenesis of trigeminal neuralgia is controversial. Notably, on MRI scanning, compressing blood vessels are seen in one-third of asymptomatic patients (15).

Treatment options

Conservative treatments

The mainstay of management of trigeminal neuralgia is the antiepileptic drugs, which have been used since 1860. However, it was the introduction of carbamazepine in 1962 that revolutionized the management of this condition, and this drug has remained the gold standard and the focus of three randomized control trials (RCTs). There have now been a variety of systematic reviews both within the Cochrane collaboration and elsewhere to evaluate the use of antiepileptic drugs, and international guidelines have been published (16,17). The selection of the pharmacological treatment is based on a systematic review of data of relatively older studies or a more up-to-date Cochrane database." The medication of choice is carbamazepine. From an observational study, carbamazepine can reduce pain symptoms in about 70% of the cases. Oxcarbazepine has shown similar efficacy. Other medica tions that can be tried, are gabapentin, pregabalin, and baclofen (15).

Interventional treatments

If the medical treatment is unsuccessful or has too many side effects, an invasive treatment can be carried out. This is currently five clinically resonable possibilities:

1. Surgical microvascular decompression (MVD).
2. Stereotactic radiation therapy, Gamma knife.
3. Percutaneous balloon micro compression."
4. Percutaneous glycerol rhizolysis."
5. Percutaneous radiofrequency (RF) treatment of the Gasserian ganglion.
6. Gasserian ganglion stimulation/neuromodulation. (12-17)

Surgical MVD

During MVD, the vessels in contact with the root entry zone are coagulated, and arteries are separated from the nerve using an inert sponge or felt (18).

Stereotactic radiation therapy, Gamma knife

The Gamma knife, a stereotactic radiotherapeutic method, entails high dose irradiation of a small section of the nervus trigeminus. This results in nonselective damage to Gasserian ganglion. The advantage is that this is a non-invasive treatment that can be applied under local anesthetic and light sedation. At the moment, while there are an increasing number of efficacy studies being carried out on this treatment, the initial efficacy appears to be limited; between 60% and 70% indicate a reduction in pain. The long-term effects are not yet known (13)

Percutaneous balloon micro compression

In micro compression of Gasserian ganglion, the nervus trigeminus is compressed by a small balloon, which is percutaneously introduced into Meckel's cavity using a

needle. The effect of this technique relies on ischemic damage of the ganglion cells. Although there are insufficient good qualitative data, this technique, with regard to efficacy, appears to be comparable with percutaneous RF treatment of Gasserian ganglion. The advantage of this technique is that it is also suitable for the treatment of trigeminal neuralgia of the first branch, allowing the corneal reflex to remain intact (19).

Percutaneous glycerol rhizolysis

During percutaneous glycerol rhizolysis, a needle is introduced into the cisterna trigeminal, visualized using fluoroscopy. In a seated patient with the head flexed, a contrast dye can be injected to determine the size of the cisterna. Then, after the contrast dye is aspirated, an equal volume of glycerol is injected (15).

Percutaneous RF treatment of the Ganglion Gasseri

RF treatment of Gasserian ganglion should be considered in the elderly patient." The outcome of treatment of Gasserian ganglion is reportedly less favorable than with open operation (MVD), but it is less invasive and has low morbidity and mortality rates (20).

Ganglion Gasseri stimulation/neuromodulation (experimental)

Gasserian ganglion electric stimulation was first described by Shelden et al. in 3 patients with trigeminal neuralgia." Meyerson and Hakansson reported Gasserian ganglion stimulation via a subtemporal craniotomy in 5 patients suffering from atypical trigeminal neuralgia. Later, a percutaneous approach was described by Meglio, and lead migration presented a technical challenge. More recently, Machado et al. reported percutaneous Gasserian ganglion stimulation in 8 patients with trigeminal neuropathic pain. Only three patients continued to have >50% pain improvement after one year of treatment.

Conclusion

The treatment of a patient with essential trigeminal neuralgia should be multidisciplinary, and the various treatment options (MVD, Gamma knife, and RF treatment of Gasserian ganglion) and their risks should be discussed with the patient.These related therapies have never been compared with one another in prospective randomized studies.Recommendations are, therefore, relative.With regard to the elderly patient with comorbidities, RF treatment of Gasserian ganglion can be recommended. In younger patients, an MVD could be considered (21).

References

1. Tolle T, Dukes E, Sadosky A. Patient burden of trigeminal neuralgia: results from a cross-sectional survey of health state impairment and treatment patterns in six European countries. Pain Pract. 2006; 6:153-160.

2. Weigel G, Kenneth F, Casey M. Striking Back! Gainsville: Trigeminal Neuralgia Association;2000
3. Merskey H, Bogduk N. Classification of chronic pain. Description of chronic pain syndromes and definitions of pain terms, 2nd ed. Seattle: IASP Press:1994.
4. Rozen TD. Trigeminal neuralgia and glossopharyngeal neuralgia. Neurol Clin. 2004;22:185-206.
5. Obermann M, Yoon MS, Ese D. Maschke M. Kaube H, Diener HC, Katsarava Z. Impaired trigeminal nociceptive processing in patients. with trigeminal neuralgia. Neurology 2007;69:835-41.
6. Dionne R, Newton-John T, Zakrzewska JM. Overall management of facial pain. In Zakrzewska JM. editor. Orofacial pain. Oxford: Oxford University Press; 2009. p. 53-68.
7. Machado A, Ogrin M, Rosenow JM, Henderson JM. A 12-month prospective study of gasserian ganglion stimulation for trigeminal neuropathic pain. Stereotact Funct Neurosurg. 2007;85:216-224.
8. Lopez BC, Hamlyn PJ, Zakrzewska JM. Stereotactic radiosurgery for primary trigeminal neuralgia: state of the evidence and recommenda tions for future reports. J Neurol Neurosurg Psychiatry. 2004;75:1019 1024.
9. Gronseth G, Cruccu G. Alksne J, Argoff C, Brainin M. Burchiel K, Nur mikko T, Zakrzewska JM. Practice parameter: the diagnostic evaluation and treatment of trigeminal neuralgia (an evidence-based review): re port of the Quality Standards Subcommittee of the American Academy of Neurology and the European Federation of Neurological Societies. Neurology 2008;71:1183-90.
10. Koopman JS, Dieleman JP. Huygen FJ, de MM, Martin CG, Sturken boom MC. Incidence of facial pain in the general population. Pain 2009;147:122-7.
11. Lemos L. Flores S, Oliveira P. Almeida A. Gabapentin supplemented with ropivacaine block of trigger points improves pain control and quality of life in trigeminal neuralgia patients compared with gabapentin alone. Clin J Pain 2008;24
12. Zakrzewska JM, Lopez BC. Quality of reporting in evaluations of surgical treatment of trigeminal neuralgia: recommendations for future reports. Neurosurgery 2003:53:110
13. Zakrzewska JM, Lopez BC. Kim SE, Cookham HB. The patients reports satisfaction after microvascular decompression and partial sensory rhizotomy for trigeminal neuralgia. Neurosurgery 2005:56:1304-11
14. Kanpolat Y, Savas A, Bekar A, Berk C. Percutaneous controlled radiofrequency trigeminal rhizotomy for treating idiopathic trigeminal neuralgia: 25-year experience with 1,600 patients. Neurosurgery. 2001;48:524-532; discussion 532-524.
15. Nurmikko T. Trigeminal neuralgia and other facial neuralgias. In: Test Cervero F, Jensen TS, eds. Handbook of Clinical Neurology, Vol. 81 (3rd Series, Vol. 3), pain. New York: Elsevier; 2006:573-596.

16. Van Kleef M, Mekhail N, Van Zundert J. Editorial; Evidence-based guidelines for interventional pain medicine according to clinical diagnoses. Pain Pract. 2009;9:247-251
17. Hall GC, Carroll D, Parry D. McQuay HJ. Epidemiology and treatment of neuropathic pain: the UK primary care perspective. Pain 2006;122:156-62.
18. He L, Wu B, Zhou M. Non-antiepileptic drugs for trigeminal neuralgia. Cochrane Database Syst Rev 2006;3:CD004029.
19. Jannetta PJ, McLaughlin MR, Casey KF. The technique of microvascular decompression. Technical note. Neurosurg Focus. 2005;18:E5.
20. Belber CJ, Rak RA. Balloon compression rhizolysis in the surgical management of trigeminal neuralgia. Neurosurgery. 1987;20: 908-913
21. Tatli M, Satici O, Kanpolat Y, Sindou M. Various surgical modalities for trigeminal neuralgia: literature study of respective long-term outcomes. Acta Neurochir (Wien). 2008;150:243-255. 28. Javadpour M, Eldridge PR, Varma TR, Miles JB, Nurmikko TJ. Microvascular decompression for trigeminal neuralgia in patients over 70 years of age. Neurology. 2003;60:520

PLACEBO I NOCEBO EFEKTI: ZNAČAJ OČEKIVANJA PACIJENTA I INTERAKCIJE LEKAR-PACIJENT ZA ISHOD LEČENJA

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Abstrakt

Placebo predstavlja supstancu bez medicinskog efekta koja može poboljšati zdravstveno stanje pacijenta zbog samog njegovog uverenja da je supstanca delotvorna. Za razliku od placeba, nocebo predstavlja upotrebu inaktivne supstance ili tretmana, koji su bez medicinskog efekta na pacijenta, ali koji pogoršavaju njegovo zdravstveno stanje usled njegovih negativnih uverenja i očekivanja. Efekti placeba najviše su tokom istorije ispitivani na polju terapije bola i uglavnom se istraživanja vezana za placebo odnose na bol. U kliničkoj praksi oba fenomena, i placebo i nocebo, mogu da utiču na terapijski efekat, pa je cilj maksimizirati efekte placeba a minimizirati efekte noceba.

Ključne reči: placebo, nocebo, placebo analgezija

Uvod

Placebo i nocebo efekat imaju veliki broj definicija koje su se stvarale tokom vekova i na neki način pratile su razvoj medicine. Placebo predstavlja supstancu bez medicinskog efekta koja može poboljšati zdravstveno stanje pacijenta zbog samog njegovog uverenja da je supstanca delotvorna. Placebo tretman predstavljaju lekovi ili procedure koje se koriste za umanjenje simptoma ili lečenje bolesti ali u stvarnosti oni nisu zaista efikasni za stanje za koje se primenjuju. Placebo efekat predstavlja rezultat, odnosno nespecifičan psihološki ili psiho-fiziološki terapijski rezultat koji je stvoren primenom placeba. Međutim, ovaj rezultat može nastati i usled spontanog poboljšanja stanja pacijenta a da u suštini ne predstavlja efekat placeba. Efekti placeba najviše su tokom istorije ispitivani na polju terapije bola i uglavnom se istraživanja vezana za placebo odnose na bol. Tako placebo analgezija u stvari predstavlja smanjenje intenziteta bola nakon primene placebo tretmana. (1,2)

Mehanizam delovanja placeba

Mehanizmi delovanja placeba nisu još uvek jasno objašnjeni. Etiološki postoji nekoliko neurobioloških i psiholoških mehanizama na kojima se zasniva placebo.

Prema opioidnom modelu nastanak placebo efekta vezan je za sekreciju i dejstvo endogenih opioida. Dokazi ovog modela delovanja placeba zasnovani su na detektovanim promenama u moždanoj aktivnosti u delovima mozga bogatim opioidima kada se primeni placebo. Primena placeba indukuje aktivaciju u strukturama uključenim u endogenoj modulaciji bola: dorzolateralnom prefrontalnom korteksu, rostralnom prednjem cingularnom korteksu i periakueduktalnoj sivoj masi. Takodje, modulacija bola koja se dešava u dorzalnim korenovima kičmene moždine preko descendentnog opioidnog puta za kontrolu bola, predstavlja osnovu placebo efekta. Placebo efekat može se blokirati opioidnim anatagonistima kao što je Nalokson što pokazuje ulogu ovog sistema u njegovom nastanku.(1)

U eksperimentalnim, kao i u kliničkim studijama placebo odgovor se izrazito razlikuje od osobe do osobe. Analgetski odgovor pacijenta na primenu placeba može varirati od nikakvog odgovora pa sve do potpune analgezije. Na osnovu sekrecije endogenih opioida u mozgu postoje pacijenti koji su placebo responderi i kod kojih je za vreme primene placeba nivo β endorfina u cerebrospinalnoj tečnosti dvostruko povišen u odnosu na placebo nerespondere. (1) Novija genetska istraživanja pokazuju da postoje genetske varijacije i razliciti polimorfizmi među osobama koji su udruženi sa niskom ili visokom reakcijom na placebo.(3)

Drugi model koji opisuje nastanak placeba jeste model ocekivanja. Želje i očekivanja pacijenta, verbalna sugestija, očekivanja socijalnog okruženja, motivacioni aspekti i emocije bitno utiču na nastanak placebo efekta. Model očekivanja objašnjava kako misli i verovanja mogu imati snažan uticaj na nastanak neurohemijskih reakcija u organizmu i mogu dovesti do hormonalnih i imunoloških odgovora pacijenta. Negativna uverenja i očekivanja mogu dovesti do pogoršanja zdravstvenog stanja odnosno nocebo efekta. Različite psihološke osobine predstavljaju prediktore placebo odgovora: anksioznost, optimizam, sugestivnost, sposobnost suočavanja, itd. a viši nivoi endogenih opioida prilikom primene placeba zabeleženi su kod pojedinaca koji imaju optimističan pogled na život. (4)

Činjenica da se placebo efekat ispoljava i nakon što se opioidini receptori blokiraju Naloksonom, ukazuje da ovaj efekat nastaje i nekim drugim mehanizmima. Model refleksnog uslovljavanja opisuje značaj dopaminergičkog puta u nastasnku ovog fenomena. Naime, tokom procesa očekivanja nagrade aktiviraju se pojedini kortikalni neuroni koji šalju signal dopaminergičkim neuronima a to se posebno odnosi na nucleus accumbens koji je odgovoran za proces očekivanja nagrade i osećaj zadovoljstva. Tokom nastanka placebo efekta registrovana je povećana dopaminska i opioidna aktivnost ovog jedra. (1, 2)

Endokanabinoidni sistem takođe učestvuje u nastanku placebo analgezije, a primena placeba aktivira CB1 kanabinoidni receptor. (5) Danas postoji mnogo eksperimentalnih dokaza da ceo lipidni put, uključujući arahidonsku kiselinu, prostaglandine i leukotrijene, ima značajnu ulogu u modulaciji placebo odgovora kod bolnih stanja. U nekim studijama kod ispitanika sa glavoboljama pokazano je da primena placeba može da menja aktivnost ciklooksigenaze i sintezu prostaglandina i tromboksana što dovodi do smanjenja bola. (6)

Nocebo

Za razliku od placeba, nocebo predstavlja upotrebu inaktivne supstance ili tretmana, koji su bez medicinskog efekta, ali koji pogoršavaju zdravstveno stanje pacijenta usled njegovih negativnih uverenja i očekivanja. Ispitivanje nocebo efekta dovodi do stresa kod pacijenata, depresije i različitih negativnih stanja, pa ovakva istraživanja nisu etički prihvatljiva. (1, 7)

Nocebo efekat udružen je sa smanjenjem aktivnosti dopamina i opioida u nucleus accumbens.(1) U nastanku ovog efekta veliku ulogu ima i holecistokinin, a njegova povećana koncentracija u nervnom sistemu povezana je sa anksioznošću, gubitkom motivacije i napadima panike. (8) Negativna verbalna sugestija, očekivanje lošeg ishoda lečenja, očekivanje pojave bola prilikom intervencije ili već prisutna anksioznost pacijenta dovode do povećanog stvaranja holecistokinina. Kada se kod anksioznog pacijenta primeni bezbolan tretman uz napomenu da je intervencija bolna dolazi do povećanja koncentracije holecistokinina i pojačanog osećaja bola. Primenom benzodijazepina kod anksioznog pacijenta smanjuje se nocebo hiperalgezija. (1)

Faktori rizika za nastanak nocebo efekta su brojni: tezi stadijum bolesti i njeno duže trajanje, ženski pol, prisustvo mentalne bolesti, pre svega anksioznosti i depresije. Od strane lekara to su: nesigurnost, ljutnja, nezadovoljstvo i njegova reputacija. Takođe, na nastanak noceba mogu uticati i neke karakteristike leka kao što su njegova boja, miris, način primene i negativan publicitet. (9)

Placebo i nocebo u kliničkoj praksi

Placebo efekat predstavlja važan faktor koji može da utiče na ishod lečenja pacijenata. U kliničkoj praksi placebo efektat ima veliki potencijal da se iskoristi u korist pacijenta. (10)

Klinička primena placebo efekta može se ostvariti kroz poboljšanje očekivanja pacijenta i to:

- Objašnjenjem mehanizma dejstva leka i njegovih efekata pacijentu
- Isticanjem pozitivnih efekata leka a izbegavanjem prenaglašavanja njegovih neželjenih efekata
- Lična, posvećena interakcija sa pacijentom, a ne samo pisani materijali
- Izbegavanjem nerealnih obećanja

U kliničkoj praksi oba fenomena, i placebo i nocebo, mogu da utiču na terapijski efekat, naročito u terapiji bola. Neka istraživanja su pokazala da 30% pacijenata sa bolom oseća olakšanje nakon uzimanja placeba. (11) Placebo analgezija je jedan od najviše proučavanih placebo fenomena. Pokazano je da pacijenti sa akutnim postoperativnim bolom mnogo bolje reaguju na analgetsku terapiju i imaju smanjenje unosa lekova za 50% kada im lekove daje lično lekar u poređenju sa onima koji terapiju primaju na drugi način, npr. infuziona pumpa. (12) Još jedan važan aspekt koji treba uzeti u obzir jeste povezanost placebo ili nocebo efekta i prethodne primene tretmana. Prethodna pozitivna iskustva povećavaju analgetski odgovor sledećeg placeba, dok prethodno negativno iskustvo smanjuje stepen placebo efekta. Ovi naučeni placebo analgetski efekti mogu se iskoristiti u kliničkoj praksi. (13)

Velika meta analiza koja je uključila vise od 15 000 pacijenata sa fibromialigijom pokazala je da su pacijenti koji su dobijali placebo u studijama imali značajno smanjenje intenziteta bola, stepena umora, poboljšanje kvaliteta spavanja i poboljšanje fizičkog funkcionisanja za razliku od onih pacijenata koji su u istraživanjima bili u grupi bez tretmana odnosno nisu dobijali placebo. Veličina placebo efekta povećavala se sa starošću pacijenta i sa većim inicijalnim intenzitetom bola a smanjivala se u studijama koje su imale više ženskih učesnika kao i sa dužim trajanjem bolesti. (14)

Placebo i nocebo efekat istraživani su i pokazani i u drugim kliničkim stanjima. Između ostalog, oni se najčešće javljaju u studijama o zamaranju, depresiji (kod kojih je pokazano 50-70% učestalosti placebo efekta), sindromu iritabilnih creva (sa placebo odgovorom 38-47%) i Parkinsonovoj bolesti. (15) Placebo efekat dosta je ispitivan u lečenju depresije. U nekim istraživanjima placebo efekat je bio toliko naglašen da je stvoreno mišljenje da ga treba koristiti kao nezavisnu opciju u lečenju pacijenta sa depresijom blagog i umerenog stepena. Pozitvna emisiona tomografija (PET) otkrila je u nekim istraživanjima da su placebo i antidepresiv fluoksetin izazvali iste metaboličke promene u delovima mozga kao što su cingulum i talamus. (2, 16)

Placebo efekat moguće je povećati farmakološki. Primena oksitocina i vazopresina intranazalno opisana je u cilju pojačanja analgezije uzrokovane pozitivnim očekivanjima. Dve studije su dale prve dokaze da vazopresin pojačava placebo efekat kod žena, a da oksitocin pojačava placebo efekat kod muškaraca. (17, 18)

U tabeli 1. predstavljen je sažetak preporuka konsenzusa eksperata za upotrebu placebo i nocebo efekta u kliničkoj praksi. (19)

Tabela 1. Sažetak preporuka konsenzusa eksperata o kliničkoj primeni placebo i nocebo efekata (19)

Razmotrite placebo efekte kao deo redovnog lečenja
Informišite pacijenta o placebo i nocebo efektima na takav način da se efekti lečenja maksimiziraju a neželjena dejstva minimiziraju
Obezbedite da odnos lekar-pacijent bude odlikovan toplinom, poverenjem i empatijom kako bi se maksimizirali efekti placeba a minimizirali nocebo efekti
Obučite pružaoce zdravstvenih usluga za komunikaciju sa pacijentom kako bi maksimizirali placebo efekte a minimizirali nocebo efekte
Dajte prednost otvorenoj primeni placeba nad skrivenom u onim slučajevima gde postoje dokazi o efikasnosti i gde je propisivanje placeba legalizovano
Ne preuzimajte rizike npr. propisivanjem invazivnih tretmana da biste maksimizirali placebo efekte
Nemojte smatrati da je obmana neophodna komponenta placebo efekta

Zaključak

Poslednjih decenija placebo je dobio značenje leka i više pažnje posvećeno je placebu kao terapijskoj opciji. Činjenica da misli i verovanja pacijenta mogu imati značajan uticaj na neurobiologiju ukazala je na to da placebo može značajno uticati na terapijski proces. Danas postoje uverljivi dokazi da placebo i lekovi dele zajedničke biohemijske puteve i aktiviraju iste puteve receptora.

Literatura

1. Palibrk I. Placebo, nocebo i bol. U: Stevanović P, Nešić D, Lađević N. Medicina bola. Medicinski fakultet u Beogradu, 2020:263-8.
2. Požgain I, Požgain Z, Degmečić D. Placebo and nocebo effect: a mini-review. Psychiatr Danub. 2014;26(2):100-7
3. Colloca L, Wang Y, Martinez PE, Chang YC, Ryan KA, Hodgkinson C, et al. OPRM1 rs1799971, COMT rs4680, and FAAH rs324420 genes interact with placebo procedures to induce hypoalgesia. Pain. 2019;160(8):1824–34.
4. Pecina M, Azhar H, Love TM, Lu T, Fredrickson BL, Stohler CS, Zubieta JK. Personality Trait Predictors of Placebo Analgesia and Neurobiological Correlates. *Neuropsychopharmacology.* 2013;38(4):639-46.
5. Jarcho JM, Feier NA, Labus JS, Naliboff B, Smith SR, Hong JY, et al. Placebo analgesia: Self-report measures and preliminary evidence of cortical dopamine release associated with placebo response. Neuroimage Clin. 2016;10:107–14
6. Benedetti F, Dogue S. Different placebos, different mechanisms, different out-

comes: lessons for clinical trials. PLoS One. 2015;10(11):e0140967.
7. Colloca L, Miller FG: The nocebo effect and its relevance for clinical practice. Psychosom Med 2011; 73:598-603.
8. Frisaldi E, Shaibani A, Benedetti F. Understanding the mechanisms of placebo and nocebo effects. Swiss MedWkly. 2020;150:w20340. doi:10.4414/smw.2020.20340.
9. Kravvariti E, Kitas GD, Sfikakis PP. The role of the Nocebo effect in the use of biosimilars in routine rheumatology clinical practice. Mediter J Reumatol 2019; 30(Supp1):63-8
10. Linde K, Fässler M, Meissner K. Placebo interventions, placebo effects and clinical practice. *Phil Trans R Soc B* 2011;366:1905-12.
11. Ernst E, Saradeth T, Resch K. The powerful placebo. *Lancet* 1991;337:611.
12. Colloca L, Lopiano L, Lanotte M, Benedetti F. Overt versus covert treatment for pain, anxiety, and Parkinson's disease. *Lancet Neurol.* 2004;3(11):679–684.
13. Andre-Obadia N, Magnin M, Garcia-Larrea L. On the importance of placebo timing in rTMS studies for pain relief. *Pain.* 2011;152:1233–7.
14. Chen X, Zou K, Abdullah N, Whiteside N, et al. The placebo effect and its determinants in fibromyalgia: meta-analysis of randomised controlled trials. Clin Rheumatol. 2017;36(7):1623-1630.
15. Sanderson C, Hardy J, Spruyt O, Currow DC. Placebo and Nocebo Effects in Randomized Controlled Trials: The Implications for Research and Practice. Jour of Pain and Szmpt Manag. 2013;46(5):722-30.
16. Kato S: Review of placebo effect and re-evaluation of psychotherapy focusing on depressive disorders. Seishin Shinkeigaku Zasshi 2013; 115:887-900.
17. Colloca L, Pine DS, Ernst M, Miller FG, Grillon C. Vasopressin boosts placebo analgesic effects in women: a randomized trial. *Biol. Psychiatry* 2016;79:794–802.
18. Kessner S, Sprenger C, Wrobel N, Wiech K, Bingel U. Effect of oxytocin on placebo analgesia: a randomized study. *JAMA* 2013;310:1733–35
19. Evers AW, Colloca L, Blease C, Annoni M, Atlas LY, Benedetti F et al. Implications of Placebo and Nocebo Effects for Clinical Practice: Expert Consensus. Psychother Psychosom. 2018; 87(4):204–10

Opioids in chronic noncancer pain-our experience compare to publications / Primena opioida u terapiji hroničnog nemalignog bola- naša iskustva u poređenju sa publikacijama

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Summary

Chronic pain is a pervasive health issue that exerts a substantial social and economic burden on both the affected individual and society. Despite advanced therapeutic technique, multimodality concept admnistration with pharmacological and non pharmacological approach, treatment results remain unchanged. Opioid use for treatment of this type of pain are related with numerous side-effects but limited therapeutic effect. Mechanisms underlying chronic pain include complex interaction of physiological,emotional, cognitive, social and enviromental factors so pain severity is not correlated with the amount of tissue damage. In Europe there has been noticed an increasing trend in prescribing opioids for chronic noncancer pain treatment mostly by a GPs. In the Republic of Serbia, according to the current rules on prescribing opioid therapy, any specialist in a certain field of medicine can prescribe it. There are several recommendations based on the EFIC guidelines (European Pain Federation) from 2021. about prescription of opioids for the treatment of chronic non-malignant pain, the German Pain Association Guidelines from 2020, the Canadian Pain Association Guidelines from 2017. and the American Pain Association Guidelines from 2016. Long-term prescribing opioids should be considered in patients who receive stable daily dose followed with functional improvement for a longer period of time, requesting three-month revision period of therapeutic effect. Prescribing opioids is not recommended for primary pain syndromes: headache, fibromyalgia, visceral pain syndromes, primary musculoskeletal pain. Start opioid therapy if other therapy methods are ineffective, or if the patient does not tolerate them, or if the applied therapy has side effects, or if non-pharmacological treatment procedures are unavailable. Instruct the patient that the opioid therapy is temporary method, it should be coadministred with physical and cognitive-behavioral procedures, resulting in improved functional capacity and reduced pain intensity score up to 30%. The initial dose of opioids should not exceed 50 mg MED (morphine

equivalent dose) per day. During the treatment period, the total daily dose should not exceed 90 mg MED. Prefere oral routh administration and weak opioids over strong opioids. Among patients examined at the Outpatient Pain Clinic, statistically significant difference was observed in the prevalence of chronic noncancer pain regarding genders (p 42.28 p>0.05). Regarding genders, the distribution of the type of chronic noncancer pain did not differ significantly, except for the primary cervical pain with radicular distribution, which was observed only in female patients. Opioid prescription was not related to patients age and gender. The most commonly prescribed opioids were tramadol and tapentadol with no gender deferences. The initial daly dose of the prescribed opioid was 20-40 mg MED. Check visit was observed in 48,76% of patients after 2-4 weeks of tretment period. In 43.84% of patients, therapy had a positive effect with additional 43,84% of patients without symptom improvement. About 12.31% of patients did not tolerate the prescribed opioid therapy. Opioids are not a panacea for all types of CNCP, and must only be used in selected and supervised pain patients as part of a comprehensive, multi-modal, multi-disciplinary approach to treatment.

Key words: chronic pain, guidelines, opioid therapy, multimodal

Uvod

Problematika lečenja hroničnog nemalignog bola aktuelna je decenijama unazad. Svetska zdravstvena organizacija procenjuje da više od 20% pojedinaca širom sveta ima neku vrstu hroničnog bola (1). Hronični nemaligni bol predstavlja zdravstveni problem koji pogađa socio-ekonomsku sferu pojedinaca i društva u celini, čemu je mnogo doprineo aktuelni stil života (2). Uprkos unapređenju tehnika lečenja, primeni koncepta multimodalnosti, kombinovanjem farmakološkog i nefarmakološkog pristupa, nije se značajno poboljšala dugoročna kontrola bola (3). Primena opioida kod hroničnog nemalignog bola je povezana sa različitim neželjenim efektima kao što su: mučnina, opstipacija, vrtoglavica, delirijum, tolerancija, zavisnost, kao i uslovi za njihovu zloupotrebu. Terapija opioidima može kupirati akutni bol i hronični maligni bol, ali se ne smatra terapijom izbora za lečenje hroničnog nemalignog bola. S obzirom na različite zakonodavne regulative o dostupnosti opioidne terapije, indikacijama za propisivanje i specijalnostima koje ih mogu propisati, problem "opioidne krize" je nejednako shvaćen i zastupljen u različitim državama (4). Kako je hronični nemaligni bol prepoznat kao značajan socio-ekonomski problem, mnoga udruženja su dala svoje preporuke o propisivanju opioida za kupiranje ove vrste bola.

Mehanizam nastanka hroničnog nemalignog bola

Fiziološki, hronični nemaligni bol nastaje putem dvojakog mehanizma: u procesima periferne i centralne senzitizacije kao posledice dugotrajnog, ponavljanog bolnog nadražaja, prouzrokujući reverzibilne potom ireverzibilne promene na nociceptivnom

putu (5). Periferna senzitizacija podrazumeva prisutnu toničku aktivnost ili promenu u aktivnosti nociceptora kao posledicu lokalizovanog akutnog tkivnog oštećenja pod uticajem medijatora inflamacije (pojačan odgovor na stimulus uz snižen receptorni prag). Centralna senzitizacija se manifestuje pojačanom aktivacijom neurona zadnjih rogova sive mase kičmene moždine i olakšanom transmisijom nociceptivnih signala (povećan odgovor nociceptivnih neurona centralnog nervnog sistema na pragovni ili subpragovni stimulus, modulisan prethodnim iskustvom ili emotivnim stanjem). S obzirom na mehanizam nastanka hroničnog bola koji uključuje kompleksnu interakciju između genetskih, fizioloških, emocinalnih, kognitivnih, socijalnih faktora i faktora okruženja, jačina bola ne korelira sa stepenom oštećenja tkiva.

Ko propisuje, koliko dugo, u kom režimu, u kojoj dozi i sa kakvim terapijskim učinkom?

Prema stavu pojedinih autora, u Evropi je zabeležen trend porasta propisivanja opioida u cilju kupiranja hroničnog nemalignog bola umereno jakog i jakog intenziteta, uglavnom propisanog od strane izabranog lekara (6). U Holandiji, izabrani lekari (*GPs*) su odgovorni za 75% prvog propisivanja opioida i za oko 90% ponovljenog propisivanja opioida u cilju lečenja hroničnog nemalignog bola. Opravdanje za ovakav trend je što GPs nisu dovoljno upoznati sa detaljima i mogućnostima nefarmakološkog tretmana, da dosadašnji neopioidni tretman nije bio dovoljno efikasan, da smatraju da nisu dovoljno učinili za pacijenta, da bi izgubili poverenje ukoliko pacijenta ostave u bolu. U Republici Srbiji, prema aktuelnom pravilniku o propisivanju opioidne terapije, svaki specijalista određene oblasti medicine je može propisati (7). Izabrani lekar iz nadležnog Doma zdravlja, na osnovu izveštaja specijaliste, izdaje dupli recept za propisani opioid. Na osnovu iskustva autora, od strane nadležnog lekara iz Doma zdravlja, uvažavanje izveštaja specijaliste je mesec dana. Nakon isteka tog perioda, pacijent se vraća na revaluaciju stanja kod specijaliste koji je u terapiju uključio opioid ili specijalisti zaposlenom u Kabinetu za terapiju bola.

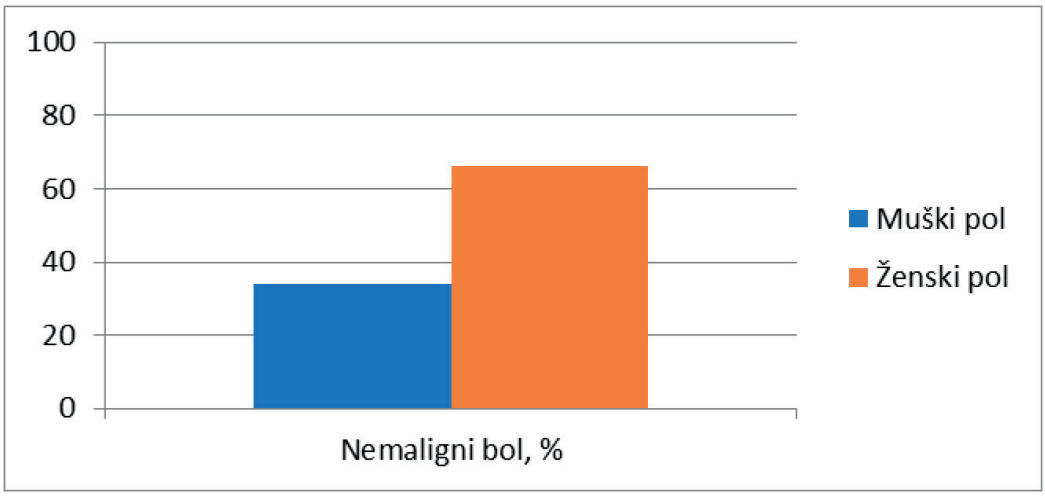
Na osnovu EFIC smernica (*European Pain Federation*) iz 2021, posvećenih ulozi opioida u terapiji hroničnog nemalignog bola, vodiča Nemačkog udruženja za kontrolu bola iz 2020, Kanadskog udruženja za kontrolu bola iz 2017. i Američkog udruženja za kontrolu bola iz 2016, formirane su jedinstvene preporuke za sprovođenje terapije opioidima (8-12). U navedenim preporukama, ističu se tri perioda u dužini primene opioida: 4-12 nedelja, 12-26 nedelja i duže od 26 nedelja, čime je definisano kratkoročno, srednjeročno i dugoročno propisivanje opioida. Dugoročno propisivanje opioida razmotriti kod pacijenata koji su na stabilnoj dnevnoj dozi uz prisutno funkcionalno poboljšanje duži vremenski period, tromesečnu reviziju terapijskog učinka-pozitivnog i negativnog. Za određene vrste hroničnih nemalignih bolova se ne preporučuje terapija opioidima, ali i kod pacijenata koji su skloni različitim oblicima zavisnosti od alkohola ili psihoaktivnih supstanci, pacijentima koji su anksiozni ili sa dijagnozom depresije. Veća incidenca opioidne zavisnosti je prijavljena kod pacijenata mlađe životne dobi i

ženskog pola. Propisivanje opioida nije preporučeno kod primarnih bolnih sindroma: glavobolje, fibromijalgije, visceralnih bolnih sindroma, primarnog muskuloskeletnog bola. Kod svih njih se ne očekuje željeni pozitivni efekat primenjene terapije uz mogućnost za nastanak novog oblika zavisnosti i tolerancije na terapiju. Pre uključenja opioida u terapiju, optimizovati drugi nefarmakološki i farmakološki metod lečenja. Opioide uključiti ukoliko su drugi metodi trenutno neefikasni, ukoliko ih pacijent ne toleriše ili primenjena terapija ima neželjene efekte, ako su nedovoljno dostupni nefarmakološki postupci lečenja. Pacijenta instruisati da je terapija privremena, da bi trebalo da se kombinuje sa fizikalnim i kognitivno-bihejvioralnim postupcima koji bi svi zajedno trebalo da poboljšaju funkcinalni kapacitet i redukuju jačinu bola do 30%. Prethodni dogovor sa pacijentom je neophodan kako bi očekivanja od opioidne terapije ne bi bila prevelika, a pacijent razočaran, što bi sve zajedno zahtevalo primenu nerealno velike doze opioida. Period titracije terapije opioidima bi trebalo da traje 4-12 nedelja. Početna doza opioida ne bi trebalo da bude veća od 50mg MED (*morphine equivalent dose*), a tokom perioda lečenja, ukupna dnevna doza ne bi trebalo da bude veća od 90mg MED. Opioid ne propisivati kao monoterapiju. Tokom terapije opioidima sprovoditi nefarmakološke postupke lečenja: fizikalnu terapiju, kognitivno-bihejvioralnu terapiju. Tokom perioda lečenja, motivisati pacijenta na periodično redukovanje doze (vikendom). Opioide primenjivati oralnim putem. Kod insuficijencije jetre i bubrega, primenjivati opioide bez aktivnih metabolita: hidromorfon, fentanil, tapentadol, buprenorfin. Primenjivati slabe opioide pre nego jake opioide. Opioidnu terapiju postepeno isključiti ukoliko: izostaje terapijski efekat bez funkcionalnog poboljšanja, postoje znaci tolerancije ili tendencije ka nemedicinskoj upotrebi.

U Kabinetu za terapiju bola Univerzitetskog kliničkog centra Srbije, u poslednje dve godine, paleta opioidnih preparata je bogatija za oksiodon i tapentadol, što je stvorilo dodatnu terapijsku mogućnost za kupiranje hroničnog malignog i nemalignog bola. U navedenom periodu, zastupljenost pregleda pacijenata sa hroničnim malignim i nemalignim bolom je bila podjednaka ($p\ 4{,}62\ p<0{,}05$), bez statistički značajne razlike u distribuciji među polovima ($p\ 0{,}005\ p<0{,}05$). Međutim, uočena je statistički značajna razlika u zastupljenosti hroničnog nemalignog bola među polovima ($p\ 42{,}28\ p>0{,}05$), *Grafikon 1.*

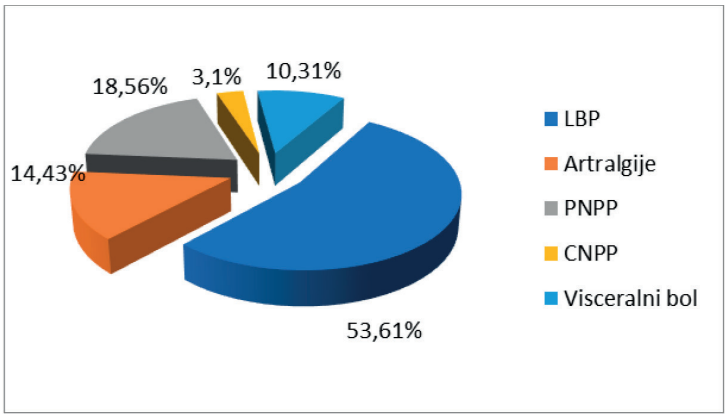
Prosečna starost pacijenata pregledanih zbog hroničnog nemalignog bola je $64{,}11\pm13{,}96$ godina, odnosno za muški pol $65{,}19\ \pm14{,}64$ god, ženski pol $63{,}53\pm13{,}59$ godina, bez uočene statistički značajne razlike ($p\ 0{,}355$). Primenom T-testa za određivanje razlike u starosti pacijenata kojima je propisivan opioid i kojima nije propisivan opioid, nađena je statistički značajna razlika u distribuciji pacijenata oba pola prema terapiji opioidima ($p\ 0{,}042$), gde je prosečna starost pacijenata bez opioidne terapije $61{,}79\pm14{,}13$, odnosno $65{,}39\pm13{,}47$ godina. Kod pacijenata muškog pola, nije uočena statistički značajna razlika u starosti između onih kojima je propisivan opioid u odnosu na one kojima nije propisivan, ali je razlika blizu statističkog nivoa značajnosti ($p\ 0{,}092$). Kod pacijenata ženskog pola, prosečna starost onih sa propisanim opioidom i bez propisanog opioida se nije statistički razlikovala ($p\ 0{,}355$), gde je prosečna starost

Grafikon 1: Distribucija nemalignog bola među polovima



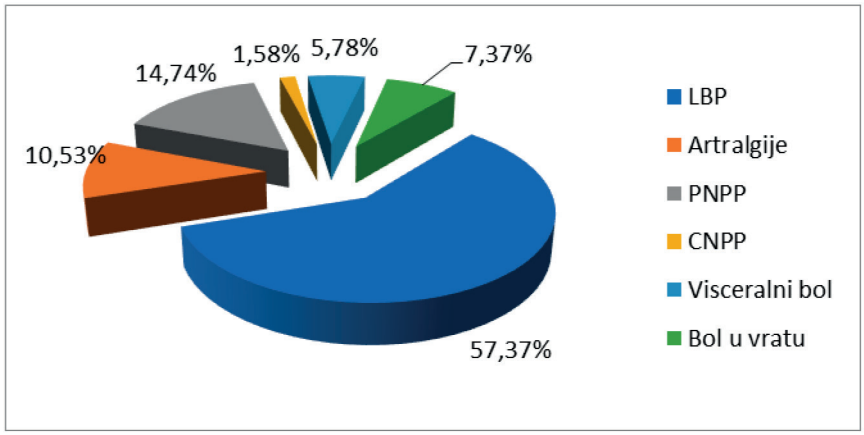
pacijentkinja sa propisanim opioidom bila 65,44±11,28 i 65,53±12,83 godina bez propisanog opioida. Prosečna propisana doza opioida kod obe populacije pacijenata je 42,13±32,25mg MED. Prosečna propisana doza opioida kod pacijenata muškog pola je 45,08±33,05mg MED. Kod pacijenata ženskog pola, prosečna propisana doza opioida je 40,66±31,05mg MED, bez statističke značajnosti u odnosu na propisanu dozu kod pacijenata muškog pola (p 0,405). Distrubucija tipa hroničnog nemalignog bola među populacijama pacijenata oba pola se nije značajno razlikovala, osim zastupljenosti primarnog cerviklanog bola sa radikularnom distribucijom koji je zabeležen samo kod pacijenata ženskog pola (*Grafikon 2, Grafikon 3*).

Grafikon 2: Distribucija vrste nemalignog bola tretiranog opioidima među pacijentima muškog pola



**LBP (low back pain), PNPP (periferni neuropatski bol), CNPP (centralni neuropatski bol)*

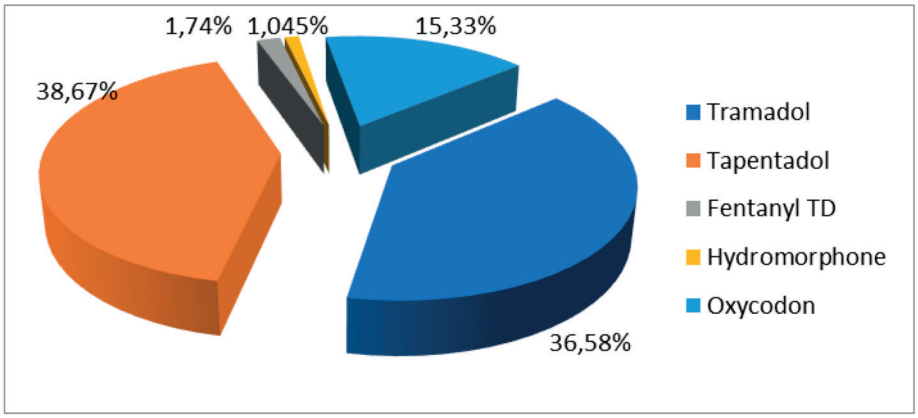
Grafikon 3: Distribucija vrste nemalignog bola tretiranog opioidima među pacijentima ženskog pola



**LBP (low back pain), PNPP (periferni neuropatski bol), CNPP (centralni neuropatski bol)*

Kod 2,43% pregledanih pacijenata, opioid je prvi put propisao drugi spacijalista (ortoped, vaskularni hirurg, neurolog). Kod svih drugih pacijenata, opioid je propisan od strane specijaliste iz Kabineta za terapiju bola (*Grafikon 4*).

Grafikon 4: Distribucija propisanih opioidnih analgetika kod pacijenata sa nemalignim bolom



Prosečno vreme za zakazivanje kontrolnog pregleda je 2-4 nedelje. U navedenom periodu, kod 45,29% pacijenata je obavljen kontrolni pregled. Kod 43,84% je terapija imala pozitivan učinak, kod istog broja pacijenata terapija je bila bez učinka, dok 12,31% njih nije tolerisalo propisanu terapiju. Početna propisana doza opioida je 20-40mg MED. Maksimalna propisna doza je 120mg MED kod ženskog pola, 240mg MED kod muškog pola, obe terapije započete pre pregleda u Kabinetu, propisane za centralni neuropatski

bol i bol u donjem delu leđa. Kod svih pacijenata, uz terapiju opioidom, savetovan je fizikalni tretman, neopioidni tretman, primena laksativa i antiemetika. Kod 8,01% pregledanih pacijenata, pre pregleda u Kabinetu, primenjen je neki invazivni postupak.

Zaključak

Terapija opioidima kod hroničnog nemalignog bola ne može biti primenjena kod svakog tipa bola i kod svakog pacijenta. Primena opioida zahteva intermitentni monitoring terapijskog efekta i neželjenih efekata, kao komponenta multimodalnog i multidisciplinarnog terapijskog pristupa.

Literatura

1. van Hecke O, Torrance N, Smith B. Chronic pain epidemiology and its clinical relevance. British Journal of Anaesthesia 2013; 111:8-13.
2. Dorner TE. Pain and chronic pain epidemiology: implications for clinical and public health fields. Wien Klin Wochenschr 2018; 130: 1-3.
3. Mills S, Nicolson K, Smith B. Chronic pain:a review of its epidemiology and associated factors in population-based studies. British Journal of Anaesthesia 2019; 123:273-83.
4. Bialas P, Maier C, Klose P, Hauser W. Efficasy and harms of long-term opioid therapy in chronic noncancer pain: systematic review and meta-analysis of open-lable extension trials with study duration ≥ 26 weeks. Eur J Pain 2020; 24:265-78.
5. Price T, Basbaum A, Bresnahan J, Chambers J, De Konick Y,et al. Transition to chronic pain:oportunities for novel therapeutics. Nature Review Neuroscience 2018; 19: 383-87.
6. Punwasi R, Kleijn L, Rijkels-Otters JBM, Veen M, Chiarotto A, Koes B. General pactitioners attitudes towards opioids for noncancer pain: a qualitative systematicreview. BMJ Open 2022; 12:e054945. doi:10.1136/bmjopen-2021-054945.
7. Pravilnik o načinu propisivanja i izdavanja lekova. Službeni list SRJ, br. 16/94, 22/97 i 52/2002.
8. Krcevski Skvarc N, Morlion B, Vowles K, Bannister K, Buchsner E, Casale R, et al. Europena clinical practice recommendations of opioids for chronic noncancer painpart 2: special situations. Eur J Pain 2021; 00:1-17.
9. Hauser W, Morlion B, Vowles K, Bannister K, Buchser E, Casale R, et al. European clinical practice recommendations on opioids for noncancer pain-part 1: role opioids in the management of chronic noncancer pain. Eur J Pain 2021;25:949-68.
10. Petzke F, Bock F, Huppe M, Nothacker M, Norda H, Radbruch L, et al. Long-term opioid therapy for chronic noncancer pain:cecond update of German guidelines. Pain 2020;5:1-9.
11. Busse J, Craigie S, Juurlink D, Buckley N, Wang L, Couban R, et al. Guideline for opioid therapy and chronic noncancer pain.CMAJ 2017; 189:659-666.
12. Dowel D, Haegerich T, Chou R. CDC guidelines for prescribing opioids for chronic pain-United States 2016. JAMA 2016; 316:1624-45.

All faces of the pain – from the perspective of a physiatrist

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Introduction

Patients with pain or functional problems come to the physical medicine and rehabilitation clinic. It is considered that pain is the most common reason for calling a doctor and is the leading cause of incapacity.The International Association for the Study of Pain defines that painful sensory and emotional experience is associated with actual or potential tissue damage or experience described in the context of such damage (1). Its manifestation depends on individual experience, but also on a complex series of interactions that include sensory, pathophysiological, affective, socio-cultural, behavioral and cognitive elements (2).

Pain is sometimes the main or accompanying symptom in a large number of acute, chronic somatic and psychological disorders, and it is necessary to assess the characteristics of pain (3,4).

The basic classification of painful disorders is in relation to the type, duration, location, etiology and pathophysiological mechanism, as well as based on the natural course of the disorder (5).The task is to take a good look at the entire history of the disease, to classify the pain and to assess whether the patient is indicated for physical and rehabilitation therapy, and to present the possibilities of treatment.

When it comes to pain, in addition to physical agents, the use of drug therapy is indicated in physiatric clinics, for both acute and chronic pain.When patients enter the physical medicine clinic, they generally have the idea that the treatment should be reduced to the application of only physical procedures. Often, that is not possible, but the use of drug and vitamin therapy is also indicated. In general, patients are stimulated to be treated with physical therapy because it is primarily non-invasive therapy and somehow they are always of the opinion that as soon as they are treated with physical therapy, their disease is not terrible.

Case 1

Patient A. A 40-year-old female was admitted to the Day Hospital of the Neurosurgery Clinic due to lower back pain and a fall in her right foot that began a month before admission. The performed magnet (MR) of the lumbosacral segment of the spinal column indicated a very initial minimal focal central protrusion L5-C1 of the i.v. The neurosurgeon prescribed corticotherapy for five days and was immediately sent for physical therapy within the day Hospital.

The patient still states pain in the spine, but of less intensity, and reports that she is rated 3/5 according to YOU. Also, we find out that he first started having pain that goes down his legs, and then, after three days, he noticed weakness in his feet.

In the personal anamnesis - without allergies to iodine and drugs. She had tonsil surgery in childhood, uterine polyps, orthopedic foot and appendix surgery. He suffers from insulin resistance.

Clinical finding - discrete sinistroconvex scoliosis, no spasm at rest, lumbar flexion up to half full amplitude. Lazarevic positive on the right at 45 degrees, motor failure of the right foot, according to the manual muscle test (MMT) 4/5 for myotomes L4, L5, S1, sensibility reports as normal, patellar reflex slightly weakened on the right, Achilles normal.

Continued drug therapy (NSAIL) was prescribed, with alpha lipoic acid, B vitamins and physical therapy started. Control scheduled for seven days.

He still complains of pain and weakness in his feet. According to the patient, the pain is unchanged even if he has both medication and physical therapy.

Clinical findings - disturbed gait pattern, limp gait. There is no spasm at rest, there is lumbar flexion with less than half the full amplitude. Lazarevic positive on both sides at 45 degrees, on DE weakness of dorsal and plantar flexion of the right foot without loss of sensibility, patellar reflexes slightly weakened on the right.

Since the progression is under control, the entire clinical finding does not impress as a problem related to lumbar disc herniation, physical treatment is interrupted and a consultation with a neurologist is requested.

Clinical findings of a neurologist - signs of bialteral affection of lumbosacral roots with peroneal weakness on the right, limp gait, difficulty getting up from squats with Gowers maneuver, extinguished MR on DE and positive Lazarevic on both sides at 45 degrees. An examination at the Day Hospital of the Clinic of Neurology - lumbar puncture, electomioneurography (EMNG) on the upper and lower extremities was indicated.

During the neurological examination, the magnet of the endocranium indicated the existence of a venous angioma in the region of the brainstem, with signs of hemorrhage, possibly in the field of cavernomas.

After this, a consultation with a neurosurgeon was requested, which indicated only further monitoring.

A series of worsening of the patient's condition follows, with the development of a neurological deficit. After one worsening, she was sent to physical therapy again, complaining of impaired hand functionality, instability when walking.

Clinical finding - actively active, gait on a slightly wider base, weakness of the right hand, without convincing lateralization of other segments.

Rehabilitation started and implemented within the Day Hospital of the Neurosurgery Clinic, focused on the Chinese program. The general clinical condition was monitored at all times and the entire rehabilitation program was carried out without the patient's efforts.

The patient is regularly monitored by neurologists and neurosurgeons with control MRI of the endocranium.

Case 2

Patient D. S, 42 years old, female, referred by a neurosurgeon to conduct physical therapy, and after receiving pulse therapy she had for five days.

Complaints in terms of intense pain in the lumbosacral spine (VAS 10) with spreading along the right leg occurred twenty days before the start of pulse therapy and after physical exertion.

Treated with medication, nonsteroidal anti-inflammatory drugs, but the pain did not subside and a lumbosacral spine magnet was performed, which showed the existence of disc extrusion at the L5-C1 level with cranial migration, smaller in size but with foramen position, and compression on the dura and right root. irritation of the right root S1 as well as protrusion of the iv discs L4-L5 and L3-L4 with irritations more pronounced of the right root L3, L4 and L5.

She received short-term pulse therapy, after which there was a moderate reduction in pain. However, two days after that, the right foot falls and is impossible foot dorsiflexion. She then contacted a neurosurgeon who prescribed pulse therapy for five days. She had similar problems two years ago.

He complains of pain in the lumbar spine that goes through the right leg, according to YOU it is 5/10, he also reports weakness of the feet. Clinical findings - Analgesic scoliosis, walking on a wider base with a cane, peroneal gait with the right foot. Moderate spasm of PVM LS of the spine, more pronounced on the right, flexion of the spine full, Lazarević negative on both sides, PR and AR are less provoked, hypoaesthesia of dermatomes L4 and L5 on the right, MMT of the right foot for m. tibialis anterior 2/5 and m. ext. hallucis longus as for m extensor digg. communis at 2- / 5 per MMT. Prescribed drug therapy and started physical therapy. The patient was regularly physiologically monitored and evaluated, medication and physical therapy were applied, which at the end of the treatment resulted in the patient being painless, with recovered muscle strength of the foot, but not completely. Advice is given for the continuation of the Chinese program of strengthening the lumbar PVM and feet at home.

Patient M. N, 28 years old, female, referred by a neurosurgeon for physical therapy, and after receiving pulse therapy. Pain in the neck and along the right arm occurred three weeks before admission, suddenly, after waking up, without a provocative

moment. Initially treated with nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroid therapy, without effect, then a cervical spine magnet was performed, which indicated a herniated disc C6-7 in extrusion and C5-6 in protrusion, without myelopathy.

The neurosurgeon first indicated surgical treatment, but since the patient was not motivated for surgical treatment, it was decided to try conservative therapy.

Pulse therapy was introduced within the Day Hospital of the Clinic for Neurosurgery for five days, the pain was rated 9/10 according to YOU. After receiving therapy, subjective improvement in terms of pain reduction by about 40%, VAS 5/10. Pain in the neck and right arm, denies tingling. Clinical findings - reduced movements in the cervical spine, spasm of PVM, Valleix points pl. brachialis right sensitive to palpation, Bickeles positive right, MTR symmetrical, weakness in myotomes C6, C7, C8 right at 4- / 5 per MMT, hypoaesthesia of dermatomes C6, C7 and C8 right.

The proposal to do EMNG was not done. Continued with drug per os therapy, without physical therapy still.

Two days after the initial examination, the patient appears due to worsening, ie increased pain in the right arm and in the area of the shoulder blade and tingling in the right arm. The intensity of pain according to YOU is now 9/10. The clinical finding, compared to the initial one, is dominated by spasm and more reduced mobility of the cervical spine, along with other findings as in the first examination. A neurosurgeon who did not indicate surgical treatment was consulted. Now administered cortico therapy intramuscularly with muscle relaxants, proton pump inhibitors, alpha lipoic acid and B vitamins, continued with topical therapy and wearing an orthosis with emphasized and potentiated rest and sparing of the right arm.

Seven days after the application of therapy to patients with minimal pain and no tingling. Clinical finding improved. Th: Medication and started physical treatment.

The patient is regularly physiologically monitored and evaluated with the control of medication and physical therapy, and states that at the end of the treatment he is completely free of pain and tingling, his right hand is still slightly weaker, but he notices constant progress. Clinical finding-. Movements in the neck possible in all directions, limited in extreme amplitudes, Valleix points pl. brachialis insensitive to palpation, minimal painful sensitivity of the medial edge of the right shoulder blade, weakness in myotomes C6, C7, C8 at 4 + / 5 per MMT. Th: Give advice that the Chinese carry out the program for which she is trained in our country every day in the pain-free phase at home, give advice on further behavior with alpha lipoic acid and B vitamins.

Conclusion

ur task is to make an assessment of the patient's condition and the way of treatment with a well-taken anamnesis, review of the performed diagnosis or to ask for a supplement to the diagnosis. The possibilities of physical therapy are great if we select

patients well and correctly after the diagnosis. Physical therapy is not a mere implementation of "currents", but a good view of the patient, diagnostics with clinical examination and the use of complete drug therapy with physical therapy.

References

1.Treede R. D., Rief W., Barke A., Aziz Q., Bennett M.I., Benolied R.,et al. A classification of chronic pain for ICD-11. Pain 2015;156(6):1003-1007.

2.Dalal S, Bruera E. Assessing cancer pain. Curr Pain Headache Rep 2012;16:314-324.

3. Clauw D. J., Essex M.N., Pitman V, Jones K.D. Reframing chronic pain as a disease, not a symptom: rationale and implications for pain management. Postgrad Med. 2019; 31:1- 14.

4. Lađević N, Stamenković D, Nešič D, Mimč A, Marković B, Lađević Likić I. Neuropathic pain in patient with malignancy. Proceedings Abstract book, XII Serbian Congress of Anesthesiologist and Intensivists with international expert participation 2014, 23- 26. October, Belgrade:266-271.

5. Vargas- Prada S, Coggon D. Psyhological and psychosocial determinants of musculoskeletal pain and associated disability. Best practice and research clinical rheumatology 2015;29 (3):374-390.

PEA in combination with primary and secondary antioxidants (EpiNeuron) – treatment of neuroinflammation, neurodegeneration and neurophatic pain

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Abstract

Palmitoylethanolamide (PEA) is an endogenous fatty acid amide, belonging to the class of nuclear factor agonists. It was discovered in 1957. PEA is an antagonist of pro-inflammatory factors by regulating the activities of mastocytes and microglia cells. Main target of PEA is the peroxisome proliferator-activated receptor alpha (PPAR-α), which is a receptor in the cell nucleus. PEA has also affinity to cannabinoid-like G-coupled receptors GPR55 and GPR119. By direct mechanism of action, PEA manifests neuroprotective features, and by indirect activation of the cannabinoid receptors (CB1 and CB2) and TRPV1 ion channels, it regulates the inflammation and pain. Presence of PEA enhances anandamide activity by an "entourage effect". Because of the synergistic effects, PEA manifests significant therapeutic effects in the central and peripheral nervous system. PEA regulates many physiological functions related to neuroinflammation, neurodegeneration and chronic pain and it is a protective factor against inflammation, pain and neuronal damage. EpiNeuron is a specially designed formulation of active compounds and can safely be used as an effective add-on treatment in numerous clinical conditions such as stroke, neurodegenerative diseases, multiple sclerosis, amyotrophic lateral sclerosis, neuropathy, compressive syndromes, osteoarthritis etc. No serious side effects nor drug-drug interacions have been reported.

Keywords: palmitoylethanolamide (PEA), endocannabinoid, antioxidants, neuroinflammation, neurodegeneration, neuropathic pain

Introduction

Endocannabinoid system

The endocannabinoid system is a very important physiological system that participates in creating and maintaining balance (homeostasis) of human health (1). It

consists of endocannabinoids (molecules) and cannabinoid receptors (CB1 and CB2). Cannabinoid receptors (CB1 and CB2) represent the largest and most widespread receptor system in our body, present in the brain, all organs and tissues. CB1 receptors play a major role in controlling pain, memory and motor skills; they are found predominantly in the central nervous system (CNS), i.e. brain and spinal cord.

Anandamid (AEA-arachydonoilethanolamide) and 2-AG (2 Arahidonil glycerol) are endocannabinoids that operate via CB1 and CB2 receptors. Anandamid was described in 1992. Its effects are visible in CNS and PNS. Anandamid is known as the "bliss molecule" because it causes a feeling of good mood, fullness and analgesic effect (2). It is important for functioning of the immune system, regulation of nutrition and in creating motivation and enjoyment. AEA increases in conditions of oxidative stress, inflammation or cellular death. AEA is created in response to injuries when confronted with inflammatory activity. This activity may be evidence of the role of the endocannabioid system in cell hemostasis. Pharmaceuticals are seeking to develop drugs that will increase levels of anandamide in the brain. This would help treat anxiety and depression. 2-AG was described in 1994-1995. It's an estar derived from omega-6 fatty acids, arahydonic acid and glycerol. It's present in CNS, and it's also found in breast milk.

Neuroinflammation

Neuroinflammation in the CNS and PNS is controlled by a complex network of regulatory mechanisms that limit its potentially dangerous effects (3). When neuroinflammation lasts longer (trauma and pathological conditions), it exceeds the limits of physiological control and causes harmful effects, including pro-inflammatory signaling pathways, increased oxidative stress and neuronal death which is the basis of genesis: chronic neuropathic pain, chronic neurodegenerative diseases (Alzheimer disease, Parkinson's disease, Sclerosis Multiplex) psychiatric illnesses, and autism spectrum disorders.

Microglia

Microglia play an active role in maintaining normal physiological conditions. Microglial activation caused by nerve tissue injury consists of changes in: morphology (from branched to amoeboid), the number (proliferation) and migration to the site of injury increases, and expression of microglial markers. In addition to the morphological changes that accompany nerve injury, there are also significant biochemical changes that are important for microglia in pain induction. Several studies have shown that inhibition of microglia activation reduces hyperalgesia and allodynia after nerve injury (4).

Mast cells

Mast cells (located near the sensory nerve endings) are the first to react to trigger, strengthen and prolong all immune and nervous reactions that arise from their activation (5). Mast cell degranulation can produce nociceptor-sensitizing factors, thus directly contributing to neuropathic pain (the reason why peripheral mast cells are considered

pro-inflammatory and pronociceptive). Furthermore, mast cells can move through the blood-brain barrier (BBB), but also through the blood-spinal cord barrier (BSCB), both in normal circumstances and in diseases. This increase in BBB and spinal cord (BSCB) permeability leads to an increase in leukocyte invasion of the CNS and PNS.

Vascular changes, together with leukocyte infiltration, are the basis of the pathophysiology of peripheral neuropathic pain. Therefore, multiple changes in vascular, metabolic, and autoimmune include consequent oxidative stress, neuroinflammation, microvascular ischemia and endoneuric edema (6).

Oxidative stress

Free radicals (oxidants) are molecules that have one or more unpaired electrons and thus have a strong tendency to take or give electrons to other molecules, which can lead to changes in the structure of molecules and their decay. An imbalance between antioxidants and oxidants in favor of oxidants is defined as oxidative stress (7). Oxidative stress is thought to be widely responsible for large lesions in the aging process as well as for serious pathological conditions such as:neurodegenerative diseases, malignant neoplasms, diabetes mellitus and cardiovascular disease. Antioxidants are molecules that can donate an electron to a free radical without becoming unstable on their own. This causes free radicals to become more stable and therefore less reactive.

ALIAmides

ALIAmides are autocoid local amide antagonists (8). The term autocoids refers to endogenous compounds or their precursors or other derivatives produced on demand and then metabolized in the same cells and / or tissues. ALIAmides are a group of endogenous bioactive lipids, including palmitoylethanolamide (PEA), oleoyl ethanolamide (OEA), and stearoyl ethanolamide (SEA), which play a central role in a number of biological processes, including pain, inflammation, and lipid metabolism. Classic drugs block only one target receptor, which leads to a sudden stop of the physiological process, but also leads to their side effects. Modern medicine deals with endogenous compounds or their derivatives that use physiological pathways to modify pathological processes, so the probability of side effects is low.

Rita Levi-Montalcini, a Nobel Prize winner, discovered that the accumulation of N-acyl ethanolamine (NAE) in the tissue occurred in pathological degenerative conditions, and this is an important biological response to the suppression of such inflammation (9). The main mechanism of action of ALIAmide is reduction of modulation of cellular hyperactivity after injury. Therefore, they are used in the treatment of numerous neuroinflammatory and painful conditions.

Palmitoylethanolamide (PEA)

Palmitoylethanolamide (PEA) is an endogenous fatty acid amide, belonging to the class of nuclear factor agonists. It was discovered in 1957. During neuroinflammatory

and neurodegenerative diseases it is a factor of protection against inflammation, pain and neuronal damage. Main target of PEA is the peroxisome proliferator-activated receptor alpha (PPAR-α) (10). PEA also has affinity to cannabinoid-like G-coupled receptors GPR55 and GPR119 (11).

The mechanism of action of PEA is the following (10,12):
- regulation of mast cell and microglia activity (proinflammatory factor antagonists)
- directly via PPAR-alpha and GPR55 receptors (neuroprotective properties)
- by indirect activation of cannabioid receptors CB1 and CB2 and TRPV1 ion channels (regulation of inflammation and pain)

Due to the synergism of the multiple mechanism of action, PEA achieves significant therapeutic effects on the CNS and PNS. PEA has several clinical effects: antineuroinfamatory, analgesic, neuroprotective, antiepileptic and anticonvulsant effects.It has been shown that the presence of PEA enhances anandamide activity by an "entourage effect" (13,14) and various clinical trials have shown the efficacy of PEA in different inflammatory and pain syndromes in daily doses from 300-1200 mg per day (15, 16,17). One systematic meta-analysis of 10 studies included data from 786 patients receiving PEA for pain-related indications and 512 controls, use of PEA was associated with pain reduction significantly greater than observed in controls ($p < 0.001$) (18). Other studies have shown benefit of PEA in diabetic neuropathic pain, sciatic pain, pelvic pain and entrapment neuropathic pain states (19, 20, 21, 22). It has also been used in patients suffering from thalidomide and bortezomib induced neuropathy and after two-month of treatment, they reported improved nerve functions and decreased (23). A case report of a woman with a previoudly undocumented variant of congenital insensitivity to pain was described (24). Significant increases in fatty acid amides including PEA, arachidonoylethanolamide, and oleoylethanolamide were noted and it was found that this is a result of a combination of a hypomorphic single nucleotide polymorphism of fatty acid amide hydrolase (FAAH), alongside a mutation of the pseudogene, FAAH-OUT. The pseudogene was found to be capable of modulating the expression of FAAH, which can be used for development of new analgetic and anxiolytic drugs in the future (25). Hesselink and Hekker (2012) selected a number of pain treatment-resistant patients and started adding PEA to the analgesic treatment regime (26). They presented seven different clinical cases, six of which showed a clear beneficial effect of PEA. Their case series included patients with polyneuropathic side-effects due to chemotherapy with sagopilone, severe chronic pain due to failed back surgery syndrome, chronic neuropathic pain due to diabetes mellitus, chronic idiopathic axonal polyneuropathy and vaginal complaints from lichen sclerosis. Only one elderly patient presented as a nonresponder to PEA. This was an 80-year-old Caucasian female with chronic idiopathic axonal neuropathy. It was thought that one of the reasons for this might have been advanced age combined with a nonspecific chronic pain.

Neuroprotective features of PEA

The use of PEA stimulates the expression of neurotrophic factors: nerve growth factor (NGF), neurotrophic factor of glial cells, neurotrophin 3 and Brain-derived neurotrophic factor (27). Thus PEA has a prominent effect on: better survival, differentiation and maturation of new neurons.

In ischemic stroke and CNS trauma, PEA reduces the infarct zone (penumbra) and reduces the neurotic edema and lesion size. It also blocks the activation and infiltration of astrocytes and neutrophils (microglia) and reduces the expression of pro-inflammatory markers as well. PEA improves neurobehavioral function by improving the motor deficit. The use of PEA in stroke and CNS trauma contributes to the improvement of clinical parameters in patients: neurological status, degree of spasticity, cognitive abilities, pain and independence in daily life activities.

In Alzheimer's disease (AD) and Parkinsonism/Parkinson's disease (PD), PEA modulates altered expression of proteins associated with this diseases, regulates pro-apoptotic markers and pro-inflammatory factors, leading to neuronal loss in the cerebral cortex and hippocampus for AD or in the substantia nigra for PD.

Therapeutic effects of PEA in Sclerosis Multiplex (SM): PEA improves spasticity and motor deficit and markedly reduces the expression of inflammatory cytokines. These effects are accompanied by reduced demyelination and axonal damage. These data suggest that exogenous PEAs may be helpful in compensating for or enhancing endogenous defense — a mechanism that cells or tissues use to counteract neurodegenerative and neuroinflammatory processes.

Patients with amyotrophic lateral sclerosis (ALS) treated with PEA showed a slowing of the deterioration of the respiratory tract compared to untreated ALS patients (28). Death and tracheotomy were more common in untreated PEA patients. Palma et al. (2016), showed that the use of PEA can contribute to the preservation of muscle excitability and be useful for ALS as an adjunct to treatment (28).

In cancer patients, PEA inhibits the production of proinfamative cytokines that contribute to tumorogenesis, reduces the chemical and air resistance of cancer cells, reduces dose-dependent side effects of various cytostatics thereby, in critical situations it provides the possibility of applying a higher dose and longer treatment. The combination of superoxide dismutase, alpha-lipoic acid with the addition of vitamin E have complete antioxidant block, acting as primary and secondary antioxidants, inhibits lipid peroxidation and free radical formation, which is a process that is one of the mechanisms of malignant neoplasia.

Safety

PEA is generally considered safe, and without adverse drug reactions (ADRs) or drug interactions. A study that analysed safety features in sixteen clinical trials, six case reports/pilot studies and a meta-analysis of PEA as an analgesic, concluded that for treatment periods up to 49 days, no serious side effects were reported, at an incidence

of 1/200 or greater (29). Another pooled meta-analysis that evaluated twelve studies reported that no serious side effects were registered (30). No data on interactions with PEA have been reported.

EpiNeuron

It is a specially designed formulation of active ingredients whose strong synergistic effect determines its treatment for various pathological conditions accompanied by neuroinflammation, neurodegeneration and neuropathic pain:stroke and CNS trauma, neurodegenerative CNS diseases (Parkinson's disease,Alzheimer's disease, Multiple sclerosis, Amyotrophic Lateral Sclerosis (ALS), neuralgia, viral infections of the nervous system (Herpes Zoster, HIV), cancer and chemotherapy-induced neuropathic pain, phantom pain etc.Thanks to the strong synergistic effect of the combination of active ingredients, EpiNeuron can be used in the treatment of various pathological conditions that lead to pain. EpiNeuron is unique due to advanced methods in its manufacturing technology. It consists of:

- Palmitoylethanolamide - PEA 300 mg (umPEA - highly absorbable ultramicronized form)
- Superoxide dismutase 70 IU (SOD-GlySODin® - gastroresistant form of SOD)
- Alpha-lipoic acid 300 mg (Physio Release Technology ® that is a form of prolonged action that guarantees a constant effective level of active substance in the blood during treatment)
- Vitamin E 7.5 mg, Vitamin B1 - 1.1 mg, Vitamin B3 - 9 mg;Vitamin B6 - 1.5 mg, Vitamin B12 - 2.5 mcg
- Magnesium - 30 mg and Zinc - 2.5 mg

Dosage and method of administration

Dosage of EpiNeuron is 1-2 times daily after a light meal, for a period of 3-6 months. EpiNeuron is not an opioid and is not addictive. Its use is safe, without serious side-effects and does not interact with other drugs. Patients with impaired renal and hepatic function may take EpiNeuron, as its metabolism is independent of renal and hepatic function.

Conclusion

PEA in combination with primary and secondary antioxidants (EpiNeuron) is a promising addition to the standard treatment of variety of conditions, with good tolerability and no serious side effects.

References

1. Lu HC, Mackie K. An Introduction to the Endogenous Cannabinoid System. Biol Psychiatry. 2016 Apr 1;79(7):516-25. doi: 10.1016/j.biopsych.2015.07.028.

2. Scherma M, Masia P, Satta V et al. Brain activity of anandamide: a rewarding bliss?. Acta Pharmacol Sin 2019; 40, 309–323. https://doi.org/10.1038/s41401-018-0075-x
3. Kwon HS, Koh SH. Neuroinflammation in neurodegenerative disorders: the roles of microglia and astrocytes. Transl Neurodegener 9, 42 (2020). https://doi.org/10.1186/s40035-020-00221-2
4. Chen G, Zhang YQ, Qadri YJ, Serhan CN, Ji RR. Microglia in Pain: Detrimental and Protective Roles in Pathogenesis and Resolution of Pain. Neuron. 2018;100(6):1292-1311. doi:10.1016/j.neuron.2018.11.009
5. Gupta K, Harvima IT. Mast cell-neural interactions contribute to pain and itch. Immunol Rev. 2018;282(1):168-187. doi:10.1111/imr.12622
6. Lugrin J, Rosenblatt-Velin N, Parapanov R, Liaudet L. The role of oxidative stress during inflammatory processes. Biological Chemistry, vol. 395, no. 2, 2014, pp. 203-230.
7. Pizzino G, Irrera N, Cucinotta M, et al. Oxidative Stress: Harms and Benefits for Human Health. Oxid Med Cell Longev. 2017;2017:8416763. doi:10.1155/2017/8416763
8. D'Amico R, Impellizzeri D, Cuzzocrea S, Di Paola R. ALIAmides Update: Palmitoylethanolamide and Its Formulations on Management of Peripheral Neuropathic Pain. Int J Mol Sci. 2020 Jul 27;21(15):5330. doi: 10.3390/ijms21155330.
9. Hesselink JMK. Professor Rita Levi-Montalcini on Nerve Growth Factor, Mast Cells and Palmitoylethanolamide, an Endogenous Anti-Inflammatory and Analgesic Compound. J Pain Relief 2013; 2:114. doi: 10.4172/2167-0846.1000114
10. O'Sullivan SE. Cannabinoids go nuclear: evidence for activation of peroxisome proliferator-activated receptors. British Journal of Pharmacology. 2007; 152 (5): 576–82. doi:10.1038/sj.bjp.0707423.
11. Godlewski G, Offertáler L, Wagner JA, Kunos G. Receptors for acylethanolamides-GPR55 and GPR119. Prostaglandins & Other Lipid Mediators. 2009; 89 (3–4): 105–11. doi:10.1016/j.prostaglandins.
12. Keppel Hesselink JM, de Boer T, Witkamp RF. Palmitoylethanolamide: A Natural Body-Own Anti-Inflammatory Agent, Effective and Safe against Influenza and Common Cold. International Journal of Inflammation. 2013; 151028. doi:10.1155/2013/151028.
13. Jonsson KO, Vandevoorde S, Lambert DM, Tiger G, Fowler CJ. Effects of homologues and analogues of palmitoylethanolamide upon the inactivation of the endocannabinoid anandamide". British Journal of Pharmacology. 2001; 133 (8): 1263–75. doi:10.1038/sj.bjp.0704199.
14. Ho WS, Barrett DA, Randall MD. Entourage' effects of N-palmitoylethanolamide and N-oleoylethanolamide on vasorelaxation to anandamide occur through TRPV1 receptors. British Journal of Pharmacology. 2008; 155 (6): 837–46. doi:10.1038/bjp.2008.324.

15. Indraccolo U, Barbieri F. Effect of palmitoylethanolamide-polydatin combination on chronic pelvic pain associated with endometriosis: preliminary observations. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2010; 150 (1): 76–9. doi:10.1016/j.ejogrb.2010.01.008.
16. Conigliaro R, Drago V, Foster PS, Schievano C, Di Marzo V. Use of palmitoylethanolamide in the entrapment neuropathy of the median in the wrist. Minerva Medica. 2011; 102 (2): 141–7.
17. Rankin L, Fowler CJ. The Basal Pharmacology of Palmitoylethanolamide". International Journal of Molecular Sciences. 2020; 21 (21): 7942. doi:10.3390/ijms21217942.
18. Artukoglu BB, Beyer C, Zuloff-Shani A, Brener E, Bloch MH. Efficacy of Palmitoylethanolamide for Pain: A Meta-Analysis. Pain Physician. 2017; 20 (5): 353–362.
19. Darmani NA, Izzo AA, Degenhardt B et al. Involvement of the cannabimimetic compound, N-palmitoyl-ethanolamine, in inflammatory and neuropathic conditions: review of the available pre-clinical data, and first human studies. Neuropharmacology. 2005; 48 (8): 1154–63. doi:10.1016/j.neuropharm.2005.01.001.
20. Phan NQ, Siepmann D, Gralow I, Ständer S. Adjuvant topical therapy with a cannabinoid receptor agonist in facial postherpetic neuralgia. Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology. 2010; 8 (2): 88–91. doi:10.1111/j.1610-0387.2009.07213.x.
21. Petrosino S, Iuvone T, Di Marzo V. N-palmitoyl-ethanolamine: Biochemistry and new therapeutic opportunities. Biochimie. 2010; 92 (6): 724–7. doi:10.1016/j.biochi.2010.01.006.
22. Keppel Hesselink JM, Kopsky DJ. Treatment of chronic regional pain syndrome type 1 with palmitoylethanolamide and topical ketamine cream: modulation of non-neuronal cells. Journal of Pain Research. 2013; 6: 239–45. doi:10.2147/JPR.S42417.
23. Truini A, Biasiotta A, Di Stefano G et al. Palmitoylethanolamide restores myelinated-fibre function in patients with chemotherapy-induced painful neuropathy. CNS & Neurological Disorders Drug Targets. 2011; 10 (8): 916–20.
24. Habib AM, Okorokov AL, Hill MN et al. Microdeletion in a FAAH pseudogene identified in a patient with high anandamide concentrations and pain insensitivity. British Journal of Anaesthesia. 2019; 123 (2): e249–e253.
25. Mikaeili H, Yeung C, Habib AM et al. CRISPR interference at the FAAH-OUT genomic region reduces FAAH expression". bioRxiv 2019; 10.1101/633396.
26. Hesselink JM, Hekker TA. Therapeutic utility of palmitoylethanolamide in the treatment of neuropathic pain associated with various pathological conditions: a case series. J Pain Res. 2012;5:437-442. doi:10.2147/JPR.S32143
27. Duncan RS, Chapman KD, Koulen P. The neuroprotective properties of palmitoylethanolamine against oxidative stress in a neuronal cell line. Mol Neurodegeneration 2009; 4, 50. https://doi.org/10.1186/1750-1326-4-50

28. Palma E, Reyes-Ruiz JM, Lopergolo D et al. Acetylcholine receptors from human muscle as pharmacological targets for ALS therapy. Proc Natl Acad Sci U S A. 2016 Mar 15;113(11):3060-5.
29. Gabrielsson L, Mattsson S, Fowler CJ. Palmitoylethanolamide for the treatment of pain: pharmacokinetics, safety and efficacy. British Journal of Clinical Pharmacology. 2016; 82 (4): 932–42.
30. Paladini A, Fusco M, Cenacchi T et al. Palmitoylethanolamide, a Special Food for Medical Purposes, in the Treatment of Chronic Pain: A Pooled Data Meta-analysis". Pain Physician. 2016; 19 (2): 11–24.

Optimal dosing of analgesics to improve adherence

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Introduction

The task of the doctor in the treatment of pain is to make a diagnosis based on the anamnesis, clinical examination and targeted diagnosis, and to start the treatment of pain as soon as possible, especially when it comes to acute pain. The initiation of therapy is preceded by consideration of pain, comorbidity of the patient, proper dosing of the drug with respect to the indications and contraindications, side effects and safety profile of the drug.

What we don't think about enough, although we think about it more and more often, is compliance or adherence ("compliance / adherence") roughly translated as obedience, consent or fidelity in respecting the treatment recommendations given by the doctor to the patient (1). Compliance can be viewed in a broader context, as a general adherence to treatment recommendations, including lifestyle changes. One of the widely accepted definitions of patient compliance in pharmacotherapy says that it is "the degree of agreement of the real history of drug dosing with the prescribed therapeutic regimen" (2).

What we as doctors blindly believe is that the patient, after the visit to the doctor, the diagnosis and the prescribed treatment, will cooperate to the maximum in accordance with his abilities, and will optimally follow the recommended treatment regimen. However, in reality, it has been shown that even highly individualized pharmacotherapy, measured according to the best available modern scientific evidence, given in good practice guides, does not give the expected success.

Numerous studies have been conducted examining the effect of drugs on the control of epidemiological and economically significant diseases in the world and it has always been significantly higher in controlled conditions of clinical studies (3).

It is understood that the lack of expected response to drugs of proven efficacy in the outpatient population can be predominantly attributed to the fact that about half of

all patients with chronic diseases, according to World Health Organization statistics, do not consistently follow treatment recommendations (4).

The attitude of the patient that precedes the conscious decision to participate in therapy (5), which results in intentional and unintentional negative compliance, is very important.

We come to the fact that what is interpreted as ineffectiveness or resistance to the drug, actually represents the improper use of the drug.

The main factor would therefore be what happens after the patient leaves the office with the prescribed medication. It is estimated that up to 30% of prescriptions in industrialized societies never actually get into the hands of pharmacists for the drug to be dispensed (6). Then, for the issued drugs, it was discovered that, in a large number of cases, the given technological form is not used correctly, that the interdose intervals are not fully observed and thus the level of active principle in the blood is not constant in the therapeutic range. time, and based on the relief of symptoms (7).

Failure to adhere to the prescribed treatment regime leads to a number of consequences - not getting the maximum benefit from the applied treatment and modest treatment results through significantly reduced quality of life to markedly increased treatment costs, which burden both national health insurance funds and the budget of the citizen medical services (8).

There are a number of factors that lead to the problem of poor compliance in therapy, and the World Health Organization (WHO) assessed it globally in its 2003 report of the expert commission entitled "Compliance in Long-Term Therapies: Evidence for Action". Among the most frequently mentioned causes of unsatisfactory participation of the patient in the treatment process, forgetting to take the medicine is mentioned in the first place, and also the complicated regimen of dosing the medicine is mentioned. The traditional approach was the expectation that the patient would blindly follow the doctor's decisions even if he did not understand them and was not sufficiently informed (4).

We must emphasize that insufficient awareness of health care employees about the importance of the problem of poor compliance for the long-term success of therapy (4). Building a relationship of trust and motivating a person to participate in the treatment process is considered key. It is necessary for the patient to understand that success is possible and directly proportional to the self-discipline of the individual.

On the other hand, it is known that, on the example of inconsistent pharmacotherapy, underdose or overdose of the active principle leads to two categories of complications - complications of poor disease control as well as side effects and toxicity of the drug.

In addition to some psychological techniques, doctors have at their disposal a number of technical solutions to significantly increase the possibility of optimal patient compliance. These are favoring monotherapy or therapy with as few drugs as possible, thus reducing the risk of unpredictable interactions and increased toxicity, simplifying

dosing regimens and reducing dosing frequency, choosing pharmaceutical-technological definition of active substance (retard form, syrup, parenteral depot preparation, aerosol, medical plaster, gel ...) that best suits the needs of a given person or the use of electronic monitoring of the regularity of therapy (9, 10). All types of struggle to win the patient to actively participate in the fight against the disease, have extremely useful outcomes.

Increasing compliance allows us to progress on three fronts: more successful treatment of the sick, saving enormous financial resources as well as a better quality of life for the individual. The WHO guide on this topic argues that a significant improvement in the compliance of various essential medical interventions would probably have a much greater effect on a nation's health potential than the discovery of any epochal successful treatment for any of the diseases considered (4). Improve the mechanism of cooperation of patients in the treatment process.

In addition to all the above, from a good and confidential relationship with the patient, through understanding the causes of acute pain, the entire diagnosis, we must know and be sure when prescribing drug therapy. For that reason, support monotherapy whenever possible and the form of medicine that is the easiest to use.

Prescribe a drug that has a favorable safety profile and good tolerability. Ibuprofen belongs to the group of drugs with the lowest relative risk of complications in the upper gastrointestinal tract, has low hepatotoxicity and is in the group of drugs with the lowest cardiovascular risk (11). Brufen is rapidly resorbed from the GIT and reaches maximum blood concentrations in 1-2 hours. The half-life of Brufen® is 2 hours and there is no accumulation with repeated doses. Due to this pharmacological profile, it is necessary to properly dose the drug 3-4 times a day, in order to maintain effective concentrations of the drug in the systemic circulation (12, 13).

The pain begins to subside after the first dose, but it takes one to two weeks for the full analgesic effect. To achieve the full anti-inflammatory effect of NSAIDs, it is necessary to three weeks of therapy have passed. In accordance with that, we must always keep in mind why we are introducing the drug, whether due to analgesia or we also want an anti-inflammatory effect.

The daily dose for adults is 1200-1800mg, the maximum daily dose is 2400mg and the maintenance dose is 600-1200mg (14). We must always be careful who we prescribe the dose of the drug.

Brufen Retard contains 800 mg of Ibuprofen. It is characterized by a prolonged-release formulation and has a unique pharmacological profile and therapeutic activity for a full 24 hours, indicated in patients with chronic and persistent pain. It is best to take therapy 3-4 hours before going to bed (18 - 20h) after a meal (14, 15).

Conclusion

After a detailed history, diagnosis and examination, consider the treatment options for the patient. When choosing drug therapy, give preference to the one that

satisfies the indications, for which there are no contraindications, and then it is better to dose in order to achieve the desired effect of the drug and be sure to respect the length of medication. Dedicate time to the patient and explain to him the advantages of taking the prescribed therapy and what will happen if he does not accept the proposed therapy, all with the aim of good adherence with the applied therapy.

References

1.Grujic B, Sr|evic I , / The New Standard Dictionary English-Serbian Serbian-English, Obod / P&N, 2006.

2. Düsing R, Lottermoser K, Mengden T, Compliance with drug therapy - new answers to an old question, Nephrol Dial Transplant (2001) 16: 1317-21

3. Land SR, Ritter MW, Costantino JP, Julian TB, Cronin WM, Haile SR, et al. Compliance with patient-reported outcomes in multicenter clinical trials: methodologic and practical approaches. J Clin Oncol. 2007 Nov 10;25(32):5113-20.

4. Sabate E, ed. Adherence to long-term therapies: evidence for action. Geneva, World Health Organization, 2003.

5. Gennaro RA, Remington - The science and practise of pharmacy, University of the Sciences in Philadelfia, Lippincott Williams & Wilkins, Baltimore, Maryland USA, 2000.

6. Hardman JG, Limbird LE, Gilman AG, Goodmann & Gilman's The Pharmacological Basis of Therapeutics, 10th edition, McGraw Hill, USA, 2001.

7. Osterberg L, Blaschke T. Adherence to Medication N Engl J Med 2005; 353:1972-1974, Nov 3, 2005.

8. Segal JZ."Compliance" to "concordance": a critical view. J Med Humanit. 2007;28(2):81-96.

9. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH.Fixed-dose combinations improve medication compliance: a meta-analysis. Am J Med. 2007; 120(8):713-9.

10. Bader HI. The oral/systemic link and patient compliance: a review. Dent Today. 2007;26(4):68, 70.

11. Castellsague J, Riera-Guardia N, Calingaert B, et al; Safety of Non-Steroidal Anti-Inflammatory Drugs (SOS) Project.Drug Saf. 2012 Dec 1;35(12):1127-46.

12. Benvenuti C et al. Int J Clin Pharma Ther Toxicol. 1986; 24 (6): 308-312

13. Glass RC et al. Br J Clin Pharmaco. 1978; 6: 454

14. Sažetak karakteristika leka Brufen®, Predstavništvo BGP Products Switzerland GmbH Beograd,decembar 2018.

15. Wilson CG, Washington N and Greaves JL. Int J Pharmaceutics, 1989; 50: 155-16

31 Chronic pelvic pain

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Abstract

Chronic Pelvic Pain has a significant impact on men and women of reproductive and nonreproductive age, with a considerable burden on overall quality of life and on psychological, functional, and behavioural status. An understanding of a condition's mechanisms is important for appropriate clinical interpretation of symptoms and signs and, as a consequence, management and outcome. Problems arise when the pathologic process is poorly understood and the condition cannot be reliably diagnosed or defined.

Key words: Chronic Pelvic Pain, management, diagnosis

Introduction

Chronic Pelvic Pain (CPP) is defined by the European Association of Urology (EAU) as chronic or persistent pain perceived in structures related to the pelvis of either men or women. It is often associated with negative cognitive, behavioural, sexual and emotional consequences as well as with symptoms suggestive of lower urinary tract, sexual, bowel, pelvic floor or gynaecological dysfunction. An understanding of a conditions mechanisms is important for appropriate clinical interpretation of symptoms and signs and, as a consequence, management and outcome. Problems arise when the pathologic process is poorly understood and the condition cannot be reliably diagnosed or defined, so it is often a diagnosis of exclusion. The EAU further defines Chronic Pelvic Pain Syndrome (CPPS) as the occurrence of CPP when there is no proven infection or other obvious local pathology that may account for the pain.(1) Pain perception in CPPS may be focused within a single organ, more than one pelvic organ and even associated with systemic symptoms such as Fibromyalgia or Sjogren's Syndrome. Terminology 'syndrome' indicates that, although peripheral mechanisms may exist, CNS

neuromodulation may be more important and systemic associations may occur. As a part of classifying chronic pelvic pain syndromes, the EAU also took on board the approach of the International Society for the Study of Pain in its guidelines on chronic pelvic pain.(2) They suggested an axial flow approach where the diagnostician starts with a general diagnosis (such as chronic pelvic pain) and moves towards a more specific diagnosis depending on symptoms and signs. The diagnosis of Bladder Pain Syndrome (BPS) would thus become a subgroup of chronic pelvic pain only arrived at if there are clear symptoms, signs, or investigation results to suggest that the pain is perceived to be related to the urinary bladder. "End organ" terminology reflects the site in which pain presents, and therefore specific terms for the involved organ (such as Bladder Pain Syndrome and Prostate Pain Syndrome) are classified in EAU guidelines. In more detail, the guidelines distinguish Urological, Gynaecological, Gastrointestinal, and Musculoskeletal Pain Syndromes.(3)

Urological Pain Syndromes include Prostate Pain Syndrome, Bladder Pain Syndrome (BPS), Scrotal Pain Syndrome, Testicular Pain Syndrome, Epididymal Pain Syndrome, Postvasectomy Scrotal Pain Syndrome, Penile Pain Syndrome, and Urethral Pain Syndrome . Bladder Pain Syndrome which is often termed as "Interstitial Cystitis" by several authors, and Prostate Pain Syndrome, is often termed "Chronic Prostatitis.

Gynaecological Pain Syndromes include Vulvar Pain Syndrome , Vestibular Pain Syndrome, Clitoral Pain Syndrome, Dysmenorrhea, and Endometriosis-Associated Pain Syndrome.

Gastrointestinal and Musculoskeletal Pain Syndromes include Irritable Bowel Syndrome and Pelvic Floor Muscle Pain Syndrome.

CPP has a significant impact on women of reproductive and nonreproductive age, with a considerable burden on overall quality of life (QoL) and on psychological, functional, and behavioural status. CPP prevalence varies in a wide range, according to different cohort sampling, from 5,6% to 30,9% (4)

The prevalence of CPP/CPPS in men is also variable in different studies, although lower than their prevalence in women; the reported prevalence of CPP symptoms in men ranges between 2% and 17% . Prostate Pain Syndrome/Chronic Prostatitis is a high prevalent syndrome (prevalence ranges between 4,5 and 9% in different cohorts) (5). Chronic Scrotal Pain is as well a likely underestimated syndrome, with reported prevalence ranging between 2,5 and 5% . While acute pelvic pain is considered as the fifth vital sign in the same way as other acute pain conditions, CPP is generally considered to be a description of a clinical condition rather than a diagnosis. Up to 55% of women with CPP/CPPS have no clear and definite pathological findings even after laparoscopic

evaluation. Top four diagnoses include Endometriosis, Adhesion , Irritable bowel syndrome, Interstitial cystitis.(6)

An equally controversial area is the role of psychology in these pain syndromes. All pain syndromes are associated with a degree of psychological response . Psychological risk factors are identified in a range of pain syndromes and they include Somatoform disorder, Depression, Bipolar disorder, Panic disorder, Anxiety. Sexual behaviour and intercourses are often impaired and disturbed by painful syndromes both in men and women. Some patients, both male and female, can even present pain catastrophizing features, which are exaggerated negative responses to imagined pain or actual pain, affecting an individual's belief system. Pain catastrophizing has been recognized as an essential risk factor for chronic pain and could also serve as an important predictor of cognitive distress, pain-related disability, analgesic use, and dysfunctional adjustment to pain in clinical situations.(7)

Patient Assessment: Diagnosis and Clinical Presentation

Proper evaluation of CPPS requires a general gynecologic and urologic workup with an organized approach. Upon symptom inquiry, clinicians should be suspicious of chronic pain in the perineum, testicles, tip of penis, or pubic areas that has lasted for at least 3 months. Palpation of the pelvic floor and prostate, urine culture, pre- and post-prostate massage urine test, cystoscopy, Pap smear, urodynamics, and ultrasound can be used to exclude other diagnoses. Some women can present with concurrent abdominal wall pain . Patients with CPPS can also exhibit tenderness in the pelvic floor, suprapubic area, pubic symphysis, and posterior superior iliac spine.(8) Finally, symptomatically similar diseases such as UTI, bacterial prostatitis, benign prostrate hypertrophy (BPH), overactive bladder, pelvic floor dysfunction, malignancy, calculi, must be ruled out before diagnosis of CPPS.

Notably, EAU guidelines underscore the fact that central sensitization mechanisms and Central Nervous System (CNS) neuromodulation and neuroplasticity are relevant pathophysiological mechanisms in CPP/CPPS, and indeed many patients report neuropathic pain symptoms. (9) Besides anamnestic interview and clinical examinations, pain scales and questionnaires are fundamental tools when approaching, assessing, and evaluating CPP/CPPS patients.

Conservative Management

For optimal patient management, an individualized and multimodal approach is recommended. Successful management of any chronic pain condition begins with a discussion of realistic goals. Since chronic pelvic pain is often associated with dysfunctional pelvic floor muscles, many treatment plans begin with physical therapy.(10) Pharmaceutical management is another essential component of CPPS treatment; alpha-blockers, antibiotics, acetaminophen, nonsteroidal anti-inflammatory drugs, and

Tabela 1. Differential Diagnosis chronic pelvic pain (men and women).

Gynecologic	**Gastrointestinal**
- Endometriosis - Chronic PID - Gynecologic malignancies - Pelvic congestion syndrome - Adhesions - Uterine fibroids - Adenomyosis - Ovarian cysts - Atypical dysmenorrhea or ovulatory pain - Intrauterine device - Cervical or endometrial polyps - Symptomatic pelvic relaxation - Ovarian ovulatory pain	- Irritable bowel syndrome - Constipation - Inflammatory bowel disease o Colon cancer - Celiac disease - Colitis - Diverticulitis - Chronic intermittent bowel obstruction anal fissures, hemorrhoids
Genitourinary	**Musculoskeletal**
- Interstitial Cystitis - Bladder adenocarcinoma - Radiation cystitis - Benign prostrate hypertrophy - Chronic urethritis - Renal calculi - Varicocele - Epididymitis - Testicular neoplasm	- Chronic coccygeal or back pain - Fibromyalgia - Abdominal wall myofascial pain - Abdominal wall nerve entrapment - Faulty or poor posture (Scoliosis) - Pelvic floor myalgias - Peripartum pelvic pain syndrome - Neoplasia of spinal cord or sacral nerve - Spondylosis / spondylolisthesis - Hernias - Osteoarthritis - Muscle strain - Rectus tendon strain
Neurologic	**Infection**
-Low thoracic or lumbar herniated disk - Lumbar stenosis, - Parkinson disease, - Diabetic cystopathy, - Demyelinating disease, - Pudendal Neuralgia	- Sexually transmitted diseases, - Chronic bacterial prostatitis, - Fungal infection

gabapentenoids have been demonstrated to offer symptomatic relief. (11) Patients who do not respond to these first line agents may be treated with duloxetine and other selective 5-serotonin and norepinephrine reuptake inhibitors, which provide safe and effective pain management. Muscle relaxants, 5- phosphodiesterase inhibitors, and anxiolytics have also all been used second-line with promising reports. While relieving functional impairment in CPPS is often the primary treatment goal, psychological burden must also be considered. The prevalence of somatoform, mood, and anxiety disorders is significant, and effective treatment involves addressing all biopsychosocial

factors that contribute to chronic pelvic pain . Conventional use of biofeedback and cognitive behavioral therapy (CBT) can be beneficial in addressing comorbid depression or anxiety, as depression is often correlated with symptom severity and can have a large impact on quality of life.(12)

Interventional Therapy

Similar to its role in persistent myofascial pain, trigger point injection (TPI) therapy may offer some benefit to patients with CPPS. Methods vary, but typically, a local anesthetic, botulinum toxin, or a dry needle is used to target the piriformis, iliococcygeus, pubococcygeus, levator ani, coccygeus, obturator internus, or superficial and deep transverse perinei. Peripheral nerve blocks have also been used for the management of CPPS. Pudendal nerve blockade or ablation may relieve chronic perineal pain via interruption of pudendal innervation within the penis, clitoris, bulbospongiosus muscle, ischiocavernosus muscles, perineum, and anus. Additionally, the superior and inferior hypogastric plexuses, ilioinguinal nerve, iliohypogastric nerve, and genitofemoral nerve have been targets of nerve blocks for chronic pelvic pain. Inferior hypogastric plexus blocks can be performed for chronic pain conditions of the lower pelvic viscera, particularly in females, as well as pelvic cancer pain . Ganglion impar blocks may also be utilized; patients with chronic pelvic and perineal pain who were given ropivacaine ganglion impar blocks had a shortterm reduction in pain intensity as well as some intermediate-term effects in up to 50% of patients.(13)

Surgical Procedures

If patients do not experience adequate pain relief from noninvasive or minimally invasive interventions, surgery may be cautiously considered. Such procedures are typically reserved for patients who present with an identifiable lesion or a specific condition that can be targeted by invasive intervention. Any surgical intervention should be considered in conjunction with a multidisciplinary and multimodal approach, with attention given to other organ systems including musculoskeletal, urological, gastroenterological, and psychological. Among female patients presenting with CPPS, surgical intervention is beneficial when identifying adhesions or endometriosis.(14) Several studies have reported the use of hysterectomy for pain management, although its use remains controversial and patient selection is critical before performing a hysterectomy due to high morbidity and limited benefit. Among male patients, there is currently insufficient evidence to recommend surgical intervention for CP/CPPS. The possibility of bacterial origin remains uncertain, further pointing away from the benefit of a surgical intervention . Some studies do report that prostatectomy is effective within a carefully selected patient population.

Conclusion

CP/CPPS is a frustrating entity for many practitioners and patients. Correct assessment of CPP patients painful experience can help physicians to properly develop appropriate therapeutic protocols specially tailored for those patients, taking into account pain symptoms as well as eventual comorbidities, psychological features, and functional QoL status. At present there is no universally accepted paradigm for the treatment of CPP in men and women.

References

1) D. S. Engeler, A. P. Baranowski, P. Dinis-Oliveira et al., "The 2013 EAU guidelines on chronic pelvic pain: Is management of chronic pelvic pain a habit, a philosophy, or a science? 10 years of development," European Urology. 2013;64(3): 431–439.
2) J.T. Sigalos and A. W. Pastuszak, "Chronic orchialgia: epidemiology, diagnosis and evaluation," Translational Andrology and Urology. 2017; 6(1):37–43.
3) Steurer J, Bachmann LM, Miettinen OS. Etiology in a taxonomy of illnesses. Eur J Epidemiol 2006;21:85–9.
4) A. Ahangari "Prevalence of chronic pelvic pain among women: An updated review," Pain Physician 2014; 17(2):141–147.
5) A. S. Polackwich and D. A. Shoskes, "Chronic prostatitis/ chronic pelvic pain syndrome: a review of evaluation and therapy," Prostate Cancer and Prostatic Diseases.2016;19(2):132–138.
6) P. Vercellini, E. Somigliana, P. Vigano, A. Abbiati, G. Barbara, ` and L. Fedele, "Chronic pelvic pain in women: etiology, pathogenesis and diagnostic approach," Gynecological Endocrinology.2009; 25(3) : 149–158.
7) C. E. Martin, E. Johnson, M. E. Wechter, J. Leserman, and D. A. Zolnoun, "Catastrophizing: A predictor of persistent pain among women with endometriosis at 1 year," Human Reproduction. 2011;26(11): 3078–3084.
8) Yang CC, Miller JL, Omidpanah A, Krieger JN. Physical examination for men and women with urologic chronic pelvic pain syndrome: a MAPP (Multidisciplinary Approach to the Study of Chronic Pelvic Pain) Network Study. Urology. 2018;116:23–9.
9) A. P. Malykhina "Neural mechanisms of pelvic organ crosssensitization" Neuroscience. 2007; 149(3): 660–672.
10) Berghmans B. Physiotherapy for pelvic pain and female sexual dysfunction: an untapped resource. Int Urogynecol J. 2018;29(5): 631–8
11) Qin Z, Wu J, Tian J, Zhou J, Liu Y, Liu Z. Network meta-analysis of the efficacy of acupuncture, alpha-blockers and antibiotics on chronic prostatitis/chronic pelvic pain syndrome. Sci Rep. 2016;6(October):1–11
12) Brünahl C, Dybowski C, Albrecht R, Riegel B, Höink J, Fisch M, et al. Mental disorders in patients with chronic pelvic pain syndrome (CPPS). J Psychosom Res. 2017;98:19–26.

13) Nagpal AS, Moody EL. Interventional management for pelvic pain. Phys Med Rehabil Clin N Am. 2017;28(3):621–46.
14) Simpson LR, Mahmood T. Medical and surgical management of chronic pelvic pain. Obstet Gynaecol Reprod Med. 2017;27(1): 14–21.

32 The use of alpha lipoic acid and superoxide dismutase (Combinerv) in the treatment of diabetic polyneuropathy

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Abstract

Diabetic neuropathy is the most common complication of diabetes mellitus. Neuropathy is not only a late complication of diabetes mellitus, but also can develop at any time during the course of the disease including patients with prediabetes. Approximately half of all patients with diabetes mellitus have a distal symmetric polyneuropathy. Hyperglycemia is the major causal factor in the development of endothelial dysfunction in diabetes mellitus. Strict glycemic control is shown to delay the progression of diabetic polyneuropathy. Endoneurial microvascular damage, and hypoxia leads to nerve damage. Recent evidence shows that oxidative stress is central to the pathogenesis of diabetic polyneuropathy. The effectiveness of alpha lipoic acid alone and in combined preparations in peripheral neuropathy was assessed in various clinical trials. Combination of four elements: alpha lipoid acid, superoxide dismutase, acetyl-carnitine and vitamin B12 (Combinerv) led to an improvement in clinical manifestation in patients with diabetic polynuropathy.

Key words: Diabetes mellitus, Neuropathy, Oxidative stress, Alpha lipoic acid

Introduction

It is well known that peripheral neuropathy is a common complication of diabetes and may appear as the first manifestation of the disease. It is increasingly recognized in patients with prediabetes who are at high risk of developing diabetes mellitus (1, 2). Neuropathy resulting from diabetes is estimated to affect 60 %–70 % of people with diabetes depending on age, duration of diabetes, definition of neuropathy used, presence or absence of pain, and whether or not other causes of neuropathy are excluded (3). Risk factors for developing neuropathy include age, gender, duration of diabetes,

uncontrolled glycaemia, height, overweight and obesity, and insulin treatment. Epidemiologic studies have identified duration and severity of hyperglycemia as the major risk factors for the development of diabetic neuropathy in patients with both type 1 and type 2 diabetes.

Classification

There is no universally accepted classification for diabetic neuropathies, and a classification based upon the clinical manifestation is most preferred in clinical practice (4). Diabetic neuropathy can be divided into symmetrical and asymmetrical neuropathies. The American Diabetes Association classified diabetic neuropathies into three main categories: 1. Diffuse symmetric (distal symmetric polyneuropathy and autonomic); 2. Mononeuropathy (mononeuropathy, mononeuritis multiplex, atypical forms); 3. Radiculopathy or polyradiculopathy (5). The most common forms of diabetic neuropathy (DN) are diabetic distal symmetrical sensorimotor polyneuropathy and diabetic autonomic neuropathy. Distal symmetric polyneuropathy affects the limbs symmetrically in a characteristic "glove and stocking" pattern. Common symptoms of distal symmetric polyneuropathy include numbness, tingling, weakness, pain, and many patients experience sensations similar to bunched-up socks or ill-fitting shoes. Painful diabetic neuropathy (PDN) is also common complication of chronic diabetes. Pain has also been reported in twice as many patients with DM and neuropathic symptoms (60%) than those with DM but no neuropathy (6).

Pathophysiology

The pathophysiology of this condition is due to primarily metabolic and vascular factors. There is increase in sorbitol and fructose, glycated endproducts, reactive oxygen species and activation of protein kinase C in the diabetic state. All these factors lead to direct damage to the nerves (7). Diabetic neuropathy develops on a background of hyperglycemia and associated metabolic imbalances, mainly oxidative stress (OxS). The role of oxidative stress in nerve damage has been extensively studied in experimental diabetes and in diabetic subjects. Hyperglycemia-induced overproduction of free radicals, in particular, reactive oxygen species (ROS), has been recognized as the source of further complications (8).

Treatment of Diabetic Neuropathies

Treatments for diabetic polyneuropathy include therapies that alter pathological pathways and those that reduce symptoms (9). The cornerstone of pharmacologic interventions to prevent complications of diabetic peripheral neuropathy is medications and strategies that improve glucose control. Key pharmacologic interventions that address comorbid conditions in patients with diabetes are statins and antihypertensives. These agents may also contribute to preventing diabetic polyneuropathy complications (10).

Various supplements demonstrated nerve generative properties, as has been shown in animal models. Acetyl-L-carnitine can be seen as a prototype of the class of rational supplements. This drug significantly increased the number of fibers and regenerating clusters in patients suffering from NP in diabetes (11). Alpha-lipoic acid has comparable nerve regenerating properties, as has been demonstrated via nerve conduction velocity studies Antioxidant administration, and in particular α-lipoic acid (ALA), has been demonstrated to be able to prevent the neurovascular abnormalities associated with diabetic neuropathy, to improve nerve blood flow and peripheral nerve fiber conduction, and to increase endoneurial glucose uptake and energy metabolism in diabetic polyneuropathy (12).

Antioxidants are available endogenously as a normal defense mechanism of the cell or obtained exogenously from diet. Alpha lipoic acid is a potent lipophilic antioxidant in vitro and in vivo conditions, which plays a main role as cofactor in many mitochondrial reactions, easily absorbed from gastointestinal tract and can easily cross the blood brain barrier (13). The effectiveness of ALA alone and in combined preparations in peripheral neuropathy was assessed in various clinical trials. Combinerv is an innovative quadruple combination of 2 antioxidants of alpha-lipoic acid and superoxide dismutase along with acetylcarnitine and vitamin B12. It is a specially formulated nutritional supplement to support nerve function and help with the treatment of neuropathic pain. Superoxide Dismutase (SOD) and alpha lipoic acid exert an antioxidant action, SOD by preventing formation of free radicals, and ALA by removing already formed free radicals (14-16). The amino acid acetyl-L-carnitine plays a role in the transfer of long-chain fatty acids into mitochondria for β-oxidation. The amino acid acetyl-L-carnitine supplementation also induces neuroprotective and neurotrophic effects in the peripheral nervous system (17). Vitamin B12 levels are often low in DM patients, due to metformin treatment. The population at risk of vitamin B12 deficiency induced by metformin is very high and screening for vitamin B12 deficiency is justified, especially in groups at higher risk, such as people with diabetic neuropathy receiving high doses of metformin (18).

Conclusion

Diabetic neuropathies are a heterogeneous group of pathological manifestations with the potential to affect every organ, with clinical implications such as organ dysfunction, which leads to low quality life and increased morbidity. It is likely to occur in even the mildest cases of diabetes. Hyperglycemia-induced oxidative stress induces programmed cell death of nerves, which contributes to the pathology of diabetic neuropathy. Glycemic control can help to prevent or slow the progression of diabetic polyneuropathy but not to reverse existing nerve damage. Antioxidant administration, and in particular α-lipoic acid, has been demonstrated to be able to prevent the neurovascular abnormalities associated with diabetic neuropathy. Alpha-lipoic acid exhibits a strong neuroprotective effect. It is used to treat diseases caused by oxidative stress such

as diabetic neuropathy and to alleviate the inflammatory response. It is also used as a modulator of various inflammatory signaling pathways. Combination of four elements: alpha lipoid acid, superoxide dismutase, acetyl-carnitine and vitamin B12 (Combinerv) led to an improvement in all indices of peripheral neuropathy including neurophysiological parameters, pain, and quality of life in patients with diabetic polyneuropathy.

Abbreviations:

ALA - alpha lipoic acid
DN - diabetic neuropathy
OxS - oxidative stress
PDN - painful diabetic neuropathy
ROS - reactive oxygen species
SOD - superoxide dismutase

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References

1. Whitsell LJ. Neurologic Complications of Diabetes.California Medicine. 1962; 96(1):14-20.
2. Russell JW, Zilliox LA. Diabetic Neuropathies. Peripheral Nervous System Disorders. Continuum (MinneapMinn). 2014; 20(5): 1226–1240.
3. Galer B, Gianas A, Jensen M. Painful diabetic polyneuropathy: epidemiology, pain description, and quality of life. Diabetes Res Clin Pract. 2000; 47:123–8.
4. Yavuz DG. Classification, risk factors, and clinical presentation diabetic neuropathy. Diabetic Neuropathy. 2022; 1-9.
5. *Busui RP, Boulton AJM, Feldman EL, Bril V, Freeman R, Malik RA et al. Diabetic neuropathy: a position statement by the American Diabetes Association Diabetes*
Care. 2017; 40 (1):136-154.
6. *Staudt MD, Prabhala T, Sheldon BL, Quaranta N, Zakher M, Bhullar R, Pilitsis JG, Argoff CE. Current Strategies for the Management of Painful Diabetic Neuropathy. Journal of Diabetes Science and Technology. 2020; 1–12.*
7. *Kaur S, Pandhi P, Dutta P. Painful diabetic neuropathy: an update. Annals of neurosciences. 2011; 18:4.*
8. Fiorentino TV, Prioletta A, Zuo P, Folli F. Hyperglycemia-induced oxidative stress and its role in diabetes mellitus related cardiovascular diseases. Current Pharmaceutical Design. 2013; 19(32):5695–5703.
9. Nguyen N, Jody K, Takemoto JK. A Case for Alpha-Lipoic Acid as an Alternative Treatment for Diabetic Polyneuropathy. J Pharm Pharm Sci. 2018; 21(1):192 – 199.
10. Wu S, Cao X, He R, Xiong K. Detrimental impact of hyperlipidemia on the peripheral nervous system: A novel target of medical epidemiological and fundamental research study. Neural Regen Res. 2012; 15:7(5):392-9.

11. Kopsky D. Nerve Regeneration in Neuropathic Pain. Pain Medicine 2010; 11:1576.
12. Zilliox L, Russell JW. Treatment of Diabetic Sensory Polyneuropathy. Curr Treat Options Neurol. 2011; 13(2):143–159.
13. Tasci I, Demir CF, Kuloglu T. Effects of Alpha Lipoic Acid on Loss of Myelin Sheath of Sciatic Nerve in Experimentally Induced Diabetic Rats. Med Arch 2018; 72(3):178-181.
14. Romao S. Therapeutic value of oral supplementation with melon superoxide dismutase and wheat gliadin combination. Nutrition. 2015; 31:430–436.
15. Papanas N, Ziegler D. Efficacy of alpha-lipoic acid in diabetic neuropathy. Expert Opin. Pharmacother. 2014; 15:2721–2731.
16. Didangelos T, Karlafti E, Kotzakioulafi E, Kontoninas Z, Margaritidis C, Giannoulaki P, Kantartzis K. Efficacy and Safety of the Combination of Superoxide Dismutase, Alpha Lipoic Acid, Vitamin B12, and Carnitine for 12 Months in Patients with Diabetic Neuropathy. Nutrients 2020; 12:3254.
17. Rolim LCSP, da Silva EMK, Flumignan RLG, Abreu MM, Dib SA. Acetyl-L-carnitine for the treatment of diabetic peripheral neuropathy. Cohrane Database Syst Rev. 2019; 6: CD011265.
18. Alvarez M, Sierra OR, Saavedra G, Moreno S. Vitamin B12 deficiency and diabetic neuropathy in patients taking metformin: a cross-sectional study. Endocr Connect. 2019; 8(10): 1324–1329.

Gut microbiota and pain regulation: molecular mechanism and potential therapeutic strategies

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Abstract

The gut microbiome is attracting growing attention as a therapeutic target in pain regulation. In recent years, there are numerous evidence from preclinical animal studies and human clinical trials that supports the importance of gut-brain interaction in pain perception and points to the gut microbiota as a possible key factor in pain processing. Numerous signaling molecules derived from gut microbiota act on their receptors and regulate the peripheral and central sensitisation, which in turn mediate the development of chronic pain. Microbial dysbiosis can lead to numerous disorders such as visceral hypersensitivity, stress induced hyperalgesia, allodynia, inflammatory pain and functional disorders. Targeting gut microbiota by diet and pharmabiotic interventions may represent a new therapeutic strategy for management of chronic pain.

Key words: gut microbiota, pain, probiotic, gut-brain axis

Introduction

Pain, which affects millions of people worldwide, is a complex protective mechanism. According to the International Association for the study of Pain (IASP) it is defined as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.[1] Experience of pain is the result of the interplay between several compartments: receptors, neurotransmitters involved in the regulation of pain perception, pain-related emotions and memory.

Although still limited, emerging research reports the involvement of the gut microbiota in the release of signal molecules (i.e., metabolites, neurotransmitters, neuromodulators), which are directly involved in pain transmission and modulation.

Microbiota and gut-brain axis

Bacteria, archaea, viruses, fungi, protozoa, helminths that populate our bodies are a thriving dynamic population forming a symbiotic superorganism. Current estimates suggest that approximately 10^4 microbes live on or in our body with the number of microbial cells outnumbering human cells.[2] Gut microbiota presents a complex system composed of trillions of microbes, which participates in food digestion, production of vitamins, absorption of energy, modulation of intestinal homeostasis, regulation of immune function, brain development and behavior.[3] The complexity and diversity of the gut microbiota are established early in the first few years of life and are influenced by a number of external factors, including delivery (vaginal or Cesarian section), breastfeeding or formula nutrition, diet, antibiotic medication, infection and stress. Under pathological conditions it can cause microbial dysbiosis with systemic complications. Among them are gastrointestinal disorders such IBD and IBS, but also extra-intestinal pathologies such as fibromyalgia, cancers, metabolic syndrome, rheumatic diseases, allergic and atopic disease, heart disease and neuropsychiatric diseases.[4]

The gut-brain axis is a bidirectional communication system between the gastrointestinal tract and central nervous system (CNS) which involve the autonomic nervous system, the hypothalamic-pituitary-adrenal axis (HPA), and the immune inflammatory system. The gut microbiota, via its metabolites, is able to communicate with the CNS, through neural (n. Vagus, Enteric nervous system (ENS) and spinal nerves), endocrine (cortisol) and immune (cytokines) pathways. Gut microbiota can directly or indirectly modulate peripheral sensitisation of pain underlying chronic pain through multiple mediators, including microbial by-products (PAMPs), metabolites (SCFAs) and neurotransmitters or neuromodulators release (GABA). Some microbial derived mediators (Toll-like receptors (TLR) agonist) can directly activate or sensitise primary nociceptive neurons in dorsal root ganglia (DRG) to enhance pain, whereas other microbiota-derived mediators like protease can directly decrease excitability of DRG neurons to inhibit the pain. On the other side, gut metabolites (TLR agonist and SCFAs) can indirectly increase the excitability of DRG neurons by inducing pro-inflammatory factors release from immune cells to enhance pain. [5] Microbial inputs are considered fundamental for the development and function of the peripheral immune system and for the maturation and activation of microglia. Cytokines and chemokines can be produced by the brain's immune cells or arrive at the brain through direct transport across the blood-brain barrier (BBB). The permeability of BBB is influenced by the gut microbiota and inflammation. Innate immune receptors (TLRs) are important for sensing components of microbial cells, such as lipopeptides, peptidoglycans, glycolipids and lipopolysaccharides (LPS), and are also defined as microbial-associated molecular patterns (MAMP) receptors. Microbes are able to produce a large number of metabolites,(such as short chain fatty acids (SCFAs) and tryptophan metabolites (such as 5-HT, kynurenines, tryptamine) and neurotransmitters (GABA, noradrenaline, serotonin and

dopamine, glutamate), that are involved in microbiota-gut-brain communication.[6] SCFAs (butyrate, propionate) constitute an energy source for colonocytes and maintain colonic epithelium homeostasis. They are produced by microbial fermentation of dietary polysaccharides in the cecum and colon . There are conflicting evidence on the role of SCFAs in visceral pain modulation. Butyrate, by promoting mucosal repair and reducing bowel inflammation, has been proposed to have an indirect effect on inflammatory visceral pain.[7]

As reported above, there is an growing body of evidence that microbiota may play role in modulating visceral pain and inflammatory and neuropathic pathways.

Gut microbiota and pain regulation

Visceral pain refers to pain of internal organs, such as abdominal pain caused by IBS, IBD, functional dyspepsia, functional abdominal pain syndrome, infantile colic. It has been demonstrated that dyshomeostasis of gut microbiota and host is associated with pathogenesis of many GI disorders. A high proportion of patients with IBS show gut barrier dysfunction and an altered microbiota. In recent years, there are numerous evidence from preclinical animal studies and human clinical trials that supports a crucial role of the gut microbiota in the regulation of visceral and abdominal pain. The application of psychological or physical stress either chronic or in early life can influence the composition of microbiota, and disturbed bacterial colonization postnatally can alter pain pathways. Furthermore, early-life stress produces a reduction of tight junction expression in the gut which increase gut permeability. The translocation of LPS, cytokines and bacteria cause the reduction of nociceptive threshold and the increase of neuronal excitability that contributes hyperalgesia.

Few preclinical studies showed that germ-free (GF) mice displayed visceral hypersensitivity to colorectar distension accompanied by an up-regulation of Toll-like receptors (TRL) and cytokines in spinal cord, which were abolished by postnatal colonization with microbiota.[8] These finding indicate that gut microbiota is crucial for balancing the excitability of colonic sensory neurons. Clinical studies further pointed out that the use of antibiotics early in life induce visceral hypersensitivity in adulthood. Strikingly, visceral hypersensitivity can be transferred in GF rats by fecal microbiota transplantation (FMT) from IBS patients. Although, colorectal compliance, epithelial paracellular permeability and density of colonic mucosal mast cells remained normal, recipient mice exhibited visceral hypersensitivity to colorectal distension.

Inflammatory pain. Inflammation decreases the pain threshold of nociceptors and increase individual pain response. The inflammatory environment can lead to hyperalgesia or allodynia. Many preclinical studies indicate gut microbiota may play an important role in inflammatory pain. In one study carrageenan-induced inflammatory pain was reduced in the GF mice and was reversed by reposition of the microbiota or systemic administration of LPS.[9] The reduced pain hypersensitivity of the GF mice was

significantly aggravated after being transplanted with the stool of conventional mice. Notably, decreased pain hypersensitivity in GF mice was associated with enhanced expression of interleukin 10 upon stimulation and can be reversed by anti-IL-10 neutralizing antibody. Finally, it is important to highlight that the gut microbiota may exert important anti-inflammatory effect through the production of SCFAs (acetate, butyrate and propionate) and other microbial metabolites that restore normal gut permeability. In rats, L rhamnosus (LR-2) is able to reduce pain severity and cartilage destruction in induced osteoarthritis. Based on these considerations, targeting gut microbiota or using specific probiotics may be promising for attenuating pain hypersensitivity in many inflammatory settings.

Therapeutic implications of targeting gut microbiota in chronic pain

Probiotics and prebiotics

Probiotics represent nutritional supplements, that are referred to living microorganisms that give health benefits to host when they are administered in appropriate dose. However, to date, the beneficial effect of probiotics to prevent or treat diseases still needs to be demonstrated and fully clarified. Probiotics can affect the inflammatory response affecting cytokines, including pro-inflammatory and anti-inflammatory cytokines. Few studies showed that treatment with probiotics can alleviate pain and improve quality of life in patients with rheumatoid arthritis.[10] Moreover, probiotics might regulate pain through gene expression of pain-related receptors on epithelial cells. For example, L. acidophilus NCFM up-regulated the expression of cannabinoid receptor 2 and colonic m-opioid receptor, leading to reduced pain sensation. Together, probiotics may be potential reagents for the treatment of chronic pain. Various studies demonstrate the efficacy of probiotic administration on visceral pain. In fact, Rifaximin, neomycin or specific probiotics (L. rhamnosus GG or De Simone formulation) may reduce pain by reducing stress-induced hyperalgesia, skeletal muscle hyperalgesia, neuropathic cutaneous mechanical allodynia, and thermal hyperalgesia by altering the microbiota . Treatment with L. rhamnosus GG reduced abdominal pain in children with functional GI disorders, and a mixture of few strains of Bifidobacterium infantis improved abdominal pain in children with IBS. L. acidophilus NCFM reduced functional abdominal pain in adults.

Prebiotics, on the other hand, are defined as food additives that stimulate the growth and activity of specific gut bacteria. Prebiotics are selectively fermented by probiotics to produce SCFA in order to downregulate inflammation, modulate oxidative stress, enhance gut barrier function and prevent adhesion of pathogens that try to attach to epithelial linings.[11] In humans, a prebiotic galacto-oligosaccharide mixture was shown to reduce abdominal pain associated with GI disorders in adults. Another study showed that the symbiotic containing Bacillus coagulans and fructo-oligosaccharides seems to be effective for the treatment of functional abdominal pain in children.

Identification of personalized microbiota alterations may be necessary for developing a targeted approach to restore specific populations of beneficial bacteria for the management of chronic pain.

Fecal microbiota transplantation (FMP)

Recently, the restoration of gut microbiota to the predisease state has become a vital novel treatment. Fecal microbiota transplantation is the infusion or engraftment of liquid filtrate faeces from healthy donor into the gut of a recipient. In clinical settings, fecal microbiota transplantation is approved for treatment of antibiotic-associated diarrhea and intestinal bowel diseases with proved efficacy in reducing dysbiosis, but in few cases bacteriemia with E.coli developed, thus raising doubts about the safety of fecal microbiota transplantation. Surprisingly, it is reported that a patient diagnosed with fibromyalgia, with a predominant symptom of pain, completely recover after FMT, making chronic refractory pain-related diseases a potential therapeutic indication of the treatment.[12] The underlying mechanism of FMT in modulating pain were proposed, including direct competition of pathogenic bacteria with commensal microbiota, protection of the intestinal barrier, restoration of secondary bile acid metabolism, and stimulation of the intestinal immune system. Although, the exact treatment mechanism of FMT has not yet been revealed, its significant potential in the treatment of chronic pain cannot be ignored.

Low-FODMAP diet

Low-FODMAP diet (foods high in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) modifies the complex and diverse nature of gut microbiota and its metabolic output. A high-FODMAPs diet results in increasing levels of LPS derived from the microbial community and the imbalance of gut microbiota, whereas a low-FODMAP diet has a lower level of LPS. The low-FODMAP diet protect the intestinal barrier by reducing gut mucosal inflammation and therefor alleviating visceral pain. In addition, some research suggested that the low-FODMAP diet may also lead to the decreased production of SCFAs in the gut. An animal study demonstrated that SCFAs are correlated with abdominal hypersensitivity. Given that a higher concentration of SCFAs is linked to the symptomatology of IBS, reducing SCFAs may be another approach by which this dietary intervention plays its role. Many studies have confirmed the effectiveness of this dietary intervention on curing IBS through potential gut microbiota-related pathways. A clinical study showed that psyllium fibre reduce the number of abdominal pain episodes in children with IBS, whereas psyllium did not alter gut permeability or microbiome composition.

Conclusion

Although our understanding of the role of gut microbiota in pain is still in its early stages, emerging evidence suggests that dysregulation of gut microbiota participates

in chronic pain. Therefore, we propose that targeting gut microbiota through dietary intervention, pharmabiotic approaches, or faecal microbiota transplantation, offers a promising fruitful strategy for chronic pain management.

References

1. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, Keefe FJ, Mogil JS, Ringkamp M, Sluka KA, Song XJ, Stevens B, Sullivan MD, Tutelman PR, Ushida T, Vader K. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. 2020;161(9):1976-1982.
2. Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. PLoS Biol 2016; 14:e1002533.
3. Battaglini D, Pimentel-Coelho PM, Robba C , et al. Gut microbiota in acute ishemic stroke: from pathophysiology to therapeutic implications. Front Neurol. 2020;11:598.
4. Defaye, M. , Gervason, S., Altier, C. et al. Microbiota: a novel regulator of pain. J Neural Transm 2020; 127: 445–465 .
5. Guo, R.; Chen, L.-H.; Xing, C.; Liu, T. Pain regulation by gut microbiota: Molecular mechanisms and therapeutic potential. Br. J. Anaesth. 2019;123(5):637-654.
6. Bistoletti, M.; Bosi, A.; Banfi, D.; Giaroni, C.; Baj, A. The Microbiota-Gut-Brain Axis: Focus on the Fundamental Communication Pathways. In Progress in Molecular Biology and Translational Science; Elsevier: Amsterdam, The Netherlands, 2020; 17643–110.
7. Morais, L.H.; Schreiber, H.L., IV; Mazmanian, S.K. The gut microbiota–brain axis in behaviour and brain disorders. Nat. Rev. Microbiol. 2021, 19, 241–255.
8. Lin B, Wang Y et al. Gut microbiota regulates neuropathic pain: potential mechanisms and therapeutic strategy. The journal of Headache and Pain2020;21:103
9. Amaral FA, Sachs D, Costa VV, et al. Commensal microbiota is fundamental for the development of inflammatory pain. Proc Natl Acad Sci U S A 2008; 105:2193.
10. Mandel DR, Eichas K, Holmes J. Bacillus coagulans: a viable adjunct therapy for relieving symptoms of rheumatoid arthritis according to a randomized, controlled trial. BMC Complement Altern Med 2010; 10: 1.
11. Cerdo T et al. Probiotic, Prebiotic, and Brain Development Nutrients 2017; 9(11): 1247.
12. Thurm T, Ablin J, Buskila D, Maharshak N.Faecal microbiota transplantation for fibromyalgia: a case report and review of the literature. Open J Gastroenterol. 2017; 7: 131.

Cardiovascular complications of opioid use / Efekat hronične upotrebe opioida na kardiovaskularni sistem

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Apstrakt

Opioidni analgetici su najpotentniji od svih analgetika. Iako se najčešće koriste kao deo balansirane anestezije, za ublažavanje akutnog postoperativnog bola i hroničnog malignog bola, u poslednje vreme se sve više koriste za lečenje hroničnog nemalignog bola. Sve to povezano je i sa porastom propisivanja ovih lekova od strane lekara različitih specijalnosti. Kao posledica ovoga dolazi do povećanog broja komplikacija, a najznačajnije jesu aritimije. Efekti koje opioidi ostvaruju na kardiovaskularni sistem su značajni jer kao neprepoznati mogu dovesti do smrtnog ishoda. Ovo polje dejstva opioida je i dalje nedovoljno istraženo i potrebne su nove studije na tu temu.

Ključne reči: opioidi, bol, kardiovaskularni sistem, aritmije

Uvod

Termin opioidi se široko odnosni na jedinjenja koja se vezuju za opioidne receptore. Opijati su lekovi ekstrahovani iz soka maka. Prema strukturi opioide možemo kalsifikovati na: prirodne (morfin,kodein), semisintetske (heroin, oksikodon, buprenorfin) i sintetske (fentanil, alfentanil, sulfentanil, tramadol). Pema dejstvu sve opioide možemo klasifikovati na: agoniste, delimične agoniste, antagoniste, mešani agonista-antagonista (1). Opiodi se vezuju za specifične opioidne receptore (μ,κ,δ i NOP) koji se nalaze u centralnom nervnom sistemu, ali i u ostalim tkivima uključujući i kardiovaskularno . Receptori pripadaju porodici receptora vezanih sa G proteinom, a aktivacijom dolazi do hiperpolarizacije membrane (2).

Efekti opioida na kardiovaskularni sistem

Akutni efekti opioida na kardiovaskularni sistem obuhvataju: bradikardiju posredovanu vagusnim nervom, oslobađanje histamina i posledično smanjenje vaskularnog tonusa, hipotenzija, ortostatska hipotenzija i sinkopa (3).

Efekti hronične upotrebe opioda na kardiovaskularni sistem su multifaktorijalni. Zavise od zdravstvenog stanja bolesnika, prisutnih komorbiditeta, a takođe sami ekekti opioida mogu biti pojačani usled interakcije između njih i lekova koje pacijent već koristi. Hronična upotreba opioida dovodi do vaskularnih, valvularnih i aritmogenih sekvela (4). Najznačajniji i najispitivaniji efekat koji opioidi ostvaruju na kardiovaskularni jeste produženje QT intervala koji dodvodi do nastanka artmija.

Produženje QT intervala

QT interval se definiše kao vreme između početka Q talasa i kraja T talasa i predstavlja depolarizaciju i repolarizaciju komora. Normalno vreme QT intervala je 360ms. Produženje dovodi do produžene sprovodljivosti kroz komore, a samim tim i različitih poremećaja ritma (5,6). Mehanizam nastanka je produžena repolarizacija kardiomiocita usled izaska K^+ iz ćelija. Ukoliko je QT interval duži od 500ms može doći do pojave aritmije *Torsades de pointes.* Ukoliko se ne prepozna i na vreme ne leči, ovaj tip poremećaja ritma može da vodi ka atrijalnoj fibrilaciji i cardiac arrestu (7).

Metadon je snažan agonista μ opioidnih receptora koji koristi se za lečenje bola, kao i supstituciona terapija kod heroinskih zavisnika. Od svih opioidnih analgetika on je povezan sa najvećim brojem aritmogenih komlikacija, a posledično tome i sa najviše smrtnih ishoda (8). Brupernorfin i oksikodon takođe uzrokuju aritmije (9,10).

Efekat upotrebe opioida na srčane valvule

Jedna od posledica zloupotrebe opioida je valvularni endokarditis među intravenskim uživaocima narkotika, posebno heroina, na koju treba misliti. On nastaje kao posledica kontaminacije pribora za unošenje narkotika bakterijama i gljivicama. Najčešći prouzrokovač jeste *Streptococcus aureus.* Češće su zahvaćene desne srčane valvule, zbog mesta ulaska infekcije, a to su periferne vene. Komplikacije koje mogu nastati su: sepsa i embolijski moždani udari (11).

Zaključak

Opioidni analgetici su važno sredstvo za lečenje kako malignog tako i nemalignog hroničnog bola, zbog čega je važno da lekari budu svesni rizika upotrebe ovih lekova. Neophodan je pažljiv izbor pacijenata, edukacija o pravilnoj upotrebi lekova kao i mogućim neželjenim dejstvima. Potrebno je obratiti pažnju na indikacije za propisivanje lekova i moguće interakcije među njima. Posebna pažnja je neophodna kod pacijenta koji već imaju neke kardiovaskularne smetnje i one koje su na terapiji metadonom. Svakako su potrebne dodatne studije i istrživanja u ovoj oblasti.

Literatura

1. Miller R. Miller's anesthesia. 9th edition, Philadelphia, Elsevier; 2019.
2. McIntosh M, Kane K, Parratt J. Effects of selective opioid receptor agonists and antagonists during myocardial ischaemia. Eur J Pharmacol 1992;210:37–44.

3. Lessa MA, Tibirica E. Pharmacologic evidence for the involvement of central and peripheral opioid receptors in the cardioprotective effects of fentanyl. Anesth Analg 2006;103:815–21.
4. Krantz MJ, Palmer RB, Haigney MCP. Cardiovascular Complications of Opioid Use: JACC State-of-the-Art Review. J Am Coll Cardiol. 2021 Jan 19;77(2):205-223.
5. Morganroth J, Brozovich FV, Mc Donald JT, et al: Variability of the QT measurement in healthy men, with implications for selection of an abnormal QT value to predict drug toxicity and proarrhythmia. Am J Cardiol 1991; 67:774–776.
6. Roden DM, Viswanathan PC. Genetics of acquired long QT syndrome. J Clin Invest. 2005 Aug;115(8):2025-32.
7. Keller GA, Alvarez PA, Ponte ML, et al: Drug induced QTc interval prolongation: A multicenter study to detect drugs and clinical factors involved in every day practice. Curr Drug Saf 2016;11:86–98.
8. Chou R, Cruciani RA, Fiellin DA, et al. Methadone safety: A clinical practice guideline from the American Pain Society and College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society. J Pain 2014;15:321–37.
9. Fanoe S, Jensen GB, Sjogren P, Korsgaard MP, Grunnet M. Oxycodone is associated with dosedependent QTc prolongation in patients and lowaffinity inhibiting of hERG activity in vitro. Br J Clin Pharmacol 2009;67:172–9.
10. Fareed A, Patil D, Scheinberg K, et al. Comparison of QTc interval prolongation for patients in methadone versus buprenorphine maintenance treatment: a 5-year follow-up. J Addict Dis 2013;32:244–51.
11. Rudasill S, Yas S, Mardock AL, et al. Clinical outcomes of infective endocarditis in injection drug users. J Am Coll Cardiol 2019;73:559–70.

Tapentadol – uvodno predavanje

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Ublažavanje bola je prva dužnost lekara (Sedare dolore divinum est!). Bol je subjektivno iskustvo, tako da se njegov intenzitet ne može izmeriti instrumentima. Subjektivnost bola otežava njegovu dijagnostiku i lečenje, tim pre što se bolovi kreću u rasponu od fizioloških, odnosno uzrokovanih jasno definisanim lezijama tkiva, pa do psiholoških. Akutni (odbrambeni) bol nastaje kao posledica povrede tj oštećenja tkiva ili kao simptom drugog oboljenja, prolazi izlečenjem bolesti koja ga izaziva i ne ostavlja psihološke posledice. Smatra se da akutni bol traje do 90 dana od trenutka nastajanja povrede. Adekvatno zbrinjavanje akutnog bola predstavlja veliki izazov za svakog lekara. Neadekvatno zbrinut akutni bol može da dovede do anksioznosti, poremećaja spavanja, depresije i jako može da utiče na mentalnu i socijalnu aktivnost pacijenta. Takođe akutni bol ima uticaja i na povećanje srčane frekvencije i krvnog pritiska, suprimira imuni sistem i usporava oporavak bolesnika, odnosno produžava njegovo lečenje i troškove lečenja. Dodatno, produženi akutni bol dovodi do senzitizacije u centralnom i perifernom nervnom sistemu što dovodi do razvoja hroničnog bola koji se najčešće jako teško leči i terapija hroničnog bola je veoma skupa. Za terpiju akutnog bola koriste neopioidni analgetici (nesteroidni antiinflamatorni lekovi - NSAIL, paracetamol, metamizol) i opioidni analgetici (tramadol, fentanil, oksikodon, morfin). NSAIL imaju ograničenu mogućnost dejstva jer imaju limitiran terapijski efekat kojim se deluje na blag i umeren bol a i zbog neželjenih efekata koje izaziva njihova višednevna primena i primena kod bolesnika sa kardiovaskularnim i bubrežnim oboljenjima. Takođe, kontrainidkovani su kod pacijenata koji imaju ulkus i opasnost od krvarenja. Opioidi ostvaruju svoj analgetski efekat preko opioidnih receptora koji se nalaze duž čitavog puta za prenošenje bola što dovodi do smanjenja otpuštanja neurotransmitera i smanjenja bola. Ali oni deluju i na opioidne receptore van ovog puta što uslovljava neželjene efekte, najčešće od strane GIT sistema kao što su mučnina, povraćanje i konstipacija, zatim neželjene efekte od strane CNS-a, svrab i urtrikariju. Tapentadol je novi centralno delujući analgetik, sa dvostrukim

mehanizmom dejstva (MOR –NRI) sa kojim ostvaruje dobru efikasnost sličnu drugim opioidnim analgeticima, ali sa manje neželjenih efeketa naročito od strane GITa.(1)

Tapentadol u terapiji akutnog bola

Lek je indikovan za terapiju umerenog do teškog akutnog bola kod odraslih, kada se on može adekvatno kupirati samo opioidnim analgeticima. Režim doziranja treba individualno podesiti u skladu sa težinom bola koji treba lečiti, na osnovu prethodnog terapijskog iskustva i mogućnosti za praćenje pacijenta. Pacijent treba da započne terapiju pojedinačnim dozama od 50 mg tapentadola u obliku film tableta koje se daju u intervalima od 4 do 6 sati. Možda mogu biti potrebne i veće početne doze, što zavisi od intenziteta bola i prethodne istorije pacijenta tj. njegove potrebe za analgezijom. Prvog dana doziranja može se uzeti dodatna doza već jedan sat posle inicijalne ako se ne postigne kontrola bola. Dozu potom treba individualno titrirati do nivoa koji obezbeđuje adekvatnu analgeziju i na najmanju meru svodi rizik od javljanja neželjenih dejstva pod strogim nadzorom ordinirajućeg lekara. Nisu ispitivane dnevne doze preko 700 mg tapentadola prvog dana terapije i doze održavanja veće od 600 mg tapentadola, pa se stoga takve doze i ne preporučuju. Čim se postigne stabilni režim doziranja, a predviđa se duža terapija, treba uzeti u obzir mogućnost nastavka terapijetabletama sa produženim oslobađanjem (Tapentadol SR). Kao u slučaju svake simptomatske terapije, kontinuirana upotreba tapentadola mora se redovno preispitivati.

Farmakodinamika i farmakokinetika tapentadola

Tapentadol je snažan analgetik, agonista na mi-opioidnim receptorima i dodatnom inhibicijom ponovnog preuzimanja noradrenalina. Tapentadol svoje analgetičko dejstvo vrši direktno, bez farmakološki aktivnog metabolita. Tapentadol je pokazao efikasnost u pretkliničkim modelima nociceptivnog, neuropatskog, visceralnog i zapaljenskog bola. Efikasnost je potvrđena u kliničkim ispitivanjima sa tapentadol film tabletama gde su bila obuhvaćena stanja nociceptivnog bola uključujući postoperativni ortopedski i abdominalni bol, kao i hronični bol usled osteoartritisa kuka ili kolena. Po pravilu, analgetičko dejstvo tapentadola u ispitivanjima nociceptivnog bola bilo je slično dejstvu snažnog opioida koji je korišćen za poređenje. Dejstva na kardiovaskularni sistem: U opsežnom ispitivanju QT intervala, tapentadol nije pokazao uticaj ponavljanih terapijskih i subterapijskih doza na QT interval. Takođe, tapentadol nije imao relevantnog uticaja na ostale parametre EKG-a (puls, PR interval, trajanje QRS, T-talas ili morfologiju U-talasa). Tapentadol se brzo i potpuno resorbuje posle oralne primene leka Palexia. Srednja apsolutna biološka raspoloživost posle davanja pojedinačne doze (našte) iznosi približno 32% zbog ekstenzivnog metabolizma tokom prvog prolaza.Maksimalne koncentracije tapentadola u serumi tipično se beleže otprilike 1,25 sati posle unošenja film tableta. Dozno proporcionalni porast vrednosti Cmax i PIK tapentadola zabeležen je posle davanja film tableta u celom rasponu oralnih terapijskih doza. Ispitivanje sa ponavljanim (na svakih 6 sati) dozama u rasponu od 75 mg do 175 mg tapentadola primenjivanog u obliku film tableta pokazao je koeficijent nagomilavanja između 1,4 i 1,7 za osnovnu

aktivnu supstancu i 1,7 odnosno 2,0 za glavni metabolit tapentadol-O-glukuronid, što je primarno određeno intervalom između doza i prividnim poluvremenom eliminacije tapentadola i njegovog metabolita. Kod ljudi, tapentadol se ekstenzivno metaboliše. Oko 97% osnovnog jedinjenja se metaboliše. Glavni put metabolizma tapentadola je konjugacija sa glukuronskom kiselinom pri čemu se dobijaju glukuronidi. Posle oralne primene, približno 70% doze se izluči urinom u vidu konjugovanih formi (55% glukuronida i 15% sulfata tapentadola). Uridin difosfat glukuronil transferaza (UGT) je glavni enzim uključen u glukuronidaciju (uglavnom UGT1A6, UGT1A9 i UGT2B7 izoforme). Ukupno 3% aktivne supstance izlučuje se urinom u neizmenjenom obliku. Tapentadol se dodatno metaboliše u N-desmetil tapentadol (13%) pomoću CYP2C9 i CYP2C19 i u hidroksi tapentadol (2%) pomoću CYP2D6, koji se zatim metaboliše konjugacijom. Prema tome, metabolizam aktivne supstance preko sistema citohroma P450 je manje važan od faze 2 konjugacije.Nijedan od metabolita ne doprinosi analgetičkoj aktivnosti. Tapentadol i njegovi metaboliti se skoro isključivo (99%) izlučuju preko bubrega. Ukupni klirens nakon intravenske primene iznosi 1530 +/- 177 mL/min. Terminalno poluvreme eliminacije u proseku iznosi 4 sata posle oralne primene.

Akutni postoperativni bol, bol u jednodnevnoj hirurgiji i bol prouzrokovan povredom

Nekontrolisani bol sa svojim fizičkim i psihičkim posledicama , često dovodi do ponovnog primanja u jedinicu intenzivnog lečenja ali i u bolnicu posle operacija. Akutni postoperativni bol koji je jakog intenziteta i nije dobro kontrolisan dovodi usporenog oporavka pacijenta a glavni je preduslov za razvoj hroničnog postoperativnog bola koji se teško i dugotrajno čeći. Retrospektivna analiza medicinskih kartona skoro 20.817 pacijenata koji su bili na jednodnevnoj hirurškoj intervenciji, pokazala je da je najčešći razlog ponovnog primanja u bolnicu u periodu do 30 dana od intervencije upravo nekontrolisani bol.(1)

Tabela 1. Studije koje su ispitivale efikasnost tapentadola IR (3)

Author (year)	Type of study	Total number of patient	Tapentadol IR dose and number of patients	Active control	Placebo	Indication
Stegmann JU *et al*.	Phase II,	269	Tapentadol IR	Oxycodone HCl	yes	Unilateral metatarsal
(2008)	DB, R		50, 100 mg n = 67, 68	10 mg n = 67	n = 67	Bunionectomy

Lee YK *et al.* (2014) Biondi D *et al.*	Phase III, DB, R, MC Phase III,	352 585	Tapentadol IR 50, 75 mg n = 121, 117 Tapentadol IR	no Oxycodone HCl	yes n = 114 no	Bunionectomy Acute low back pain
(2013) Kleinert R *et al.*	DB, R, PG Phase II,	400	50, 75, 100 mg n = 287 Tapentadol IR	5, 10, 15 mg n = 287 Morphine sulfate	yes	with radiculopathy Dental surgery
(2008) Daniels S *et al.*	DB, R Phase III,	901	25, 50, 75, 100, 200 mg n = 49, 50, 50, 48, 50 Tapentadol IR	60 mg Ibuprofen 400 mg n = 51, 51 Oxycodone HCl	n = 51 yes	Bunionectomy,
(2009)	DB, R, PG, MC		50, 75 mg n = 275, 278	10 mg n = 278	n = 69	acute pain
Daniels SE *et al.*	Phase III,	603	Tapentadol IR	Oxycodone HCl	yes	Bunionectomy,
(2009)	DB, R		50, 75, 100 mg n = 119, 120, 118	15 mg n = 125	n = 121	post-operative pain
Hartrick C *et al.*	Phase III,	659	Tapentadol IR	Oxycodone HCl	yes	End-stage joint
(2009)	DB, R		50, 75 mg n = 153, 166	10 mg n = 171	n = 169	disease, awaiting joint replacement surgery

Jedna od gore navedenih studija koje su prikazane u radu je i studija Danijels i saradnika (4). To je randomizovana, duplo slepa, placebo i aktivno kontrolisana studija u fazi III u koju su uključena 603 pacijenta sa umerenim do teškim bolom koji je nastao nakon bunionektomije.

Randomizirani pacijenti primali su tapentadol IR 50 mg (n = 119), tapentadol IR 75 mg (n = 120), tapentadol IR 100 mg (n = 118), oxycodone HCl 15 mg (n = 125) or placebo (n = 121) svaka 4 sata tokom perioda od 72 sata posle operacije čukljeva. Pacijenti u svim grupama tapentadola IR imali su značajno poboljšanje u vidu smanjenja intenziteta bola u poređenju sa placebom. Takođe studija je pokazala da sve tapentadol dozne grupe obezbeđuju odgovarajuću efikasnost a da tapentadol IR ima bolji profil GIT podnošljivosti u odnosu na oksikodon HCl. (5-6)

Akutni bol u donjem delu leđa

Randomizirana, duplo slepa studija, paralelne grupe koju su 2013. godine uradili Biondi i saradnici (7) ispitivala je pacijente sa umerenim do teškim akutnim bolom u donjem delu leđa a koji su primili tapentadol IR (50, 75, ili 100 mg) ili oxycodon HCl IR (5, 10, ili 15 mg) na svakih 4 do 6 sati po potrebi tokom 10 dana. Pacijenti su dva puta dnevno procenjivali intenzitet bola na 11 – numeričkoj skali procene (NRS). Primarni ishod efikasnosti bio je zbir razlike intenziteta bola (SPID= sum of pain intensity differences) tokom 120 sati od početka bola u donjem delu leđa. Studiju je od početnih 645 pacijenata završilo 585. Najčešći razlozi za prekidanje studije bili su neželjeni efekti (tapentadol IR, 6.5% [21/321]; oxycodone IR, 7.1% [23/324]). Na kraju studije i u tapentadol IR i u oxycodone IR terapijskuoj grupi skoro 2/3 pacijenata(66.2% vs 66.2%) i lekara(67.9% vs 66.6%) ocenili su opšte stanje kao „ veoma mnogo poboljšano" ili „veoma poboljšano" a više od 75%(79.3% vs 78.9%) pacijenata je bilo „veoma zadovoljno" ili „zadovoljno" sa terapijom. U grupi tapentadol IR i oxycodone IR grupi 52.3% (168/321) i 58.0% (188/324) pacijenata prijavili su bar jedan neželjeni efekat povezan sa terapijom; najčešće su to bili (≥ 10%) povraćanje (15.9% vs 24.7%),mučnina (15.9% vs 20.7%), i vrtoglavica(11.8% vs 10.5%). Povraćanje (odds ratio [95% CI], 1.74 [1.17 - 2.57]) i konstipacija (3.43 [1.45 - 8.11]) su se značajnije više pojavljivale u grupi koja je primala oxycodone IR.

Zaključak studije kaže da tapentadol IR ima efikasnost i ukupnu podnošljivost koja može da se poredi sa oksikodonom IR u terapiji umerenog do teškog bola u donjem delu leđa sa udruženom radikulopatijom i sa bolom u nogama , kada se koristi fleksibilni dozni režim koji reflektuje tipično korišćenje u kliničkoj praksi. Pa ipak tapentadol je pokazao bolju gastrointestinalnu podnošljivost naročito za najčešće neželjene efekte koji su povezani sa upotrebom opioida : povraćanje i konstipacija.

Osteoartritis

Hale i saradnici (8) su izveli studiju faza III koja je randomizovana, duplo slepa , akivno kontrolisana studija, paralelene grupe, multicentrična. Vođena je da bi se procenila podnošljivost tapentadol IR (50 or 100 mg, na 4-6h, p.o.) i oxycodone IR (10 ili 15 mg, na 4-6h, p.o.) tokom 90 dana u terapiji bola u donjem delu leđa ili ostoartritisa (OA) kuka ili kolena. Korišćeno je fleksibilno doziranje koje reflektuje kliničku upotrebu opioida. Efikasnost je bila sekundarni izlazni rezultat, jer je studija trebalo da pokaže dugotrajno izlaganje tapentadolu IR (a samim tim dobija se podatak o bezbedosti) u poređenju sa studijama primarne efikasnosti. Ukupno je uključeno 679 pacijenata u tapentadol IR group i 170 pacijenata u oxycodone IR grupu.Osnovne karakteristike na početku studije bile su slične iznmeđu ove dve grupe. Procenat pacijenata koji su ranije prekinuli terapiju bio je 42% u grupi tapentadol IR u odnosu na 49% u grupi oxycodone IR.Najčešći razlog za prekid terapije bili su neželjeni efekti i to u tapentadol IR grupi 21% u odnosu na oxycodone IR grupu 31%. U zaključku studije se navodi da fleksibilno

doziranje tapentadol IR (od 50 do 100mg) u trajanju do 90 dana za terapiju akutnog bola kod OA kuka ili kolena i bola u donjem delu leđa , obezbeđuje adekvatnu efikasnu analgeziju sa poboljšanom GIT podnošljivošću u poređenju sa oksikodon IR (10 do 15 mg). Rezultati iz upitnika koji su pacijenti popunjavali pri prekidu terapije pokazuju nizak intenzitet I malu frekvenciju simptoma udruženih sa opioidima i sugerišu da možda nije neophodno smanjivanje doze leka u produženoj terapiji sa tapentadolom

Literatura

1. Afilalo M, Stegmann JU, Upmalis D Tapentadol immediate release: a new treatment option for acute pain management. J Pain Res 20108;3:1-9
2. Sažetak karakteristika leka Palexia®, 50 mg, film tablet Palexia®, 75 mg, film tablet Palexia®, 100mg, film tableta, Datum revizije teksta Maj 2019.
3. Nebojsa Nick Knezevic, Tatiana Tverdohleb, Ivana Knezevic , Kenneth D Candido. Unique pharmacology of tapentadol for treating acute and chronic pain, Expert Opinion on Drug Metabolism & Toxicology 2015;11(9):1475-1492.
4. Daniels SE et al. A randomized, double-blind, phase III study comparing multiple doses of tapentadol IR, oxycodone IR, and placebo forpostoperative (bunionectomy) pain. Current Medical Research And Opinion 2009;25(3):765–776
5. Lee YK et al. Acute postoperative pain relief with immediate- release tapentadol : randomized ,double -blind, placebo – controlled study conducted in South Korea. Current medical Research and opinion 2014;30(12):2561-2570.
6. Kwong WJ et al. Cost-Effectiveness Analysis of Tapentadol Immediate Release for the Treatment of Acute Pain. Clin Ther 2010;32:1768–1781
7. Biondi Det al. Tapentadol Immediate Release Versus Oxycodone Immediate Release for Treatment of Acute Low Back Pain. Pain Physician 2013;16:E237-E246
8. Hale M et al. Tolerability of tapentadol immediate release in patients with lower back pain or osteoarthritis of the hip or knee over 90 days: a randomized, double-blind study, Current Medical Research And Opinion 2009;25(5):1095–1104

36 PAIN IN WOMAN

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Introduction

Every day, millions of women around the world deal with some kind of chronic pain, but unfortunately, many remain untreated. There are several reasons why certain barriers to treatment remain. Psychosocial and biological factors, together with economic barriers, which still exist in many countries, leave large numbers of women without proper treatment every day. Chronic pain is more common in the female population, but women are less likely to receive therapy. Certain conditions, such as fibromyalgia, inflammatory bowel disease, chronic pelvic pain, and migraine headaches, are more common in women than in men. There are also painful conditions specific to women, primarily of pelvic origin, including pain during the menstrual cycle and pain from diseases such as endometriosis and pain after a caesarean section.

Dysmenorrhea

Dysmenorrhea is the appearance of severe pain in the lower abdomen during menstruation. The pain can spread in the direction of the thigh or lower back, and it can be accompanied by vomiting, headache, back pain, diarrhea, and fatigue. Dysmenorrhea is the most common gynecological disease in women in their reproductive period and one of the most common causes of pelvic pain. However, women themselves do not diagnose it enough, treat it insufficiently, and even underestimate it, accepting it as a normal part of the menstrual cycle. It often has a great impact on the quality of life, limiting daily activities and being one of the main causes of absence from school and work.

Primary dysmenorrhea is defined as menstrual pain in the absence of pelvic disease. Secondary dysmenorrhea is caused by acquired lesions in the pelvis, which can occur in various conditions such as endometriosis, chronic pelvic inflammation, and other functional abnormalities of the reproductive organs.

Despite many studies, the pathomechanism of dysmenorrhea itself is not fully understood. Some scientists believe that menstruation can be viewed as an inflammatory event because leukocyte invasion and subsequent production of inflammatory mediators are observed during menstruation. It is known that the menstrual cycle depends on cyclic changes in hormone levels in the ovaries and thus on cyclical changes in prostaglandin levels and uterine contractile activity. Prostaglandins lead to narrowing of the blood vessels that supply the uterus as well as abnormal contractile activity of the uterus, which consequently leads to ischemia, uterine hypoxia, and increased sensitivity of nerve endings. Progesterone has an anti-inflammatory effect. With a decrease in its concentration, the secretion of prostaglandins and leukotrienes begins, which causes uterine contractions but also causes problems such as vomiting, tympanism, nausea and headaches.

In 1978, a study by Lundstrom and Green compared prostaglandin levels in women with severe menstrual pain and control groups of women who had no pain during menstrual days. Significantly higher concentrations of prostaglandins were found in the endometrium and plasma of women who have painful menstruation. Women with high levels of prostaglandins in their endometrium and plasma had stronger uterine contractions.

Numerous studies have examined the role of vasopressin in the pathomechanism of dysmenorrhea. Opinions and evidence are divided. Some studies have shown that vasopressin levels were lower in women with dysmenorrhea than in healthy women during ovulation, while no differences were observed in other studies.

Activated macrophages produce proinflammatory cytokines such as TNF, IL1, and IL6. Plasma IL6 and TNF levels were found to be higher in women with dysmenorrhea compared to women without menstrual disorders. TNF is a cytokine responsible for inhibiting endometrial proliferation. Endometrial cells produce an increased concentration of TNFa during menstruation.

Non-steroidal anti-inflammatory drugs (NSAID) are the drugs of first choice for dysmenorrhea. They inhibit cyclooxygenase, the enzyme responsible for prostaglandin synthesis.

Decreased prostaglandin production has been shown to reduce the strength of uterine contractions, which alleviates discomfort in women. Studies have shown that treatment is most effective if therapy is started 1-2 days before the start of menstruation. Long-term use of NSAIDs is associated with a number of side effects, such as headaches, dizziness, loss of appetite, nausea, vomiting, gastrointestinal bleeding, dysuria, and acne.

Another option for treating menstrual pain lies in the use of oral contraceptives. The endometrium produces prostaglandins and leukotrienes that contribute to the development of dysmenorrhea. The role of hormonal contraceptives also consists of inhibiting ovulation and consequently reducing the production of progesterone, which also reduces the synthesis of prostaglandins and leukotrienes.

Calcium channel blockers are another group of drugs that are being investigated in the treatment of dysmenorrhea. By reducing the contractility of vascular smooth muscle, they also inhibit uterine contractions. Calcium channel blockers, such as nifedipine, reduce the amount of calcium that passes into the muscle cells and so prevent them from contracting. In a dose of 20–40 mg of Nifedipine, it provides women with a reduction in menstrual pain, but certain side effects such as tachycardia, hot flashes, and headaches are also possible. Yoga can lower homocysteine levels, which may be involved in the pathogenesis of dysmenorrhea. Acupuncture is believed to stimulate receptors and nerve pathways that block the transmission of painful impulses by interacting with mediators such as serotonin and endorphins. Intense aerobic exercise not only reduces the levels of prostaglandin metabolites but also TNF. The program, which consists of stretching exercises, pelvic floor muscle exercises, jogging and short relaxation, proved to be the best.

Pulsed high-intensity laser therapy is effective in reducing primary dysmenorrhea due to its significant effect on reducing pain intensity and prostaglandin levels in the blood. The analgesic effect is achieved by creating photomechanical waves that act on A fibers, interrupting the transition of pain.

Endometriosis

Endometriosis is a chronic inflammatory disease defined as the presence of endometrial-like tissue outside the uterus, which causes pelvic pain and often leads to infertility. It usually affects women in the reproductive period. This disease should be viewed as a public health problem with a large impact on women's quality of life as well as a significant economic burden because the costs that accompany endometriosis are comparable to the costs of other chronic diseases, such as diabetes mellitus. The most common symptom is pain that occurs immediately before, during, or after menstruation. For some women, this pain may be disabling and may occur during bowel movements or urination or during or after sexual activity. However, women may have mild or no symptoms. Sometimes the first or only symptom of endometriosis is a pregnancy problem. Unfortunately, the wide range of symptoms that characterize this condition depend on estrogen, which often makes it difficult to make an accurate diagnosis.

Currently, there is no cure for endometriosis. The various treatments available for endometriosis aim to reduce the severity of symptoms and improve the quality of life of women with endometriosis. Drug treatment is aimed at controlling pain and suppressing hormonally active tissue. Hormone therapy that relies on the suppression of endometriotic tissue includes combined oral contraceptives, progestogen-only pills, gonadotropin-releasing hormone (GnRH) agonists, and aromatase inhibitors.

Surgery's efficacy is similarly restricted, with up to a 20% lesion recurrence rate and frequent postoperative endometrial lesions. All official recommendations give priority to laparoscopic surgery over laparotomy in the treatment of infertility and chronic

pain caused by endometriosis due to less pain, shorter hospital stays, and faster postoperative recovery.

Non-steroidal anti-inflammatory drugs (NSAID) are widely used for the symptomatic treatment of dysmenorrhea and pelvic pain. NSAIDs are considered a first-line symptomatic treatment.

Alternative heat treatments at home, with warm water or a warm bath, can help reduce pain. The heat relaxes the pelvic floor muscles, which can reduce cramps and pain. Castor oil has been used for hundreds of years to treat endometriosis. Massage of the pelvic muscles can help relax them and reduce inflammation. Turmeric has strong anti-inflammatory properties that can be beneficial. It can also be used for the long-term treatment of endometriosis. Some studies have even found that it has the ability to inhibit endometrial growth.

In order to eliminate pain as one of the most significant problems of endometriosis, there is a possibility of using hormone therapy. Recent studies have shown that endometriosis recurs at a rate of 20% to 40% within five years after conservative surgery.

Metformin is the most widely prescribed medicine for controlling blood glucose levels in people with type 2 diabetes. It improves cell sensitivity to insulin, lowering insulin resistance and the quantity of glucose generated by gluconeogenesis. Metformin has been shown to have anti-inflammatory, antiproliferative, and antiestrogenic effects on endometriotic tissue. It can also improve the pregnancy rate in women with infertility associated with endometriosis. Studies have shown that metformin works by:

- uppressing the production of IL-8,
- reducing aromatase activity.
- reducing endometrial cell growth and proliferation,
- It blocks the action of prostaglandin E2 (PGE2).

As a new strategy for the treatment of endometriosis, studies have been conducted examining the use of lipid nanoparticles as drug carriers. The challenge was to design an appropriate nanoparticle that could primarily collect in endometrial lesions without being toxic to the body while still recording and heating. Endometriosis tissue multiplies quickly, and a large amount of cholesterol is needed to build new cells. This causes low-density lipoprotein (LDL) receptor overexpression to allow cells to take in the required LDL cholesterol. The need of these cells for cholesterol was the basis of the study of the use of LDL for the purpose of effective targeted chemotherapy on rapidly multiplying tissues, such as malignant cells and endometriosis cells. Artificial lipid nanoparticles (LDE) were created. They are similar in structure to LDL and also have the ability to carry chemotherapeutic agents to target tissues.The findings of this study are preliminary. Additional research is needed to assess various treatment options and their side effects.

Chronic pain after a caesarean section

Chronic pain after a caesarean section is one of the most common and serious complications of a caesarean section. Given the apparent increase in the prevalence of caesarean procedures around the world, the emergence of chronic pain after a caesarean section could be a public health issue.

Compared to 2000, when about 13 million caesareans were performed worldwide, only fifteen years later, that number has increased to about 29 million. This increase is worrying because, in addition to the benefits for mother and child, the caesarean section itself carries numerous risks of postoperative complications. Despite the high rate of caesarean section worldwide, little is known about the mechanisms underlying the development of this pain and its incidence. There is an impression that this is an area to which not enough attention has been paid, although it represents a potentially important source of information about the process of developing chronic pain.

In a significant number of women, a caesarean section is associated with moderate to severe postoperative pain, which can delay recovery and return to daily activities. This pain can disrupt the mother-child bond, affecting the mother's psychological well-being and thus breastfeeding. Early recovery is especially important for patients who are expected to take care of newborns soon after surgery.

Literature about the factors potentially involved in the development of chronic pain after cesarean section is not enough to draw concrete conclusions. Severe pain in the early postoperative period, the duration of the cesarean surgery, the anxiety of the pregnant woman right before the caesarean section, and smoking are all risk factors, according to some studies.

Longer procedures are related to more severe tissue injuries during surgery, which is thought to raise the risk of nerve damage in the area, potentially leading to chronic pain. The relationship between anxiety and the frequency of persistent pain after a caesarean section received little attention in the research that was undertaken.

Due to the special characteristics of this type of operation and the increased risk of certain anxiety disorders during pregnancy, it is critical to evaluate the impact of this risk factor as well as the pregnant woman's preoperative conversation.

Severe pain in the period seven days after surgery has been found as a risk factor for chronic postoperative pain. This leads us to the question of how much pain is actually stopped in mothers after discharge from the hospital. Hyperalgesia and prolonged postoperative pain might occur if the patient is not appropriately treated in the early postoperative period after a caesarean section.

Chronic pain after a caesarean section can lead to numerous problems with the digestive and urinary tract, such as pain when urinating or emptying the bowel, but also to pain during basic activities such as sitting, walking, lifting. Patients most often come to the doctor after experiencing pain during sexual activities. All of these limitations may be the cause of postpartum depression.

Pain after a caesarean section is often insufficiently treated due to unfounded fears that analgesics could cause side effects in both mother and newborn, but also because the severity of pain after a caesarean section is often underestimated. Unless there are contraindications, basic analgesia following caesarean section should consist of paracetamol and NSAIDs, starting intraoperatively and continuing postoperatively.

Systemic nonsteroidal anti-inflammatory drugs (NSAID) relieve pain, reduce opioid usage, diminish opioid-related side effects, and improve patient satisfaction. Dexamethasone intravenously prolongs the effects of analgesics, lowers opioid intake, and reduces the requirement for postoperative antiemetics. Patients with glucose intolerance should be treated with caution.

Various local anesthetic techniques, such as TAP blocks, lumborum block quadrates, and wound infiltration with local anesthetics, are effective in reducing pain and opioid requirements. Since the potential side effects of these regional analgesic techniques are limited, they are recommended. The surgical approach is the last option in treatment.

Conclusion

Every day, millions of women around the world suffer from chronic pain, most of which derives from the pelvis. Women are more likely than men to suffer from chronic pain. Chronic pain has a negative impact on a woman's life, and it often causes them to miss work or school. A better understanding of the causes of chronic pain in women can result in effective therapy and, over time, improve the quality of life for millions of women around the world.

References

Lanlan Zhang, Gender Biases in Estimation of Others' Pain. The Journal of Pain, 2021; DOI: 10.1016/j.jpain.2021.03.001

Inês Guimarãesand Ana Margarida Póvoa, Primary Dysmenorrhea: Assessment and Treatment, PubMed,2020 Aug;42(8):501-507.

Pamela Stratton and Karen J. Berkley, Chronic pelvic pain and endometriosis: translational evidence of the relationship and implications, National Library of Medicine; 2011 May-Jun; 17(3): 327–346.

Amimi S. Osayande and Suarna Mehulic, Diagnosis and Initial Management of Dysmenorrhea, Am Fam Physician. 2014 Mar; 89(5):341-346.

PriyaKannan and Leica Sarah Claydon, Some physiotherapy treatments may relieve menstrual pain in women with primary dysmenorrhea: a systematic review; 2014 March;Pages 13-21.

Hye Lin Woo at al., The efficacy and safety of acupuncture in women with primary dysmenorrhea: A systematic review and meta-analysis, PubMed, 2018 Jun; 97(23):e11007.

Aalia Sachedina and Nicole Todd., Dysmenorrhea, Endometriosis and Chronic Pelvic Pain in Adolescents, PubMed, 2020 Feb 6;12(Suppl 1):7-17.
Rui Li et al., Association between dysmenorrhea and chronic pain: a systematic review and meta-analysis of population-based studies, PubMed, 2020 Mar 7 ;223(3):350-371.
Zofia Barcikowska et al., Inflammatory Markers in Dysmenorrhea and Therapeutic Options, PubMed, 2020 Feb 13 ;17(4):1191.
Rachel A Earl and Rosalie M Grivell, Nifedipine for primary dysmenorrhoea, PubMed central, 2017 Dec 2017(12): CD012912.
Maedeh Sharghi et al., An update and systematic review on the treatment of primary dysmenorrhea, PubMed, 2019 Jan-Mar, ; 23(1): 51–57.
Ali A. Thabet, Pulsed high-intensity laser therapy versus low level laser therapy in the management of primary dysmenorrheal, PubMed, 2021 Sep; v.33(9).
Abraham S. Moses et al., Nanomedicines for Endometriosis: Lessons Learned from Cancer Research, PubMed, 2021 Feb ; 17(7): e2004975.
Pranay R and Anu Aldakah, Laparoscopic management of moderate: Severe endometriosis, PubMed, Jan-Mar 2014 ; 10(1): 27–33.
Dimitrios Rafail Kalaitzopoulos et al., Treatment of endometriosis: a review with comparison of 8 guidelines, BMC Women's Health, 2021 Nov 21;397 (2021).
Elizabeth Ball and Khalid S Khan, Recent advances in understanding and managing chronic pelvic pain in women with special consideration to endometriosis, PubMed, 2020 Feb 4 F1000 Faculty Rev-83.
Andrew Kintu et al., Postoperative pain after cesarean section: assessment and management in a tertiary hospital in a low-income country, PubMed, 2019 Jan 25;19(1):68.
Natália Carvalho Borges et al., The incidence of chronic pain following Cesarean section and associated risk factors: A cohort of women followed up for three months, PubMed, 2020 Sep 4; 15(9): e0238634.
Juying Jin et al., Prevalence and risk factors for chronic pain following cesarean section: a prospective study, PubMed, 2016 Oct 18;16(1):99.
Jian Wang et al., The Efficacy and Safety of Local Anesthetic Techniques for Postoperative Analgesia After Cesarean Section: A Bayesian Network Meta-Analysis of Randomized Controlled Trials, 2021 Jun; 14: 1559–1572.

Life is pain: an exploration of suffering in art

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Introduction

Chronic pain in elderly population is reaching epidemic proportions (1). Giving that pain is personal and unique experience, and that living with chronic pain has significant impact on psychosocial well-being of patient (6), good understanding of psychological effect that pain has on sufferers is needed in order to meet the patient needs and to help them maintain quality of life. Efficient comunication between patient and physician through verbalisation alone can be challenging, and multimodal approach may be needed as a way for a patient to express their feelings. Creative process, for centuries, has been the most efficient way for a person to express themselves and deal with complex emotions. There are many examples where famous artist communicated their pain and suffering through art. On the other hand, creative process gave them a way to reduce stress and suffering related to chronic pain.

Science and art

Art and science have been inseparable from each other for centuries. With the aim of understanding and explaining natural laws, visual art was an indispensable tool in the interpretation and communication of scientific ideas and knowledge. Santiago Ramon y Cajal, a Spanish physician and pathologist from the 19th century, studied nervous tissue and the anatomy of the nervous system. His discoveries, for which he was subsequently awarded the Nobel Prize, are not only of scientific significance, but his sketches and drawings are exhibited in galleries around the world and have exceptional artistic value.

Nowadays, the relationship between art and science is complex. Traditionally, science and art are considered dichotomous disciplines, although it is impossible to draw a clear line between these two categories given that neither is clearly defined or homogeneous. Although through different methodologies and ways of expression, scientists

and artists strive to observe, interpret and communicate knowledge about the world in which we live.

The universal, yet personal experience of pain

One of the most prevalent concepts that medicine and art have been dealing with for thousands of years is the concept of pain. Pain is a universal human experience through all ages and cultures. There is no person who has not experienced pain at some point in their life.

In some countries, chronic pain in the elderly population is reaching epidemic proportions (1). Nevertheless, the impact of chronic pain on people's lives is still poorly understood. Although significant progress has been made in understanding the pathophysiology of pain and improving pain therapy, the treatment of patients with chronic pain in some social groups remains inadequate (2, 3).

Pain is a complex and personal experience. The subjective experience of pain is to some extent influenced by many factors such as gender, age, culture, education, social enviroment (3), and previous experiences.

In order to better understand the complex concept of pain and its impact on the psychosocial well-being of the patient, in 2020, after 41 years, the IASP published a revised definition of pain that was expanded by additional articles. Among other things, it is stated that verbal description is only one of the ways to express a feeling of pain, and that the absence of verbalization does not exclude the possibility that a person feels pain.

Pain assessment is mainly performed using visual and verbal scales, as well as questionnaires, which rely on data obtained from patients, on their subjective feeling. Chronic pain increases the risk of accelerated cognitive decline in the elderly population (4), which affects the perception of pain and the quality of communication between patient and physician. On the other hand, in children, due to underdeveloped cognitive functions, understanding the concept of pain and pain assessment scales may be difficult. Objective quantification of pain intensity remains one of the greatest challenges in pain therapy. This indicates the need for careful and efficient communication between the patient and the doctor, which sometimes needs to be carried out in different modalities depending on individual needs.

Visual art has always been a medium for communicating feelings that are difficult to verbalize in an effective way. The uniqueness of the artistic process lies in the possibility of transforming the complexity of human feelings into works of enchanting beauty and artistic value. The creative process is still one of the most effective forms of human expression and a way to express complex emotions.

One approach of treating chronic pain, although there are many gaps in the literature discussing the topic, involves implementing art therapy as a part of the treatment. Art can be a powerfull tool of non-verbal expression of emotions through the creative process. It is based on the work of certified therapists with the patient, guiding him

through the creative process and researching its relationship with pain. What is significant is the process, not the product. The creative process does not have the role of distraction, but can be a way to overcome anxiety related to pain .

The life of Vincent van Gogh, one of the most famous artists to this day, was marked by suffering and pain. For the artist, misunderstood by the society, socially isolated, repeatedly hospitalized in a psychiatric clinic, painting was the only therapy for emotional pain and a way to deal with his increasingly frequent hallucinations and depressive episodes. In the yard of a psychiatric clinic, he created some of his most famous works. Through the analysis of his paintings, one can sense the course of his illness and the emotional state he was in during the process of creation. Through his paintings, in a non-verbal way, he tried to communicate his emotions with the environment. In one of the many letters he wrote to his brother Theo during his hospitalizations, Vincent wrote: "I thought I would be understood without words."

The sense of agency and acceptance

Modern medicine has led to significant discoveries and advances in understanding the functioning of the human body. It is based on evidence and medical expertise, focused on the human body and the biological processes within it. However, man is a complex being; within every man there is a rich inner world that is inseparable from the physical body, which constantly interacts with the environment and affects the body and the processes within it, and vice versa.

Do we, as physicians, guided by objectivity and reason, taking control of the physical body of a patient with chronic pain in our own hands, lead to the passivity of the patient in the treatment process? Do we unconsciously neglect the patient's inner world, the immeasurable and subjective component of every human being that gives meaning to his being?

Rita O Hara is an artist who was diagnosed with rheumatoid arthritis at the age of 34. As a result of autoimmune disease, despite multiple surgeries and drug therapy, she lost most of the functionality in her wrists. By painting, she regained some of the flexibility in her right wrist and wrist joint, which led to relief of symptoms. The creative process, which she chose as a form of therapy, gave balance to life with suffering and pain.

Loss of agency, a sense of active role in one's own life and participation in decision-making about one's own choices, leads to stress, depression and social isolation. The impact of social isolation on mortality can be compared with already established risk factors for early death (5). Can stress, as a consequence but also a risk factor for the development of chronic pain, be modified to a certain extent through the creative process?

Frida Kahlo, one of the most influential artists of the 20th century, is known for her self-portraits that represent an intimate and emotional insight into life with chronic pain and suffering. As a child, she developed polio. As a consequence of the disease, atrophy and inadequate development of the right leg occurred, after which she developed

functional scoliosis. At the age of 17, while returning from school, she was involved in a traffic accident in which she suffered multiple fractures of the clavicle, ribs, spine and pelvis. The metal bar of the car broke through the left hip and into the pelvic floor. After a long hospitalization and multiple spine surgeries, she began her life with chronic pain. Physical as well as psychological traumas throughout life have led to depression, alcohol and drug abuse. Despite of that, chronic pain and suffering were catalysts for creating works of art that give us a unique insight into life with chronic pain and marginalization. Today, her paintings are on display in galleries around the world and, in addition to being one of the most significant works of art today, some psychologists use them as tools to empower women living with chronic and emotional pain. Frida wrote: "Painting completed my life. I lost three children and a series of other things that would have fulfilled my horrible life. My painting took the place of all of this. I think work is the best. "

There is growing evidence that suffering in patients with chronic pain, as well as in these artists, is related not only to the feeling of pain itself, but also to the consequences that pain has on the psychological and social functioning of a person (6).

Chronic pain can be a limiting factor in daily functioning, choice of occupation and hobby, participation in social interactions. Often these activities are linked to a sense of personal identity (7) and give meaning and purpose to our lives. A sense of self-agency is essential to human experience. There is evidence that modifying life goals in patients with chronic pain can have a positive effect on psychological well-being(6). To what extent should we strive towards changing things, or rather, to accept them? Is acceptance a key element of life with chronic pain?

The philosophical school of Stoicism dealt with this concept. Marcus Aurelius, Roman emperor and one of the representatives of the Stoic school, was known for his fragile health. His biographers state that he suffered from chronic pain in his chest and abdomen, although at that time it was not possible to discover the cause of the pain. Still, he was considered a man of great strength and endurance. In "Meditations", his personal notes during the practice of stoicism, Marcus Aurelius gives an insight into the psychological strategies of coping with chronic pain.

At the core of the Stoic approach is the separation of factors that are under our control from those that are not. Or rather, comparing the consequences of accepting the problem on one side, and struggling to change something on the other. Stoics write that pain is not what bothers us, but our fear of pain. Fighting things we can't change increases suffering. The ancient Stoic doctrine: "Pain is not what bothers me, but my attitude towards it", is the basic premise of modern Cognitive-behavioral therapy. Marcus Aurelius writes that pain and discomfort are natural and unavoidable in life, but that sensation should not be consciously added to an opinion and classified as good or bad. "Take away the complaint" I have been harmed ", and the harm is taken away." Philosophy is a science, but the skill of dealing with pain and channeling pain through writing is an art.

Conclusion

There are numerous examples of people who have chosen the path of accepting their pain and modifying their life goals by finding their voice in artistic expression. They used negative emotions as an instrument for personal transformation. Artistic expression transcends all human differences. For many people, as well as for these artists, who have struggled with pain, mental illness and addiction, the creative process can be a way to process and communicate complex emotions with the rest of the world.

Art therapy has shown promise as a part of the treatment of chronic pain in some individuals. In the absence of the possibility of verbalization, visual art gives patients the opportunity to express and communicate their emotions, to find meaning in creation and to connect with people who have similar experiences in their social environment.

Although interest has been shown in the use of art therapy for chronic pain treatment, it remains an important topic for future research in the means of exploring new approach to more holistic treatment.

Literature

1) Domenichiello AF, Ramsden CE. The silent epidemic of chronic pain in older adults. *Prog Neuropsychopharmacol Biol Psychiatry*. 2019;93:284-290.
2) Kissi, Amaa,*; Van Ryckeghem, Dimitri M.L.a,b,c; Mende-Siedlecki, Peterd; Hirsh, Adame; Vervoort, Tinea Racial disparities in observers' attention to and estimations of others' pain, PAIN: April 2022 - Volume 163 - Issue 4 - p 745-752.
3) Lanlan Zhang, Gender Biases in Estimation of Others' Pain. The Journal of Pain, 2021; DOI: 10.1016/j.jpain.2021.03.001
4) Herbette G, Rimé B. Verbalization of emotion in chronic pain patients and their psychological adjustment. *J Health Psychol*. 2004;9(5):661-676.
5) Macfarlane GJ, BaWhitlock EL, Diaz-Ramirez LG, Glymour MM, Boscardin WJ, Covinsky KE, Smith AK. Association Between Persistent Pain and Memory Decline and Dementia in a Longitudinal Cohort of Elders. *JAMA Intern Med*. 2017;177(8):1146-1153.
6) Macfarlane GJ, Barnish MS, Jones GT. Persons with chronic widespread pain experience excess mortality: longitudinal results from UK Biobank and meta-analysis. *Ann Rheum Dis*. 2017;76(11):1815-1822.
7) Vlaeyen JW, Morley S, Crombez G. The experimental analysis of the interruptive, interfering, and identity-distorting effects of chronic pain. *Behav Res Ther*. 2016;86:23-34.
8) Ramírez-Maestre C, Esteve R, López-Martínez AE, Serrano-Ibáñez ER, Ruiz-Párraga GT, Peters M. Goal Adjustment and Well-Being: The Role of Optimism in Patients with Chronic Pain. *Ann Behav Med*. 2019;53(7):597-607.

Spinal Radiculopathy- from diagnosis to treatment

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Abstract

While the literature lacks concise epidemiologic data, most reports estimate about a 3% to 5% prevalence rate of lumbosacral radiculopathy in patient populations , whereas prevalence of cervical radiculopathy range from 1,8-5%.

There are a variety different conditions which can cause the dysfunction of cervical nerve root.The clinical findings are key to pinpointing the pain source. However, differential diagnosis can be challenging. In this article , we have tried to present key data regarding proper diagnosis and treatment of spinal radiculopathy.

Key words: spinal radiculopathy, lumbar spine, cervical spine

Cervical radiculopathy

The main cause of cervical radiculopathy, in younger population, is disc herniation (up to 25% of cases), whereas foramina stenosis (based on osteophyte formation, decrease disc height, arthrosis of uncovertebral and facet joints) is a main cause of radiculopathy in older population. Radhakrishnan at al., who are authors of the most widely cited epidemiological study describing the incidence of cervical radiculopathy , found that the annual incidence was 107,3/100000 for men and 63,5/100000 for women (1)

Well known risk include : white race, smoking and prior lumbar radiculopathy (2) The most commonly affected is C7 root (60%), followed by C6 (25%) and the pain is a result of mechanical compression and inflammation (pro inflammatory cascade provided by tumor necrosis factor alpha (TNF), interleukin factor-6 (IL-6), MMP. (3).

After thorough history taking (chief complaint, what activities increase pain, time of injury, previous pain episodes, changes in gait, bowel or bladder disfunction) , one must provide physical examination which include : observation (head and neck posture, active ROM), palpation (tenderness is usually present along the paraspinal muscles,

hipertonicity or spasm), motor examination (manual muscle testing) which can yield the damaged nerve (figure 1), sensor examination (decrease or loss of sensation in a dermatomal distribution), deep tendon reflexes (be aware of potential myelopathy, hence Hoffman and Babinski reflex should be obtained), provocative tests (Spurling test- the foramina compression test, manual cervical distraction and Lhermitte sign (electric shock like sensation elicited by flexion of the neck. (4,5)

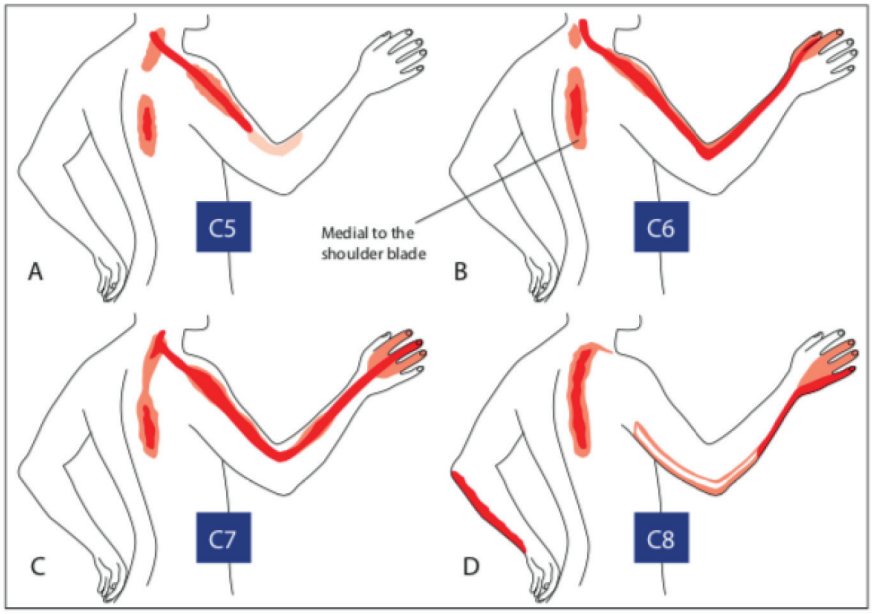

Fig. 1. Pain patterns in cervical radiculopathy C5 - C8.

Differential diagnosis:
– rotator cuff injury
– Compression syndromes (entrapment neuropathies) - carpal tunnel syndrome, pronator teres syndrome, cubital tunnel syndrome, thoracic outlet syndrome
– Syringomielia
– Brachial plexitis (Parsonage -Turner syndrome)
– Musculo tendinous syndrome
– Myofascial pain syndrome

Imaging

Plan radiography (lateral, oblique, AP and open-mouth view), but one has to be aware of low specifity and sensitivity), CT scan (provide best informations about bone integrity) and MRI (method of choice for imaging the neck, but be aware of the fact that many abnormalities in asymptomatic person can be found.

Other diagnostic tools which can be very helpful are: electromyography (EMG) and selective diagnostic nerve root block.

Treatment

The treatment of cervical radiculopathy can be nonoperative and operative. Nonoperative treatment consist of diverse modalities including immobilization, physical therapy, traction, manipulation, oral or parenteral drugs (NSAID remain mainstay of the treatment, with analgesic and anti-inflammatory effect) and steroid blocks. (6). There is currently no consensus regarding indications for surgery, but some signs and symptoms could be considered as a clear indications: progressive neurological deficit, signs of myelopathy, cervical instability, pain which does not respond to longterm nonoperative therapy (more than 6 weeks, some authors recommend 6 months as the cutoff for nonoperative treatment (7). Operative treatment can be performed from anterior (ACDF anterior cervical discectomy and fusion or disc prothesis) or from posterior (minimal invasive foraminotomy.

Lumbal spine radiculopathy

Lumbal spine radiculopathy occurs in approximately 3-5% of the population, and men and women are affected equally, opposite to cervical radiculopathy, which occur more frequently in men. The source of the pain are as in cervical radiolopathy: mechanical pressure on the root and inflammation. From a biomechanical aspect, lumbar discs are prone to herniation because they are exposed to tremendous forces. Some sport activities are under special risk , e.g. golf players and weight lifters.

Radiculopathy of L1-L3 roots cause pain to the anterior thigh and typically does not radiate below the knee, but these levels are affected in only 5% of all disc herniations. Always bear in your mind the possibilty of underlying serious condition ("red flags"): tumor, infection, fracture, especially when radiculopathy occur in younger than 20 years and older than 60 years (8).

A thorough physical examination is the key to the proper diagnosis. Evaluation of sensation, strength and reflexes should always be included. In differential diagnosis between L3 radiculopathy versus femoral neuropathy, weakness of hip adductors and quadriceps indicate L3 radiculopathy and isolated quadriceps weakness is characteristic for femoral neuropathy. Provocative maneuvers (straight leg raising or slump test) are mandatory. (figure 2)

"Hip-spine" syndrome is very common , especially in older people. Anterior thigh pain and groin pain indicate a hip pathology, rather than radiculopathy. Here are FABER and FADIR test very helpful. (9)

In differential diagnosis ,one should always be aware of tarsal tunnel syndrome, which is found to coaxst in 5% of the cases with lumbosacral radiculopathy (10)

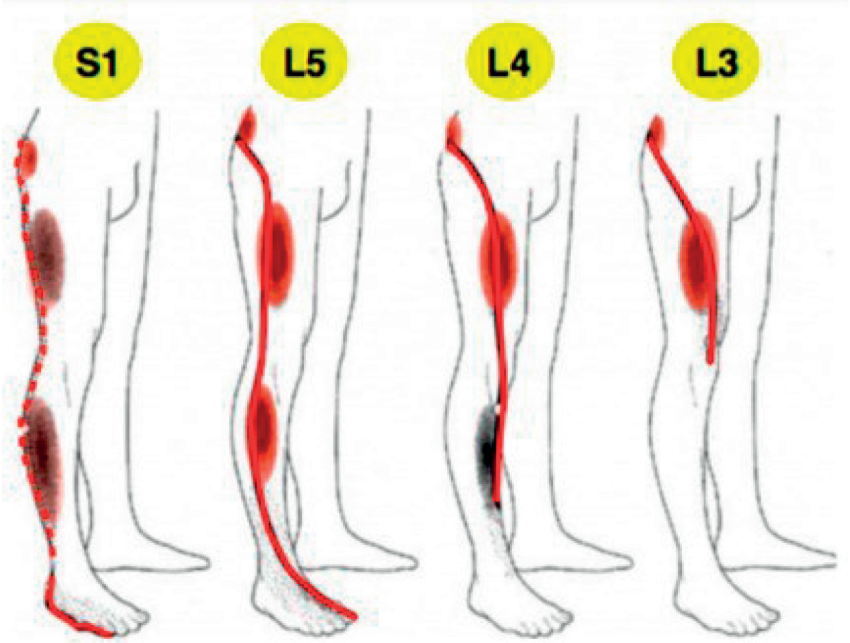

Fig .2. Pain patterns in cervical radiculopathy. L3-S1.

Imaging studies

Plain radiographs, CT, MRI and pyelogram (if MRI is contraindicated) can be used in the

detection of the cause of radiculopathy.Sometimes discography can be useful, especially in patines who does not respond to the rehabbilitation and who have a normal MRI finding. It is also helpful for surgeons in order to confirm indications for fusion. Electrodiagnostics can be helpful when the diagnosis remains unclear (peroneal neuronthy vs radiculopathy).

Treatment

The treatment of lumbar radiolopathy can be nonoperative: Drugs- NSAID, muscle relaxants,

opioid drugs, epidural steroid blocks , physical therapy- "back school", lumbar traction, vertebral axial decompression (VAX-D) or operative (minimal invasive discectomy- tubular or endoscopic, fusion chemonucleolysis, percutaneous disc decompression). Clear indications for surgical treatment: motor deficit, pain which last more then 6 weeks despite intensive physical therapy and drug treatment and emergency condition (cauda equine syndrome). (11)

Conclusion

Spinal radiculopathy is common and typically presents with unilateral arm or leg pain, neck or lumbar pain or both with or w/o neurologycal signs. It is very important

to differentiate radiculopathy from others items and it is of paramount importance not to overlook possible serious conditions (“rad flags”) - infection, tumor, fracture. Discal herniation is the most common cause of radiculopathy and up to 90% of herniaton can be treated conservatively. Surgical treatment is today very successful and it is based on minimal invasive approach.

Conflicts of interest.– I declare no conflict of interest

References

1.Radhakrishnan K, Litchy WJ, O’Fallon WM, et al. Epidemiology of cervical radiculopathy. A population-based study from rochester, minnesota, 1976 through 1990. *Brain.* 1994;117(Pt 2):325–35.

2. 2. Schoenfeld AJ, George AA, Bader JO, et al. Incidence and epidemiology of cervical radiculopathy in the united states military: 2000 to 2009. *J Spinal Disord Tech.* 2012;25:17–22.

3. Iyer S, Kim HJ. Cervical radiculopathy. Curr Rev Musculoskelet Med (2016); 9:272-280.

4.Wainner RS. Gill H. Diagnosis and nonoperative management of cervical radiculopathy. J Orthop Sports Phys There. 2000;30:728-44.

5. Rubenstein SN, Pool JJ, van Tulder MW, et al. A systematic review of the diagnostic accuracy of provocation tests of the neck for diagnosing cervical radiculopathy. Our Spine J.2007;16:307-19

6. Rhee JM, Yoon T, Riew KD. Cervical radiculopathy.J Am Acad Othop Surg.2007;15: 486-94.

7. Burneikiene S, Nelson EL, Mason A, et al. The duration of symptomsand clinical outcomes in patients undergoing anterior cervical discectomy and fusion for degenerative disc disease and radiculopathy. Spine J.2015;15:427-32

8. Cohen SP, Gupta A, Strassels SA, et al. Effect of MRI on treatment results or decision making in patients with lumbosacral radiculopathy referred for epidural steroid injections: a multi center, randomized controlled trial.Arch Intern Med. 2012; 172(2): 134.42.

9. Devin CJ, McCullough KA, Morris BJ, et al. Hip-spine syndrome. J Am Acad Orthop Surg. 2012;20:434-442. doi: 10.5435/JAAOS-20-07-434.

10.Zheng C, Zhu Y, Jiang J,Ma X, Lu F, Jin X, et al. The prevalence of tarsal tunnel syndrome in patients with lumbosacral radiculopathy.Eur Spine J. 2015;

11.Memmo PA, Nadler SF, Malanga GA. Lumbar disc herniation : a review of surgical and non-surgical indications and outcomes. J Back Musculoskelet Rahbil. 2000; 14(3): 79-88.

Preventive analgesia in endurance sports/Preventivna analgezija u sportovima izdržljivosti

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Abstract

Preventive analgesia has been studied in treatment of postoperative pain for a long time. To achieve top results in endurance sports acctivities (triathlon, cycling, marathon, ...) good physical and psychological condition are required related to the properly organized training. Analgesic therapy is an inseparable component during sports activities. In order to physical performance be adequately presented during the competition, it is necessary to optimize the maximum oxygen uptake in the muscles, by optimizing the cardiorespiratory function, through physical and psychological training. Optimizing the oxygen uptake in the muscles is a good strategy of pain prevention. Research in sports psychology dedicated to performance in endurance sports acctivities has studied muscular endurance and cardiovascular endurance. It has been proven that the ability to tolerate pain due to effort is a significant ergogenic factor in endurance sports. Also, the results show a weak ergogenic effect of paracetamol if the drug is taken 45-60 minutes before effort in a dose of 20mg /kg or 500-1500mg. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) in terms of prevention of the musculoskeletal pain was applied immediately before and during effort, more frequent than other analgesics. According to the current list of the World Anti-Doping Agency (WADA), tramadol and codeine are not banned substances in the treatment of pain in athletes. Their use can be an attempt to reduce the intensity of pain and improve the mood related to the experience of pain. The field of preventive analgesia in sports is insufficiently researched and there are not enough common designed studies with a consistent conclusion. Properly structured training, cardiovascular fitness in accordance with muscle engagement and psychological fitness are still considered the best pain preventive methods.

Key words: preventive analgesia, ergogenic factor, oxygen uptake

Uvod

U poslednjih nekoliko godina, princip preventivne analgezije zauzima značajno mesto u terapiji akutnog bola i prevencije nastanka hroničnog bolnog sindroma- značajnog, dugotrajnog socio-ekonomskog problema. Preventivna analgezija je analgetski princip koji je već duže vreme primenjivan i proučavan u okviru lečenja postoperativnog bola. U tom smislu, preventivna analgezija se primenjuje tokom celokupnog perioperativnog perioda (1,2). Sportovi izdržljivosti (triatlon, biciklizam, maraton,...) za ostvarivanje vrhunskih rezultata zahtevaju dobru kako fizičku tako i psihološku kondicioniranost sportiste, što je povezano sa strukturom organizovanih treninga. Neodvojiva komponenta tokom sprovođenja pripremnih i takmičarskih sportskih aktivnosti je i primena analgetske terapije s obzirom da je bol svakodnevni sastavni deo profesionalnih sportskih aktivnosti. Primena analgetske terapije u svrhu prevencije bola kod profesionalnog sportiste je deo svakodnevice, kako nakon povrede tako i zbog prevencije bola tokom aktivnosti (3).

Optimizacija potrošnje kiseonika: fizička i psihološka utreniranost

Kako bi fizičke performanse bile adekvatno prezentovane tokom takmičenja, neophodna je optimizacija maksimalne potrošnje kiseonika u mišićima, optimizacijom kardiorespiratone funkcije, kroz fizičku i psihološku utreniranost. Optimizacija potrošnje kiseonika u mišićima je dobar preventivni metod nastanka bola. Optimizacija potrošnje kiseonika podrazumeva formiranje aerobne mišićne aktivnosti tokom pažljivo izvedenih treninga kako bi se prevenirao nastanak bola u lokomotornom sistemu, smanjila verovatnoća nastanka povreda i prevenirala upotreba analgetika (4).

Istraživanja su pokazala da je psihološka utreniranost tokom izvođenja vežbi u sportovima izdržljivosti podjednako važan faktor dobrih performansi kao i fizička utreniranost s obzirom na strukturu aktivnosti-dugotrajni psiho-fizički napor (3). Istraživanja u sportskoj psihologiji posvećena uticaju na performanse u sportovima izdržljivosti proučavaju mišićnu izdržljivost i kardiovaskularnu izdržljivost. Mišićna izdržljivost obično angažuje jednu određenu grupu mišića, dok kardiovaskulana izdržljivost predstavlja aerobnu vežbu celog organizma kako bi se izdržao dugotrajan napor. Suština fizičkog kondicioniranja je stvaranje uslova aerobnog metabolizma u angažovanoj grupi mišića, tj.metabolička adaptacija. Trening u sportovima izdržljivosti prouzrokuje porast mitohondrijalne enzimske aktivnosti što za posledicu ima povećanu oksidaciju masti i smanjenje produkcije laktata za datu potrošnju kiseonika. Dakle, u sportovima izdržljivosti, kao preodukt metabolizma je i toplota u angažovanoj grupi mišića. Brzina produkcije laktata je najbolji fiziološki prediktor sportske performanse. Tokom fizičkog napora, bol se javlja kao fiziološka posledica naprezanja mišića i produkcije metabolita u angažovanoj grupi mišića (laktat, toplota), šireći se u druge delove tela kao što je grudni koš, postepeno, sa trajanjem napora. Međutim, bol je zaštitni znak koji bi trebalo da upozori na aktuelno ili preteće oštećenje tkiva. Dokazano je da u

sportovima izdržljivosti sposobnost tolerancije bola usled napora je značajan ergogeni faktor (5,6). Dobro utrenirani sportisti imaju veću sposobnost endogene modulacije bola. Ponavljani i strukturirani psiho-fizički treninzi dobro usklađuju intenzitet metabolizma sa količinom dopremljenog kiseonika, kontrolišući na taj način brzinu stvaranja produkata metabolizma (3).

Koncept preventivne analgezije

Nekoliko studija je ispitivalo uticaj paracetamola na performance u sportovima izdržljivosti, čiji su rezultati oprečni. Zbog toga je sprovedena meta-analiza novijeg datuma koja je sažela rezultate istraživanja u studijama visokog kvaliteta u odnosu na ispitivanje ergogenog efekta paracetamola u sportovima izdržljivosti. Paracetamol prvenstveno, ostvaruje svoj efekat preko inhibicije sinteze prostaglandina, inhibirajući specifično aktivnost COX 3 enzima, smanjujući transdukciju kroz nociceptivne neurone i transmisiju kroz nociceptivni put. Studije ističu uticaj paracetamola na smanjenje aktivacije mišića, što je primećeno u vežbama otpora, ali ostaje nejasno da li isti efekat postoji i u sportovima izdržljivosti. Meta-analizom je dokazano da postoji slab ergogeni efekat paracetamola ukoliko se lek uzme 45-60 minuta pre napora. Veća vremenska distanca od uzimanja leka do početka vežbe se nije pokazala učinkovitom u smislu prevencije bola u odnosu na placebo. S obzirom da je ergogeni efekat paracetamola dozno zavistan, primenjena doza paracetamola je varirala u uključenim studijama. U nekima je paracetamol primenjen u dozi od 20mg/kg, dok se u nekim studijama koristila apsolutna doza 500-1500mg. Upotreba paracetamola pre i posle vežbe može smanjiti fosforilaciju ribozomalnog proteina S6, što bi trebalo dalje razmotriti kao marker anabolizma (7).

Primena nesteroidnih antinflamatornih lekva (NSAIL) u smislu prevencije bolova u mišićno-zglobnom sistemu je primenjena neposredno pre napora i tokom napora, najčešće od svih analgetika. Preventivna primena duži vremenski period pre planiranog napora (3 meseca u različitim režimima primene, na dnevnom ili nedeljnom nivou) je zabeležena samo usled postojanja povrede (8).

Prema aktuelnoj listi Svetske antidoping agencije, tramadol i kodein nisu zabranjene supstance u terapiji bola kod sportista. Njihova primena može biti pokušaj da se smanji jačina bola i popravi raspoloženje u vezi sa doživljajem bola. Autori su utvrdili povećanje bihejvioralne i neuronske efikasnosti u mirovanju kod upotrebe tramadola, ali ne i ergogenog efekta (u odnosu na placebo ili 1500mg paracetamola) tokom biciklističkih vežbi visokog intenziteta (9).

Zaključak

Upotreba analgetika u populaciji sportista, naročito kod sportova izdržljivosti je značajna, a posebno je značajna povezanost upotrebe analgetika i sklonosti ka uzimanju nedozvoljenih supstanci, propisanih od strane Svetske antidoping agencije. Područje preventivne analgezije u sportovima je nedovoljno istraženo i ne postoji dovoljno

studija sličnog dizajna sa konzistentnim zaključkom. I dalje se najboljim preventivnim metodom smatra dobar i strukturiran trening, kardovaskularna kondicioniranost u skladu sa mišićnim angažmanom uz psihološku pripremljenost.

Literatura

1. Lavandhomme P.Why me? The problem of chronic pain after surgery. Br J Pain 2017;11:162-165.
2. Vadivelu N, Mitra S, Schermer E, et al. Preventive analgesia for postoperative pain-broader concept.Local and Regional Anesthesia 2014;7:17-22.
3. Assa T, Geva N, Zarkh Y, Defrin R. The type of sport matters: pain perception of endurance athletes versus strenght athletes.Eur J Pain 2018; 1-11.
4. Basset RD, Howley ET. Limiting factors for maximum oxygen uptake and determinants of endurance performance. Medeicine &Science in Sports &Excercise 2000; 17: 70-85.
5. Mc Cormick M, Meijen C, Marcora S. Psychological determinants of whole-body endurance performance. Sports Med 2015; 45: 997-1015.
6. Mc Dougall, Jutzeler CR, Scott A, Crocker PRE, Kromer JLK. Conditioned pain modulation in elite athletes: a systematic review and meta-analysis. Scand J Pain 2020; 12:1-10.
7. Grgic J, Mikulić P. Effect of paracetamol (Acetaminophen) ingestion on endurance performance: a systematic review and meta-analysis. Sports 2021; 9: 1-10.
8. Gorski T, Cardore LE, Pinto SS, de Silva EM, Correa CS, Beltram FG, et al. Use of non-steroidal anti-inflamatory drugs in triathlets: prevalence, level of awareness and reasons for use. Br J Sports Med 2009. DOI: 10.1136/bjsm.2009.062166
9. Zandonai T, Escorial M, Peiro A. Codeine and tramadol use in athletes: a potential for abuse. Frontiers in Pharmacology 2021; 12: 1-5.

40 Intra-articular injections for the treatment of chronic joint pain

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Abstract

Osteoarthritis (OA) is the most common form of arthritis, characterized by the degradation of cartilage at the joints. In patients with OA, refractory to conservative pharmacological and nonpharmacological treatment modalities, intra-articular injections of various products have demonstrated safety and efficacy towards treating the symptoms of different types of joint pain. Platelet-rich plasma (PRP) benefits include its relatively low cost, and high performance in comparative studies. It is typically effective in young or mild OA patients, at relieving pain, improving knee function and quality of life. Corticosteroids are most effective in the short-term and appropriate for treating acute and persistent synovitis. Hyaluronic acid may provide long-term pain relief in mild knee OA, particularly in combination with PRP, and is suitable for older or obese patients. Mesenchymal stem cells show good short-term efficacy and safety but remain expensive and in early stages of research. Patient characteristics, symptoms, and clinical findings may indicate the best strategy when choosing between the different injectable products.

Key words: intra-articular injection, joint injection, osteoarthritis, platelet-rich plasma, corticosteroids, hyaluronic acid, mesenchymal stem cells, regenerative therapy

Introduction

Osteoarthritis (OA) is the most common form of arthritis, characterized by the degradation of cartilage at joints due, in part, to inflammatory mediators. More specifically, the pathogenesis involves cartilage degradation, synovitis, subchondral bone remodelling, degeneration of ligaments and menisci, and hypertrophy of the joint capsule (1). In terms

of symptoms, OA produces pain, stiffness, and swelling, most commonly in the knees, hips, and hands, with an age-associated increase in incidence and prevalence. As a result, OA is the leading cause of disability in the United States (U.S.), and its prevalence is predicted to rise further due to an aging population, rising obesity rates, and high rates of traumatic knee injuries (2).

Treatment options for OA include nonpharmacological modalities, such as physical exercises, weight reduction, walking supports, and acupuncture. Oral pharmacological therapies include acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, and slow-acting drugs. If these prove ineffective, a remaining non-operative modality is the use of intra-articular (IA) injections (1). Platelet-rich plasma (PRP), corticosteroids (CS), hyaluronic acid (HA), and mesenchymal stem cells (MSC) are among the most thoroughly researched products for IA injections in the treatment of OA. Here, we summarize recent, high-quality research to identify the safest and most effective IA strategies for the treatment of joint pain.

Platelet-rich plasma

Platelet-rich plasma (PRP) is obtained from autologous blood through centrifugation in order to concentrate a sample of plasma with a four-to-five times higher platelet concentration than normal blood. This process concentrates cytokines, thrombin, various growth factors and other bioactive molecules which contribute to chondrogenesis, bone remodelling, proliferation, angiogenesis, anti-inflammation, coagulation and cell differentiation (1). One of the biggest advantages of PRP is its low-cost, as its preparation consists in a simple centrifugation process from the patient's own blood (3).

Several large, high-quality randomized controlled trials (RCTs) have been conducted on IA PRP injections, and although patients experienced pain and function improvement in response to PRP, superiority over placebo has been hard to demonstrate. Indeed, lack of superiority over placebo has been seen in response to double injections in patients with ankle OA at 26 weeks of follow-up, double injections in knee OA at 24 weeks of follow-up, and triple injection in mild-to-moderate knee OA at 12 months of follow-up (4-6). It is worth noting that an intra-articular injection of saline alone has been shown to decrease nociceptive pain in knee OA. This may be due to the placebo effect and to the efficacy of invasive treatments (3).

A systematic review and meta-analysis, including 6 studies, found moderate level evidence that PRP injections reduce pain more effectively than placebo in patients with temporomandibular joint osteoarthritis, at 6 and 12 months post-injection(7). A larger systematic review and meta-analysis on 23 RCTs found that PRP was significantly more effective at relieving knee OA symptoms than placebo, oral NSAIDs, and IA HA injections. With regards to safety, PRP showed no significant difference in adverse event rates compared to placebo and HA (3).

A variant of PRP is plasma rich in growth factors (PRGF), which is similarly harvested from autologous blood, but consists of a moderated platelet concentration

without leukocytes, meant to minimize the risk of pro-inflammatory activity within the joint. A large network meta-analysis on knee OA found that PRGF led to a significantly greater improvement in pain and function than placebo. In terms of clinically significant improvements in pain and function, PRGF came second to PRP when compared to placebo, but showed no significant difference when compared to HA and CS injections (8).

The application approach may impact the efficacy of the injections. An RCT comparing single and triple IA PRP injections has shown clinical superiority of triple infiltration for the treatment of mild knee osteoarthritis, at a 48-week follow-up. Nonetheless, a systematic review and meta-analysis found no significant difference between single and triple PRP injection in terms of short-term curative effect (3).

Corticosteroids

Corticosteroids (CS) have anti-inflammatory and immunosuppressive properties, making them useful in treating acute and chronic inflammatory conditions, including OA flares. Their anti-inflammatory activity may lead to clinical outcomes such as decreases in erythema, swelling, heat and tenderness, and an increase in viscosity via an increase in HA (1). In turn, several corticosteroid formulations have been approved by the U.S. Food and Drug Administration (FDA) for IA administration, including methylprednisolone acetate, triamcinolone acetate, betamethasone acetate and betamethasone sodium phosphate, triamcinolone hexacetonide and dexamethasone. Furthermore, the use of IA CS in treating knee OA is recommended by several major guidelines (9).

Several large RCTs, systematic reviews, and meta-analyses have found IA CS injections to be superior to placebo in the management of patients with knee OA (10). Additionally, two recent RCTs found IA CS injections to be effective in the treatment of lumbar facet joint syndrome and rotator cuff tendinopathy, although slightly inferior to IA PRP (11,12). A systematic review and meta-analysis of 15 RCTs on knee OA noted that IA CS is superior to placebo for up to 6 weeks on pain and function. In the long term, upwards of 24 weeks, IA HA, IA NSAIDs and physiotherapy appear more effective than IA CS for both pain and function outcomes, although this result may be driven by single studies with large effect sizes (9). Indeed, the shorter duration of symptomatic relief provided by IA CS for knee OA has been shown in several studies and meta-analyses.

Beyond clinical efficacy, however, one of the largest RCTs on IA CS in patients with knee OA found that, after two years of treatment, IA triamcinolone caused significantly greater cartilage volume loss and no significant difference in knee pain compared to IA saline (13). This deleterious effect on articular cartilage, with a possible time-dependent component, may explain the decreased efficacy of CS compared to other IA treatments (8).

Hyaluronic acid

Hyaluronic acid (HA), a high-molecular weight polysaccharide, is a natural component of the synovial fluid and cartilage matrix, produced by synovial cells, fibroblasts,

and chondrocytes. The purpose of HA in joints is to enhance viscosity and elastic shock absorption. The theorized mechanism of action of IA HA administration lies in "visco-supplementation", denoting the temporary restoration of lubricating and shock-absorbing effects of the synovial fluid (1). HA has also been hypothesized to slow the process of joint degeneration by forming polymers with proteoglycans, thus inhibiting its precipitation from the cartilage matrix and reducing the loss of cartilage matrix (14). For IA administration, FDA-approved HA injectable products include hyaluronate, Hylan G-F 20, and high-molecular weight hyaluronan.

Several recent RCTs have shown that IA HA improves pain and function in the short term in knee OA patients, but is inferior to PRP in the longer term, of at least 12 months (15-17). A systematic meta-analysis of 26 RCTs and a network meta-analysis of 40 RCTs found that PRP provided more pain and function improvement than HA, in the short and long term, in patients with knee OA (8,18).

Notably, some clinical trials found that the combined IA injection of PRP and HA is superior to PRP or HA alone for the treatment of knee OA, in terms of pain, function, safety, and biochemical markers of disease (19,20).

Mesenchymal stem cells

Mesenchymal stem cells (MSC), by definition, are plastic-adherent (or prospectively isolated) populations of stromal cells that can be harvested from any tissue. They express or lack specific cell surface markers, and are capable of trilineage differentiation into osteoblasts, adipocytes, and chondrocytes *in vitro*. MSCs sourced from bone marrow are able to migrate from subchondral bone to damaged sites and integrate new and surrounding tissues. MSCs sourced from adipose tissue have been hypothesized to be able to tolerate proapoptotic conditions caused by ischemia and hypoxia in the articular cartilage microenvironment. The mechanism of action of MSCs remains unclear but is likely related to the release of chemical mediators, which may play a role in the repair and regeneration of cartilaginous tissue (14,21).

The IA injection of MSC has shown successful long-term outcomes in both pain, function, and safety, in several RCTs (22-24). Systematic reviews and meta-analyses on IA MSC injections show that it provides improvement in pain outcomes and a good safety profile. A large network meta-analysis found that, compared to placebo, both bone marrow MSCs and adipose MSCs produce improvements in pain and function for up to 6 months. At the 12-month follow-up, clinical effectiveness in pain relief was only seen following IA injection of adipose MSCs (14). This may be related to the fact that adipose MSCs have been shown to have a larger cell count per unit volume of tissue, proliferate faster, and survive better than bone marrow MSCs (25). Nonetheless, the outcomes of IA MSC injections are mixed in terms of functional improvements and long-term outcomes, calling for further high-quality research (14,25,26).

Conclusion

Intra-articular injections are safe and effective towards treating the symptoms of OA and improve patient satisfaction. PRP benefits include its low cost and high performance in comparative studies. It is typically effective in young or mild OA patients at relieving pain, improving knee function, and quality of life. CS is most effective in the short-term and appropriate for treating acute and persistent synovitis. HA may provide long-term pain relief in mild knee OA, particularly in combination with PRP, and is suitable for older or obese patients. MSC show good short-term efficacy and safety but remain expensive and in early stages of research. Patient characteristics, symptoms, and clinical findings may indicate the best strategy when choosing between the different injectable products.

References

1. Ayhan E, Kesmezacar H, Akgun I. Intraarticular injections (corticosteroid, hyaluronic acid, platelet rich plasma) for the knee osteoarthritis. *World J Orthop* 2014:5: 351-361.
2. Mandl LA. Osteoarthritis year in review 2018: clinical. *Osteoarthritis Cartilage* 2019:27: 359-364.
3. Hong M, Cheng C, Sun X, et al. Efficacy and Safety of Intra-Articular Platelet-Rich Plasma in Osteoarthritis Knee: A Systematic Review and Meta-Analysis. *Biomed Res Int* 2021:2021: 2191926.
4. Bennell KL, Paterson KL, Metcalf BR, et al. Effect of Intra-articular Platelet-Rich Plasma vs Placebo Injection on Pain and Medial Tibial Cartilage Volume in Patients With Knee Osteoarthritis: The RESTORE Randomized Clinical Trial. *JAMA* 2021:326: 2021-2030.
5. Paget LDA, Reurink G, de Vos RJ, et al. Effect of Platelet-Rich Plasma Injections vs Placebo on Ankle Symptoms and Function in Patients With Ankle Osteoarthritis: A Randomized Clinical Trial. *JAMA* 2021:326: 1595-1605.
6. Dorio M, Pereira RMR, Luz AGB, et al. Efficacy of platelet-rich plasma and plasma for symptomatic treatment of knee osteoarthritis: a double-blinded placebo-controlled randomized clinical trial. *BMC Musculoskelet Disord* 2021:22: 822.
7. Li F, Wu C, Sun H, et al. Effect of Platelet-Rich Plasma Injections on Pain Reduction in Patients with Temporomandibular Joint Osteoarthrosis: A Meta-Analysis of Randomized Controlled Trials. *J Oral Facial Pain Headache* 2020:34: 149-156.
8. Singh H, Knapik DM, Polce EM, et al. Relative Efficacy of Intra-articular Injections in the Treatment of Knee Osteoarthritis: A Systematic Review and Network Meta-analysis. *Am J Sports Med* 2021: 3635465211029659.
9. Najm A, Alunno A, Gwinnutt JM, et al. Efficacy of intra-articular corticosteroid injections in knee osteoarthritis: A systematic review and meta-analysis of randomized controlled trials. *Joint Bone Spine* 2021:88: 105198.

10. Knezevic NN, Jovanovic F, Voronov D, et al. Do Corticosteroids Still Have a Place in the Treatment of Chronic Pain? *Front Pharmacol* 2018:9: 1229.
11. Wu J, Zhou J, Liu C, et al. A Prospective Study Comparing Platelet-Rich Plasma and Local Anesthetic (LA)/Corticosteroid in Intra-Articular Injection for the Treatment of Lumbar Facet Joint Syndrome. *Pain Pract* 2017:17: 914-924.
12. Dadgostar H, Fahimipour F, Pahlevan Sabagh A, et al. Corticosteroids or platelet-rich plasma injections for rotator cuff tendinopathy: a randomized clinical trial study. *J Orthop Surg Res* 2021:16: 333.
13. McAlindon TE, LaValley MP, Harvey WF, et al. Effect of Intra-articular Triamcinolone vs Saline on Knee Cartilage Volume and Pain in Patients With Knee Osteoarthritis: A Randomized Clinical Trial. *JAMA* 2017:317: 1967-1975.
14. Zhao D, Pan JK, Yang WY, et al. Intra-Articular Injections of Platelet-Rich Plasma, Adipose Mesenchymal Stem Cells, and Bone Marrow Mesenchymal Stem Cells Associated With Better Outcomes Than Hyaluronic Acid and Saline in Knee Osteoarthritis: A Systematic Review and Network Meta-analysis. *Arthroscopy* 2021:37: 2298-2314 e2210.
15. Lin KY, Yang CC, Hsu CJ, et al. Intra-articular Injection of Platelet-Rich Plasma Is Superior to Hyaluronic Acid or Saline Solution in the Treatment of Mild to Moderate Knee Osteoarthritis: A Randomized, Double-Blind, Triple-Parallel, Placebo-Controlled Clinical Trial. *Arthroscopy* 2019:35: 106-117.
16. Raeissadat SA, Gharooee Ahangar A, Rayegani SM, et al. Platelet-Rich Plasma-Derived Growth Factor vs Hyaluronic Acid Injection in the Individuals with Knee Osteoarthritis: A One Year Randomized Clinical Trial. *J Pain Res* 2020:13: 1699-1711.
17. Raeissadat SA, Ghazi Hosseini P, Bahrami MH, et al. The comparison effects of intra-articular injection of Platelet Rich Plasma (PRP), Plasma Rich in Growth Factor (PRGF), Hyaluronic Acid (HA), and ozone in knee osteoarthritis; a one year randomized clinical trial. *BMC Musculoskelet Disord* 2021:22: 134.
18. Tan J, Chen H, Zhao L, et al. Platelet-Rich Plasma Versus Hyaluronic Acid in the Treatment of Knee Osteoarthritis: A Meta-analysis of 26 Randomized Controlled Trials. *Arthroscopy* 2021:37: 309-325.
19. Xu Z, He Z, Shu L, et al. Intra-Articular Platelet-Rich Plasma Combined With Hyaluronic Acid Injection for Knee Osteoarthritis Is Superior to Platelet-Rich Plasma or Hyaluronic Acid Alone in Inhibiting Inflammation and Improving Pain and Function. *Arthroscopy* 2021:37: 903-915.
20. Sun SF, Lin GC, Hsu CW, et al. Comparing efficacy of intraarticular single crosslinked Hyaluronan (HYAJOINT Plus) and platelet-rich plasma (PRP) versus PRP alone for treating knee osteoarthritis. *Sci Rep* 2021:11: 140.
21. Jones IA, Togashi R, Wilson ML, et al. Intra-articular treatment options for knee osteoarthritis. *Nat Rev Rheumatol* 2019:15: 77-90.
22. Lee WS, Kim HJ, Kim KI, et al. Intra-Articular Injection of Autologous Adipose Tissue-Derived Mesenchymal Stem Cells for the Treatment of Knee Osteoarthritis: A

Phase IIb, Randomized, Placebo-Controlled Clinical Trial. *Stem Cells Transl Med* 2019:8: 504-511.
23. Gupta PK, Chullikana A, Rengasamy M, et al. Efficacy and safety of adult human bone marrow-derived, cultured, pooled, allogeneic mesenchymal stromal cells (Stempeucel(R)): preclinical and clinical trial in osteoarthritis of the knee joint. *Arthritis Res Ther* 2016:18: 301.
24. Garza JR, Campbell RE, Tjoumakaris FP, et al. Clinical Efficacy of Intra-articular Mesenchymal Stromal Cells for the Treatment of Knee Osteoarthritis: A Double-Blinded Prospective Randomized Controlled Clinical Trial. *Am J Sports Med* 2020:48: 588-598.
25. Ding W, Xu YQ, Zhang Y, et al. Efficacy and Safety of Intra-Articular Cell-Based Therapy for Osteoarthritis: Systematic Review and Network Meta-Analysis. *Cartilage* 2021:13: 104S-115S.
26. Migliorini F, Rath B, Colarossi G, et al. Improved outcomes after mesenchymal stem cells injections for knee osteoarthritis: results at 12-months follow-up: a systematic review of the literature. *Arch Orthop Trauma Surg* 2020:140: 853-868.

Perioperativna primena gabapentinoida/Perioperative Administration of Gabapentinoids

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Sažetak

Pojedini autori ističu neočekivano visok intenzitet bola kod malih hirurških procedura, što ukazuje na individualnu percepciju bola i odgovor na analgetsku terapiju. Pored "rizičnih operativnih zahvata", u literaturi se navodi i "rizična populacija pacijenata". Akutni postoperativni bol je nociceptivne prirode, receptorom posredovan, prouzrokvan hirurškom traumom tkiva, jasno definisanog početka i ograničenog trajanja. HPOB predstavlja bol koji traje duže od 3 meseca nastao nakon operacije ili se intezivirao nakon operacije, počinje u vreme trajanja akutnog bola ili se nadovezuje na njega nakon latentnog perioda, ukoliko su drugi uzroci bola isključeni. Bol može biti lokalizovan u hirurškom polju ili zajedničkom inervacionom području. Rezultati nedavno sprovedenih studija pokazuju da je prevalencija HPOB ostala nepromenjena uprkos napretku u istraživanju osnovnih patofizioloških mehanizama. Mnogi lekovi bili su predmet istraživanja brojnih studija sa idejom da se smanji incidencija nastanka HPOB, ali sa promenljivim rezulatima.

Mesto antikonvulziva u prevenciji nastanka nociceptivnog bola nalazi se u činjenici da oni inhibiraju otvaranje voltažno zavisnih kalcijumovih kanala na presinapsnom delu spojnice zadnjih rogova sive mase kičmene moždine, čime inhibiraju oslobađanje ekscitatornih neurotransmitera, ascendentno kretanje nociceptivne draži i percepciju bola. Ova grupa lekova vezuje se za alfa2-delta subjedinicu L -tipa voltažno zavisnih kalcijumovih kanala (cerebelum i hipokampus), čime inhibira oslobađanje glutamata, noradrenalina, supstance P, inhibicijom influksa jona kalcijuma iz primarnih aferentnih nervnih vlakana čime se potiskuje ekscitabilnost neurona nakon povrede nerva ili tkiva. Kako navode pojedini autori u publikacijama novijeg datuma, efikasnost gabapentinoida u prevenciji HPOB nije jasno dokazana uz različit režim primene, ali je dokazana efikasnost u kontroli akutnog postoperativnog bola u prvih 24 sata postoperativno. U

poslednje vreme, rutinska primena gabapentnoida kod određenh hirurških procedura koje su označene kao „rizične“ doprinela je povećanju neželjenih efekata, bez jasnih terapijskih efekata. Rutnska perioperativna primena gabapentinoida ne bi trebalo da bude deo svakodnevne kliničke prakse s obzirom na oprečne rezultate eksperimentalnih kliničkih istraživanja i vrlo jasne dokaze novijih meta-analiza koje nedvosmisleno ukazuju da perioperativna primena gabapentinoida nije opravdana.

Ključne reči: bol, HPOB, gabapentinoidi, primena

Uvod

Tokom prethodne dve decenije, nedovoljno dobro lečen akutni postoperativni bol je prepoznat

kao značajan problem u kvalitetu postoperativnog oporavka i s toga označen kao ”peti vitalni

znak” (1). Uprkos konstantnom unapređenju vodiča, kontinuiranoj edukaciji, podaci dobijeni iz statističkih izveštaja ekonomski razvijenih država, ukazuju da je ovaj problem i dalje značajan (2, 3). U kliničkoj praksi, vrsta hirurške procedure uglavnom određuje analgetski terapijski pristup. Ipak, rezultati pojedinih istraživanja ukazuju da terapiju ne bi trebalo usmeravati samo prema intenzitetu hirurške traume (4). Pojedini autori ističu neočekivano visok intenzitet bola kod malih hirurških procedura, što ukazuje na individualnu percepciju bola i odgovor na analgetsku terapiju. Pored “rizičnih operativnih zahvata”, u literaturi se navodi i “rizična populacija pacijenata”: višestruko operisani pacijenti, pacijenti ženskog pola, mlađi, određenog psihološkog profila (skolni katastrofisanju, anksiozni), pacijenti sa prethodno prisutnim hroničnim bolom, sa određenim genetskim opterećenjem. Zbog bio-psiho-socijalne osnove akutnog i hroničnog (perzistentnog) postoperativnog bola, nekoliko godina unazad se značajno ističe multimodalan koncept terapije bola (5). Multimodalni pristup terapiji akutnog postoperativnog bola primenjuje se tokom celog perioperativnog perioda pa se značajan akcenat stavlja na prevenciju nastanka bola.

Hronifikacija akutnog postoperativnog bola, incidenca hroničnog postoperativnog bola i prevencija gabapentinodima

Akutni postoperativni bol je nociceptivne prirode, receptorom posredovan, prouzrokvan hirurškom traumom tkiva, jasno definisanog početka i ograničenog trajanja (6,7). Hirurška destrukcija tkiva pokreće kaskadu oslobađanja medijatora zapaljenja, produkata razgradnje arahidonske kiseline, oslobađanje glutamata, peptida, supstance P i mnogih drugih medijatora. Istovremeno se uz ascendentne aktivirajuće signale prostiru i descendentni inhibirajući signali praćeni oslobađanjem noradrenalina, serotonina, endogenih opioida. U nivou kičmene moždine se vrši direktan presinapsni uticaj na aferentno nervno vlakno i postsinapsni uticaj preko gama-aminobuterne kiseline (GABA) i glicinskih interneurona, čime se modulira ekscitatorni signal (8). Na mestima

oslobađanja hemijskih supstanci, koje mogu pojačati ili inhibirati nociceptivni signal, može se vršiti modulacija nociceptivne draži.

Za razliku od akutnog postoperativnog bola, hronični postoperativni bol (HPOB) predstavlja značajan i dugotrajan socio-ekonomski problem pojedinaca i društva u celini. Predstavlja bol koji traje duže od 3 meseca nastao nakon operacije ili se intezivirao nakon operacije, počinje u vreme trajanja akutnog bola ili se nadovezuje na njega nakon latentnog perioda, ukoliko su drugi uzroci bola isključeni. Bol može biti lokalizovan u hirurškom polju ili zajedničkom inervacionom području. Prema različitim publikacijama, perzistentni postoperativni bol ima različitu incidencu:10-15% pa sve do 30% (9, 10, 11). Torakotomije, hirurgija dojke, ortopedske operacije i operacija preponske kile su intervencije sa najvećom incidencom postoperativnog bola 12 meseci nakon operacije (30-50%) (3). Faktori koji utiču na prelazak (tranziciju) akutnog postoperativnog bola na hronični postoperativni bol tek treba da budu razjašnjeni. Rezultati nedavno sprovedenih studija pokazuju da je prevalencija HPOB ostala nepromenjena uprkos napretku u istraživanju osnovnih patofizioloških mehanizama. Mnogi lekovi bili su predmet istraživanja brojnih studija sa idejom da se smanji incidencija nastanka HPOB, ali sa promenljivim rezulatima. Danas se farmakološka prevencija razvoja HPOB sprovodi pre svega poboljšanjem kontrole akutnog postoperativnog bola i to primenom lekova tokom perioperativnog perioda. Mesto antikonvulziva u prevenciji nastanka nociceptivnog bola nalazi se u činjenici da oni inhibiraju otvaranje voltažno zavisnih kalcijumovih kanala na presinapsnom delu spojnice zadnjih rogova sive mase kičmene moždine, čime inhibiraju oslobađanje ekscitatornih neurotransmitera, ascendentno kretanje nociceptivne draži i percepciju bola. Preventivna primena antikonvulziva zabeležena je kod operativnih zahvata koji se povezuju sa značajnim procentom pojave perzistentnog postoperativnog bola kao i kod pacijenata sa anksioznim poremećajem (hronični bol druge etiologije) (12,13).

Gabapentinoidi (pregabalin i gabapentin) predstavljaju atraktivnu klasu lekova koji se mogu koristiti u okviru multimodalnog režima. Preventivna primena antikonvulziva zabeležena je kod operativnih zahvata koji se povezuju sa značajnim procentom pojave perzistentnog postoperativnog bola. Iako su trenutno odobreni samo za hronični neuropatski bol, epilepsiju i anksioznost, oni se mogu koristiti i kao pomoćno sredstvo za preventivnu analgeziju. U poslednjih deset godina u pojedinim državama, gabapentinoidi se koriste za kontrolu akutnog nociceptivnog bola i neuropatskog bola (off-lable upotreba) zbog čega su uključeni i u rutinsku upotrebu. Međutim, ovakav način primene ne daje jasan konsenzus o režimu primene (12).

Farmakokinetske i farmakodinamske karakteristike gabapentinoida

U centalnom nervnom sistemu postoji šest tipova kalcijumovih kanala: L, N, P, Q, R, T. Ova grupa lekova vezuje se za alfa2-delta subjedinicu L -tipa voltažno zavisnih kalcijumovih kanala (cerebelum i hipokampus), čime inhibira oslobađanje glutamata,

noradrenalina, supstance P, inhibicijom influksa jona kalcijuma iz primarnih aferentnih nervnih vlakana čime se potiskuje ekscitabilnost neurona nakon povrede nerva ili tkiva. Oni mogu sprečiti centralnu senzitizaciju i naknadnu hiperalgeziju i alodiniju sa manjim efektima na normalne nociceptivne puteve. Iako su strukturno produkti gama-aminobuterne kiseline, ni jedan se ne vezuje za GABA receptor, niti utiče na metabolizam ovog inhibitornog neurotransmitera. Uvođenje ovih lekova u terapiju mora biti postepeno jer od toga zavisi terapijski efekat. Neželjeni efekti su im zajednički i najčešće su to hiperekscitatorne reakcije centralnog nervnog sistema: konvulzije, hiperkinezija, poremećaj govora, vrtoglavica. Njihova apsorbcija nije povezana sa sa unosom hrane, ali ih ne bi trebalo primenjivati oko dva sata od uzimanja antacida. Ne metabolišu se, već se u nepromenjenom obliku eliminišu putem bubrega. U okviru preventivne analgezije studije nisu pokazale konzistentnost dokaza o periodu primene , ali se smatra da ih trebalo primeniti 1-4 h pre hiruške incizije. Neki radovi ukazuju i na postoperativnu primenu različitog trajanja. Takođe ne postoji jasan dogovor ni oko primenjenih doza, ali je dokazano da su veće doze efektivnije. Gabapentin se primenjuje u dozi od 100-300 mg preoperativno, dok se postoperativno moze primenjivati u tri podjednake doze, sa poluvremenom eliminacije 6-9 h. Kod pacijenata koji su na hemodijalizi, ordiniranje leka je povezano sa danom kojim idu na hemodijalizu, kada se lek daje 4h posle procedure. Pregabalin je drugi predstavnik ove grupe, koji se dozira 50-150 mg dnevno podeljeno u dve doze, do maksimalnih 600 mg dnevno. Ima prednost u odnosu na gabapentin zbog brže nastupanja efekta i linearne kinetike (14).

Indikacije za perioperativnu primenu

Kako navode pojedini autori u publikacijama novijeg datuma, efikasnost gabapentinoida u prevenciji HPOB nije jasno dokazana uz različit režim primene, ali je dokazana efikasnost u kontroli akutnog postoperativnog bola u prvih 24 sata postoperativno. U poslednje vreme, rutinska primena gabapentnoida kod određenh hirurških procedura koje su označene kao „rizične“ doprinela je povećanju neželjenih efekata, bez jasnih terapijskih efekata (15). Drugi autori navode da bi mogao da postoji pozitivan terapijski odgovor na gabapentinoide kod lumbalne diskeketomije, artroplastike kolena, kardiohirirgije, operativnih zahvata sa velikim zahtevima za opioidnom terapijom (16). Međutim, terapijski efekat gabpentinoida nije bio dozno zavistan za razliku od neželjenih efekata koji su pokazali jasnu doznu zavisnost. Chaparro u meta-analizi i Kharasch navode da je preventivna primena antikonvulziva smanjila incidencu nastanka perzistentnog postoparativnog bola u prva 3 meseca, ali ne i u narednih 6 meseci ili godinu dana. Isti autori navode da se pitanje preventivne primene antikonvulziva postavlja ne zbog procene efikasnosti leka, već zbog neželjenih dejstava, izraženih u ranom postoperativnom periodu: vrtoglavica, zamućenost vida, sedacija (17). Ova neželjena dejstva otežavaju proces vertikalizacije i mobilizacije pacijenata, produžuju vreme boravka u postelji, povećavaju mogućnost nastanka postoperativnih komplikacija i produžuju hospitalizaciju, nezavisno od jačine akutnog postoperativnog bola (18).

Zaključak

Rutnska perioperativna primena gabapentinoida ne bi trebalo da bude deo svakodnevne kliničke prakse s obzirom na oprečne rezultate eksperimentalnih kliničkih istraživanja i vrlo jasne dokaze novijih meta-analiza koje nedvosmisleno ukazuju da perioperativna primena gabapentinoida nije opravdana.

Literatura

1. Carr DB, Goudas LC. Acute pain. Lancet 1999;353:2051-58.
2. Sommer M, de Rijke JM, van Kleef M et al. Prevalence of postoperative pain in a sample of 1490 surgical patients. Eur J Anaesthesiol 2008;25:267-74.
3. Fletcher D, Stamer U, Pogatzki-Zahn E et al. Chronic postsurgical pain in Europe. Eur J Anaesthesiol 2015;32:1-10.
4. Gerbershagen HJ, Aduckathill S, van Wijck AJ et al. Pain intensity on the first day after surgery. A prospective cohort study comparing 179 surgical procedures. Anaesthesiology 2013;34:934-44.
5. Wu CL, Raja SN. Treatment of acute postoperative pain. Lancet 2011;377:2215-25.
6. Flor H. Psychological pain interventions and neurophysiology: implications for a mechanism-based approach. Am Psychol 2014;69:188–96.
7. Brennan TJ. Pathophysiology of postoperative pain. Pain 2011;152:33-44.
8. Schug S, Palmer G, Scott D et al. Preventive and pre-emptive analgesia. In: Acute Pain Management:scientific Evidence. Australian and New Zeeland College of Anaesthetists 4th Ed 2015;1:23-24.
9. Haroutiunian S, Nikolajsen L, Finnerup NB, Jensen TS.The neuropathic component in persistent postsurgical pain- a systematic literature review. Pain 2013;154:95-102
10. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain:risk factors and prevention.Lancet 2006;367:1618-1625.
11. Mishiriky BM, Waldron NH, Habib AS. Impact of pregabalin on acute and persistent postoperative pain- a systematic review and meta-analysis. BJA 2015;114:10-31.
12. Burke S, Shorten G. Perioperative pregabalin improves pain and functional outcomes 3 months after lumbal discectomy. Anaesth &Analg 2010;4:1180-1185.
13. Clarke H, Bonin R, Orser B et al. The prevention of chronic postsurgical pain using gabapentin and pregabalin. A combined systematic review and meta-analysis. Anesthesia&Analgesia 2010;110:1180-86.
14. Ladjević N, Marković D, Milinić M, Jovičić J, Nešić D. Hronični postoperativni bol. U: Stamenković D, Lađević N. Akutni postoperativni bol. Odbrana, Beograd 2019: 371-387.
15. Zhang J, Ho KY, Wang Y. Efficacy of pregabalin in acute postoperative pain: a meta-analysis. Br J Anaesth 2000; 106: 454– 62.
16. Bonin RP, Orser BA, Englesakis M, Wijeysundera DN, Katz J. The prevention of chronic postsurgical pain using gabapentin and pregabalin: a combined systematic review and meta-analysis. Anesth Analg 2012; 115: 428–42.

17. Kharasch ED, Eisenach JC. Wherefore Gabapentinoids?: Was There Rush Too Soon to Judgment? Anesthesiology. 2016 Jan;124(1):10-2.
18. Kharasch ED, Clark JD, Kheterpal S. Perioperative Gabapentinoids: Deflating the Bubble. Anesthesiology. 2020 Aug;133(2):251-254.

Local application of capsaicin cream in the treatment of painful conditions

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Abstract

Capsaicin is the active component of chili peppers belonging to the genus Capsicum. When applied topically, capsaicin activated the transient receptor potential vanilloid-1 (TRPV1) channels which play an important role in pain transmission. Many completed studies showed beneficial effects of the 8% capsaicin patch in the treatment of Painful Diabetic Peripheral Neuropathy (PDN); HIV-related Distal Neuropathy (HIV-DN) and Trigeminal Neuralgia. A lower concentration of creams (0.025-0.075%) are more useful for the treatment of milder neuropathic conditions, musculoskeletal impairments, and osteoarthritis. When applied to mucous membranes, even lower concentration capsaicinoids can be very aggressive compounds and possibly lead to irreversible damage of the neuronal membranes after prolonged contact to sensitive neurons. Capsaicin should not be used for more than 3 weeks and should not be administered on broken skin, wounds, and eczemas.

Key words: capsaicin, pain, local, treatment, painful conditions

Introduction

Capsaicin is the active component of red hot chili peppers belonging to the genus Capsicum. It produces a sensation of burning in any tissue with which it comes into contact (1). The active ingredient in chilies that generates the burning and flare response is 8-methyl-N-vanillyl-6-nonenamide (2). Capsaicin binds to a receptor called the transient receptor potential vanilloid-1 (TRPV1) (1). The TRPV1 receptor is known to play a role in pain transmission in many organs, especially pain during inflammation. It is mainly expressed in the primary sensory neurons with unmyelinated C-fibers that have their cell bodies in the dorsal root ganglion of the spinal cord and trigeminal ganglion

(3). Studies have found that TRPV1 undergoes up-regulation in certain disease processes and could represent a cause of exacerbated pain associated with these conditions (4). Contrarily, TRPV1 expression was found to be down-regulated in neuropathic pain following an injury (4). TRPV1 – expressing epidermal nerve fibers are significantly reduced in the skin of patients with diabetic peripheral neuropathy. The researchers concluded that the low level of expression of TRPV1 is due to reduced levels of nerve growth factor (NGF) (5). Also, it was reported that capsaicin impedes the intra-axial transport of NGF from the periphery to the TRPV1- expressing neurons hypothesized to be a contributing factor to capsaicin induced-desensitization (6). Capsaicin causes a brief initial sensitization followed by a prolonged desensitization of the local pain nerves through TRPV1- expressing pain nerve fibers (7).

Pharmacodynamics

When applied topically, capsaicin activates the TRPV1 channels which open transiently and initiates a depolarization mediated by an influx of sodium and calcium ions. Capsaicin induces the depolarization of the nociceptive free nerve endings, mainly the unmyelinated C-fibers and generates an action potential that is propagated to the spinal cord and brain which is ultimately perceived as a burning, warming sensation (7). Capsaicin inactivates the voltage-dependent sodium channels which will result in low electrical excitability, followed by osmotic swelling due to chloride accumulation (8). Additionally, there is a significant calcium ion accumulation intracellularly which further results in activation of calcium-dependent enzymes. These enzymes will induce the depolymerization of microtubules (9). A significant number of mitochondria are present in the peripheral nerve terminals of nociceptors. Capsaicin can lead to mitochondrial dysfunction by overloading the calcium sequestration capabilities of mitochondria. Applying capsaicin in a higher concentration than the one required to activate TRPV1 receptors leads to a direct inhibition of the electron transport chain, ultimately leading to mitochondrial destruction (10). Lysis of mitochondria results in loss of plasma membrane integrity and loss of nerve endings. However, the depth of nerve endings destruction is concentration- dependent (10).

The authors of a study involving healthy volunteers found that epidermal nerve fiber density (ENFD) and sensitivity was reduced following application of a capsaicin 8% patch at 60 minutes and at Day 7 compared to placebo or low-dose control patch (11) 60 minutes treatment with a capsaicin 8% patch was associated with 80% reduction in the ENFD at Week 1 compared with the untreated areas, 20 % at Week 12 and almost full recovery at Week 24 (12). The degree of ENFD reduction is believed to be associated with different pain syndromes (13,14). Also, it is accompanied by alterations in nerve fiber function. It was observed that a 15% reduction in response to sharp stimuli was noted at Week 1 after patch removal. At Week 12, the perception for sharp pain stimuli normalized which translated into a recovery of the ENFD and this corresponded to the

20% reduction of ENFD. The tactile threshold also returned to normal at Week 12 when comparing exposed skin to control skin. The heat and cold pain thresholds showed no difference following capsaicin 8% patch treatment. These findings suggest that capsaicin 8% patch use is followed by minor and reversible sensory function changes in healthy individuals (11).

Pharmacokinetics

The pharmacokinetics of topical medications has its own specificity, meaning that only a small amount of the medication applied to the skin will be absorbed and the active component can solubilize or congregate. This ultimately interferes with the efficacy of the treatment. High concentration capsaicin cream 8% is contained in micro reservoirs of the patch, solubilized at 28% weight/volume that is equivalent to 918mM. When applied, it is hard to predict the possible concentration due to its significant storing in the stratum corneum of the epidermis (10). The half-life of capsaicin in the skin was estimated to be approximately 24 hours.15 Pershing et al. evaluated the pharmacokinetic parameters of capsaicinoids in human skin in vivo (15). The pharmacokinetic assessment was performed by harvesting the stratum corneum from four different sites on the volar forearm of the 12 subjects using an adhesive disc system. Capsaicin was prepared using three different vehicles consisting of 70/30 (v/v) isopropyl alcohol/distilled water (IPA), 80/20 (v/v) mineral oil/isopropyl alcohol (MO) and 80/20 (v/v) propylene glycol/isopropyl alcohol (PG). A 5μg of capsaicin, single topical application could be detected after one minute in the stratum corneum. The IPA vehicle delivered 3 times more capsaicin in the stratum corneum than MO and PG vehicles ($p<0.05$) and the Cmax recorded was significantly higher for the IPA vehicle (16.1± 2.6 μg, mean ± SD) compared to MO (6.5± 2.5 μg) and PG (6.2 ± 1.9 μg). Dihydrocapsaicin also demonstrated a significantly increased Cmax in IPA vehicle compared to both MO and PG ($p<0.05$). The elimination half-life of capsaicinoids from the stratum corneum was reported to be similar for all three vehicles. The concentrations for both capsaicin and dihydrocapsaicin had a 2-fold decrease from 15 min of application to 24 h after the removal of the solution ($p<0.05$) (15).

The systemic exposure of capsaicin 8% patch was assessed in a study on HIV-distal neuropathy patients (16). Subjects were tested for the major metabolites 16-hydroxy-capsaicin, 16,17-dehidro-capsaicin, 17-hydroxy-capsaicin at 60 minutes after immediately removing the capsaicin patch and at 1 hour and 3 hours after patch removal. There was no quantifiable capsaicin level at 60 minutes. At one hour exposure to capsaicin, there was a detected systemic level of 1.75 ng/mL in a subject with a treating area of 924 cm2. This blood level of 1.75 ng/mL is considered equivalent to the level of dietary ingestion of capsaicin from chili peppers (17).

In a study conducted by Chaiyasit et al., healthy volunteers underwent an assessment of plasma capsaicin concentration following ingestion of 5 grams of red-hot chili

peppers containing approximately 27mg of capsaicin (17). An average Cmax of 2.5ng/mL was detected and it was well tolerated. Therefore, treatment with capsaicin 8% patch is safe and the systemic levels are below a standard meal that contains capsaicin (17).

Capsaicin patch efficacy and tolerability studies

Clifford et al. studied 494 patients with pain due to HIV-associated distal sensory polyneuropathy which received a single 30-minute or 60-minute application of NGX-4010 capsaicin 8% patch (n = 332) or a low-dose capsaicin (0.04%) control patch (n = 162) (18). Patients in the total and 30-minute NGX-4010 groups felt improved on the patient global impression of change versus control (67% vs. 55%, p=0.011 and 65% vs. 45%, p=0.006, respectively) (18).

Limitations of 8% capsaicin

One of the limitations in capsaicin use is its pungent effect on the cutaneous area of the patch application. Peppin et al. has provided clinical data regarding a capsaicin exposure-pungency relationship reporting that 98% of the subjects tolerated the capsaicin 8% patch well without early removal (19). Some clinical trials reported a significant number of 55% of patients (n=1696) using opioid medications for relief of pain associated with capsaicin 8% patch application (20,21,22).

Lower concentration capsaicin

When applied to mucous membranes, even lower concentration capsaicinoids can be very aggressive compounds and possibly lead to irreversible damage of the neuronal membranes after prolonged contact to sensitive neurons. To limit the risks of the irreversible neuronal damage and reported side effects of hypersensitivity reactions, capsaicin should not be used for more than 3 weeks and should not be administered on broken skin, wounds, and eczemas (European Medicines Agency, 2015). Capsaicinoids are considered to be responsible for the relief of muscle pain, such as low back pain per EMA committee on herbal medicinal products (23).

Five randomized controlled trials (n=456) compared the analgesic effect of topical capsaicin (0.025% or 0.075%, 4 times daily) in osteoarthritis of the hand, knee, or multiple joints (hip, knee, shoulder, and hand) with placebo found that absolute VAS scores after 3-4 weeks were in favor of capsaicin. Another systematic review guideline of 5 RCTs (n=427) tested the efficacy of capsaicin gel (0.015%, 0.025%, or 0.075%, 1-4 times daily) in the treatment of hand or knee osteoarthritis when compared to placebo. After 4 weeks of treatment, there was a 33% reduction in pain intensity compared with 20% on placebo, whereas in the 12-week study, the reductions were 53 and 27%, respectively. The third systematic review with 5 RCTs and o1 case-crossover trial (n=1162) in which the analgesic effect of topical capsaicin (0.025% or 0.075%, 4 times daily) was

compared with placebo in the osteoarthritis of the hand (one study), knee (three studies), or several joints (hand, knee, hip, or shoulder) (two studies) (24).

A Cochrane review on neuropathic pain showed insufficient data proving the efficacy of low-concentration capsaicin cream (25). A more recent systematic review included studies that tested the effect of 0.075% capsaicin in patients with painful diabetic neuropathy showed that it is not more effective than placebo (26). A randomized, double-blind, placebo-controlled, multi-center study of 281 patients suffering from chronic soft tissue pain were treated either with a cream containing capsaicin 0.05% (Finalgon CPD Warmecreme, n=140) or placebo (n=141) to examine the effectiveness of topical capsaicin cream. After 3 weeks of treatment, the median pain sum score had decreased by 58% (capsicum group) and 29% (placebo group) in patients with chronic back pain ($p<0.01$). The odds ratio of the responders in favor of capsaicin was 4.3 ($p<0.0001$) (27).

A prospective randomized controlled trial with 150 patients who presented to the emergency department with acute pain from blunt upper extremity trauma compared piroxicam gel (Felden gel, containing 0.5% piroxicam) to capsaicin gel (Sanli Gel, containing 0.05% capsaicin). The results showed that topical capsaicin was more effective than topical piroxicam (85.5% of patients had a pain score ≤4 from the capsaicin group and only 50.7% from the piroxicam group) (28). Another study randomized 22 subjects in a cross-sectional study to receive either 0.025% capsaicin cream or 5% ibuprofen gel for painful knee osteoarthritis. The results showed that 18% of the subjects had a greater response to the ibuprofen and 41% of subjects had a greater response to the capsaicin (29). Predel et al. conducted randomized controlled trials with 746 patients with acute back or neck pain that were randomized to receive 0.075% capsaicin (n=223), 2% diclofenac (n=223), combination of 0.075% capsaicin and 2% diclofenac (n=225), and placebo (n=75). The results showed that capsaicin alone or a combination of capsaicin and diclofenac were better than diclofenac alone in treating acute back and neck pain (30).

Conclusion

Many completed studies showed beneficial effects of the 8% capsaicin patch in the treatment of Painful Diabetic Peripheral Neuropathy (PDN), HIV-related Distal Neuropathy (HIV-DN) and Trigeminal Neuralgia. A lower concentration of creams (0.025-0.075%) are more useful for the treatment of milder neuropathic conditions, musculoskeletal impairments, and osteoarthritis.

References

1. Smith H, Brooks JR. Capsaicin-based therapies for pain control. Prog Drug Res 2014;68:129-46
2. Szallasi A Blumberg PM. Vanilloid (Capsaicin) receptors and mechanisms. Pharmacol Rev 1999;51:159-212
3. Szallasi A, Nilsson S, Farkas-Szallasi T et al. Vanilloid (capsaicin) receptors in the rat: distribution in the brain, regional differences in the spinal cord, axonal trans-

port to the periphery, and depletion by systemic vanilloid treatment. Brain Res 1995;703:175-83
4. Niiyama Y, Kawamata T, Yamamoto J et al. Bone cancer increases transient receptor potential vanilloid subfamily 1 expression within distinct subpopulations of dorsal root ganglion neurons. Neuroscience 2007;148: 560-72
5. Facer P, Casula MA, Smith GD et al. Differential expression of the capsaicin receptor TRPV1 and related novel receptors TRPV3, TRPV4 and TRPM8 in normal human tissues and changes in traumatic and diabetic neuropathy. BMC Neurol 2007;7:11
6. Miller MS, Buck SH, Sipes IG et al. Altered axoplasmatic transport of nerve growth factor by capsaicin. Proc West Pharmacol Soc 1982;25:87-8
7. Watanabe N, Horie S, Spina D, et al. Immunohistochemical localization of transient receptor potential vanilloid subtype 1 in thee trachea of ovalbumin- sensitized Guinea pigs. Int Arch Allergy Immunol 2008;146:28-32
8. Bevan S, Szolcsanyi J. Sensory neuron-specific actions of capsaicin: mechanisms and applications. Trends Pharmacol Sci 1990;11:330-3
9. Han P, McDonald HA, Bianchi BR et al. Capsaicin cause protein synthesis inhibition and microtubule disassembly through TRPV1 activities both on the plasma membrane and intracellular membranes. Biochem Pharmacol 2007;73:1635-45
10. Bley K. Effect of topical capsaicin on cutaneous innervaation: implications for the pain management. The Open Pain Journal 2013;6:81-94
11. Malmberg AB, Mizisin AP, Calcutt NA et al. Reduced heat sensitivity and epidermal nerve fiber immunostaining following single applications of a high-concentration capsaicin patch. Pain 2004;111:360-7
12. Kennedy WR, Vanhove GF, Lu SP et al. A randomized, controlled, open-label study of the long-term effects of NGX-4010, a high-concentration capsaicin patch, on epidermal nerve fiber density and sensory function in healthy volunteers. J Pain 2010;11:579-87
13. Fields HL, Rowbotham M, Baron R. Postherpetic neuralgia: irritable nociceptors and deafferentation. Neurobiol Dis 1998;5:209-27
14. Campell JN, Mayer RA. Mechanisms of neuropathic pain. Neuron 2006;52:77-92
15. Pershing LK1, Reilly CA, Corlett JL, et al. Effects of vehicle on the uptake and elimination kinetics of capsaicinoids in human skin in vivo. Toxicol Appl Pharmacol 2004;200:73-81
16. Qutenza® (Capsaicin 8% Patch) for management of neuropathic pain associated with human immunodeficiency virus- associated peripheral neuropathy. Briefing document for the Anesthesia and Analgesia drug products. Advisory committee meeting. Meeting date February 9, 2012. Available for public disclosure without redaction. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM290279.pdf. Pages 1-169

17. Chaiyasit K, Khovidhunkit W, Wittayalertpanya S. Pharmacokinetics and the effect of capsaicin in Capsicum frutescens on decreasing plasma glucose level. J Med Assoc Thai 2009;92:108-13
18. Clifford DB, Simpson DM, Brown S, et al. A randomized, double-blind, controlled study of NGX-4010, a capsaicin 8% dermal patch, for the treatment of painful HIV-associated distal sensory polyneuropathy. J Acquir Immune Defic Syndr 2012;59:126-33
19. Peppin JF, Majors K, Webster LR et al. Tolerability of NGX-4010, a capsaicin 8% patch for peripheral neuropathic pain. J Pain Res 2011;4:385-92
20. Bhaskar A, England J, Lowe J. Management of neuropathic pain using the capsaicin 8% patch in patients with cancer. Proceedings of the 7th World Research Congress of the Euroean Association of Palliative Care; Trondheim, Norway; June 7-9, 2012.
21. Kern K-U, Poole C, Nowack W. Treatment of neuropathic pain with the capsaicin 8% patch (QUTENZATM): Is pre-treatment with lidocaine necessary? Proceedings of Pain in Europe VII, 7th Congress of the European federation of IASP Chapters; Hamburg, Germany; September 21-24, 2011.
22. Wagner T, Poole C, Roth-Daniek A. The capsaicin 8% patch for neuropathic pain in clinical practice: A retrospective analysis. Proceedings of the 15th Congress of the European Federation of Neurological Societies; Budapest, Hungary; September 10-13, 2011
23. European Medicines Agency (EMA) Herbal Medicinal Products (HMPC) Monograph on Cpasicum 2015, 5 May 2015
24. Guedes V, Castro JP, Brito I. Topical capsaicin for pain in osteoarthritis: A literature review. Reumatol Clin (Engl Ed) 2018;14:40-5.
25. Derry S, Moore RA. Topical capsaicin (low concentration) for chronic neuropathic pain in adults. Cochrane Database Syst Rev 2012:CD010111.
26. Waldfogel JM, Nesbit SA, Dy SM, et al. Pharmacotherapy for diabetic peripheral neuropathy pain and quality of life: A systematic review. Neurology 2017;88:1958-67.
27. Chrubasik S, Weiser T, Beime B. Effectiveness and safety of topical capsaicin cream in the treatment of chronic soft tissue pain. Phytother Res 2010;24:1877-85.
28. Kocak AO, Dogruyol S, Akbas I, et al. Comparison of topical capsaicin and topical piroxicam in the treatment of acute trauma-induced pain: A randomized double-blind trial. Am J Emerg Med 2020;38:1767-71.
29. Persson MSM, Stocks J, Sarmanova A, et al. Individual responses to topical ibuprofen gel or capsaicin cream for painful knee osteoarthritis: a series of n-of-1 trials. Rheumatology (Oxford) 2021;60:2231-7.
30. Predel HG, Ebel-Bitoun C, Peil B, Weiser TW, Lange R. Efficacy and Safety of Diclofenac + Capsaicin Gel in Patients with Acute Back/Neck Pain: A Multicenter Randomized Controlled Study. Pain Ther 2020;9:279-96.

The role of genetics in the treatment of chronic pain

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Abstract

In the United States, there is a high number of chronic pain patients who do not respond to treatments. One of the reasons for this is the large variability in chronic pain manifestation. Identifying the phenotypes and polymorphisms of chronic pain could facilitate the development of personalized treatments. Utilizing genetic markers in gene therapy treatments could help by minimizing healthcare costs, determining personalized treatment methods, and avoiding adverse effects with polypharmacy.

Various studies on the components of chronic pain phenotypes revealed that several hereditary factors were shared by patients with chronic back, neck, shoulder, hip, and knee pain. Additionally, studies supported that neurological and psychological components contribute to chronic pain. Gene therapy products can be tailored to counter the pathophysiological mechanisms of specific diseases, and include several targets such as channels, enzymes, receptors, interleukins, proteins, etc. Clear regulatory pathways and the extensive understanding of immune responses is required before precise medicine therapies are available to the public.

As gene therapy technologies grow more advanced, personalized medicine becomes more of a realistic possibility for patients with chronic pain. This review emphasizes the methods of identifying chronic pain phenotypes and polymorphisms and reviews the different gene therapy strategies available for chronic pain patients. Additional improvements in the gene therapy manufacturing process, further research in immune responses, and streamlining of regulation pathways are required for the process of gene therapy to become more accessible to the public.

Key words: chronic pain, genetic polymorphism, genetics, gene therapy, personalized treatment, pharmacogenetics, pain medications

Introduction

The number of Americans who currently suffer from moderate to severe chronic pain (CP) is approximately 44 million (1). In addition, the cost associated with chronic pain management is estimated to be 100 billion annually (1). Globally, the prevalence for opioid users is estimated to be 32.4 million, with approximately 70,000-100,000 opioid overdose-related deaths per year (2, 3). The number of non-responders to treatment among chronic pain patients is high, and one of the reasons for this is the large variability in manifestations of chronic pain. By identifying the phenotypes of chronic pain, tailored treatment approaches could be facilitated.

The treatment for chronic pain patients using individualized approaches can substantially improve the patients' quality of life and functionality and aid in preventing the severe adverse effects of opioid therapy such as overdose, misuse, hyperalgesia, and death. The completion of the Human Genome Project in 2000 revolutionized the field of medicine, as well as subsequent therapy possibilities. It introduced new perspectives for disease diagnosis, therapy development, and individualized medicine. Subsequent advances in technology and research thus further enable individualized genetic therapies and personalized medicine in the field of pain medicine and management.

Genetic phenotypes and polymorphisms in chronic pain

Overview

A multitude of factors influence the diagnosis and treatment process of chronic pain patients: age, sex, comorbidities, ethnicity, ongoing multi-drug therapy and lifestyle. Each of these factors, in addition to genetic influences on pain and drug efficacy, will affect pharmacotherapy outcomes in chronic pain patients.

Genetic Phenotypes in Chronic Pain

Despite accessible intensive multimodal treatment, the number of non-responders to treatment amongst patients with CP is high. One of the reasons for this is the large variability in CP manifestation. By identifying the phenotypes of CP, the development of tailored treatment approaches could be facilitated. In a latent class analysis using retrospective data (n=411 patients) with CP of different origins, all patients experienced severe physical and psychological consequences undergoing multimodal pain treatments (4). Four latent classes were developed from this study: High, Extreme, Moderate, and Low pain burden; it was found that class 4 patients (Low pain burden) had high levels of emotional distress, which corresponded to the levels of pain burden in other classes; meanwhile within class 1 patients (High pain burden), pain, physical and mental health improved.

In a study of genetically independent components of chronic musculoskeletal pain phenotypes, hereditary factors were revealed to be shared by chronic back, neck/

shoulder, hip, and knee pain (5). Furthermore, this study supported that neurological and psychological components are important contributors to chronic pain. Using the matrix of genetic covariances synthesized, 4 genetically independent phenotypes (GIPs) were identified, with GIP1 responsible for 78.4% of the genetic variance of the analyzed conditions. Five GIP1-associated loci, and one GIP2-associated loci; GIP1 correlated with multiple CNS-related terms, anthropometric traits (weight, height, and BMI), sociodemographic, psychiatric/personality traits and osteoarthritis (5) were identified.

The complex regional pain syndrome (CRPS) signs observed during neurologic examination display a structure allowing for the alignment of patients to particular phenotype clusters (6). In a study of three independent samples (n=444; 391; and 202) of patients with CRPS, a 2-cluster structure emerged in sample 1 and was replicated in sample 2. Cluster 1 (the central phenotype) had minor injury eliciting CRPS, motor signs, allodynia, and glove/stocking-like sensory deficits resembling a CRPS phenotype most likely reflecting a CNS pathophysiology. Cluster 2 (the peripheral phenotype) consisted of edema, skin color/temperature changes, sweating, and trophic changes, which may represent peripheral inflammation. In sample 3 (the mixed phenotype), individual phenotype scores were calculated as the sum of the mean values of signs from each cluster (cluster 1 coded with 1 and from cluster 2 with -1). These statistically determined CRPS phenotypes may reflect major pathophysiologic mechanisms of peripheral inflammation and central reorganization.

In patients with common musculoskeletal pain, the multidimensional array of clinical features and prognostic factors make optimized management difficult. A longitudinal observational study aimed to identify phenotypes across prognostic factors and musculoskeletal pain, patients (n=435; ages 18-67 years) with neck, shoulder, low back or multisite/complex pain were observed in primary healthcare physiotherapy (7). Latent class analysis (LCA) identified 5 phenotypes based on 11 common prognostic factors within 4 biopsychosocial domains (pain, beliefs and thoughts, psychological and activity and lifestyle). Phenotypes 1 (n=77, 17.7%) and 2 (n=142, 32.6%) had the lowest scores across all biopsychosocial domains, with Phenotype 2 showing somewhat higher levels of symptoms across all biopsychosocial domains. Phenotypes 3 (n=89, 20.5%) and 4 (n=78, 17.9%) had more affected across all domains, but opposite patterns in the psychological and pain domains. Phenotype 5 (n=49, 11.3%) had worse symptoms across all domains, indicating a complex phenotype. The phenotypes had good external and concurrent validity when differentiating for the phenotypes in function and health-related quality of life outcome at 3-month follow-up. These phenotypes may help develop and improve the efficacy of targeted interventions in patients with musculoskeletal disorders.

Genetic Markers and Polymorphisms in Chronic Pain

In a genome-wide meta-analysis of 158,000 individuals of European ancestry, three loci were identified and associated with chronic back pain (CBP) (8). In this study,

novel associations between specific genetic markers and CBP were identified, as well as the biological mechanisms underlying this condition. Genome-wide association studies (GWAS) meta-analysis of CBP was performed on adults of European ancestry from 16 cohorts (n=158,025; of which 29,531 CBP cases), with each cohort conducting genotyping using commercially available arrays followed by imputation (8). A genome-wide significant association was found for the intronic variant rs12310519 in SOX5. Associations at 3 other loci were identified, 2 of which exceeded genome-wide significance in joint meta-analysis: rs7833174, an intergenic variant located between CCDC26 and GSDMC, and rs4384683, an intronic variant in DCC (8). The findings were subsequently replicated in 283,752 (50,915 CBP cases) UK Biobank participants not included in the discovery sample, and a joint (discovery-replication) meta-analysis was performed (8).

Several genetic polymorphisms were investigated in different chronic pain conditions such as fibromyalgia, low back pain, migraine, painful diabetic neuropathy, and trigeminal neuralgia. Fibromyalgia has 50% heritability and is associated with familial aggregations of psychological features such as depression and personality traits (1). Pain medication pharmacogenomics include Duloxetine (CYP1A2, 2D6, and 2D9), amitriptyline (CYP2C19), and hydroxyl metabolites (CYP2D6). Clinical implications include avoiding the co-administration of duloxetine with a CYP2D6 substrate such as risperidone and aripiprazole. The TRPV3 gene – rs395357 SNP is associated with symptom severity, while the COMT gene – Met/Met genotype (Val158Met SNP) is associated with increased pain sensitivity (1).

The etiology of back pain is multifactorial and somewhat heritable, with chronic pain more so than acute. Genes associated with chronic low back pain (cLBP) code for receptors, enzymes, cytokines and their associated receptors, and transcription factors (9). Receptor related genes include DCC, ESR1, OPRM1, ADRB2, and CNR2. Enzyme-related genes include COMT, GCH, MMP2, MMP3, CASP9, and FAAH. Genes related to cytokines and their associated receptors include CCL2, IL18R1/IL18RAP/IL1A, and GDF5. Genes related to transcription factors, neurotransmission, and other unknown functions include SOX5, CCDC26/GSDMC, and PNOC.

Polypharmacy is related to drug-drug interactions (DDIs), with the prevalence of DDIs in CLBP patients being 27% (9). A retrospective analysis of DDIs in 57,752 chronic pain patients taking opioids matched the 9 most commonly prescribed opioids against 19 precipitant CYP450-inducing drugs, and found that 5.7% (n=3,302) patients were exposed to potential major drug-drug interaction (9). In chronic low back pain, genetic factors increase susceptibility by 50% (1). Pain medication pharmacogenomics include NSAIDs (CYP2C9) and Opioids (CYP2D6 and CYP3A4). Clinical implications include CYP2D6 genotyping based on scores for level of evidence and clinical relevance, as well as genotyping for methadone treatment initiation, which may identify patients at risk for addiction population (1). The OPRM1 gene – A118G SNP is associated

with significant morphine consumption, while the COMT gene – Met/Met genotype (Val158Met SNP) is associated with significantly more pain compared to Val/Met and Val/Val (1).

Migraine has a 50% heritability, and in patients with rs11172113, an AT2 Rc-antagonist, have lower effects in patients with typical aura and with migraine without aura (1). Clinical implications include individualized prophylactic treatment. Painful diabetic neuropathy has the same CYPs implicated for fibromyalgia treatment, and clinical implications include correcting risk factors, as well as the same precautions as with fibromyalgia treatment. Trigeminal neuralgia pharmacogenomics include 5-HTTLPR polymorphisms and poor carbamazepine response, with clinical implications including reassessing poor carbamazepine therapeutic response (1).

Gene therapy strategies for chronic pain

Overview of Treatments for Chronic Pain

Despite the overwhelming numbers of people suffering from pain worldwide, the efficacious treatments available are limited. Currently, common treatments include opioids, nonsteroidal anti-inflammatory drugs, acetaminophen, glucocorticoids, botulinum toxin, and epidural steroid injections. These treatments may be associated with negative barriers and associations such as lack of efficacy, poor financial reimbursement, limited availability, and addictive effects.

Gene Therapy Technologies

Genetic factors account for 30-76% variance in pain response and can also account for both pain threshold and susceptibility to chronic pain in patients (10). Novel technologies have expanded our current ability to target RNA and DNA without the need of gene replacement. One example of this is through RNA interference (RNAi), which is a gene silencing method mediated by double-stranded small interfering RNAs (siRNAs). This leads to the degradation of their target mRNA and thus a reduction in the amount of protein encoded. Currently, 2 RNAi drugs are FDA-approved, Onpattro (patisiran) and Givlaari (givosiran) (10). Onpattro was FDA-approved on August 10, 2018, and is an RNAi treatment of polyneuropathy in people with hereditary transthyretin-mediated amyloidosis (hATTR), a rare and often fatal genetic neurodegenerative disease characterized by the buildup of abnormal amyloid protein in peripheral nerves, the heart, and other organs. Givlaari was FDA-approved on November 20, 2019, and is an RNAi treatment of adult patients with acute hepatic porphyria, a genetic disorder resulting in the buildup of toxic porphyrin molecules which are formed during heme production. Another example of novel gene therapy is through antisense oligonucleotides (ASO), which are short, synthetic, single-stranded oligodeoxynucleotides that can interfere with mRNA processing, leading to endonuclease-mediated protein silencing.

Currently, there are 7 ASO drugs that are FDA-approved: Fomivirsen (1998), Eteplirsen (2016), Golodirsen (2019), Viltolarsen (2020), Mipomersen (2013), Inotersen (2018), and Nusinersen (2016) (10).

Other technological advancements in gene therapies have also been developed. Chemogenetics refers to the technique of redesigning channels or other macromolecules so that they recognize synthetically made small molecules rather than their endogenous counterparts (10). These then allow for the selective control of the excitability of neuronal subpopulations. Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-Cas9 involve the use of a catalytically inactive version of the Cas9 enzyme (dCas9 also known as CRISPRi) with a guide-RNA as well as a repression domain (Krüppel-associated box (KRAB)) (10). This then allows the binding of the gene using dCas9 for targeted specificity while ensuring that no genetic mutations are made, and thus decreases the transcription levels of the gene of interest. The clinical implications are that CRISPRi-KRAB allows for greater specificity, increased therapeutic longevity, and decreased application frequency than other approaches. Zinc Finger proteins (ZF) may be fused to a KRAB repressor and used as another form of gene therapy. ZFs are among the most abundant proteins in eukaryotic genomes, and the Cys2His2ZF DNA-binding domain is the most common domain in humans. As this is endogenous to humans, lower immune responses could be caused when compared to dCas9 usage. Additionally, DNA recognition capacities of ZFs have shown similar results as CRISPRi to target NaV1.7, a member of the voltage-gated sodium channel family (NaV) (10).

Virus-mediated gene therapy (GT) aims to deliver nucleic acids (DNA or RNA) or synthetic derivatives to target cells. Currently, there are over 50 clinical trials underway which are using GT to treat a variety of neurological disorders (11). This GT technology commonly uses key components including a vector and an enclosed expression cassette. An enclosed expression cassette consists of an enhancer/promoter, a transgene with associated polyadenylation signal, and occasionally introns or post-transcriptional regulatory elements. These act together to perform transduction of the cell target, which refers to the process of correcting the underlying defect in a host cell. Several strategies exist in GT, including loss-of-function, gain-of-function, editing, and ex-vivo techniques (11). In loss-of-function, a transgene is introduced so that the host cell can perform a specific therapeutic protein. With gain-of-function, expression of the mutant gene is targeted. Editing refers to the insertion, removal, or modification of genetic sequences using methods such as CRISPS/Cas-9 toolkits or ZF nucleases, and the break repaired to form a functional DNA sequence. Finally, ex-vivo techniques involve extracting and genetically modifying in vitro an individual's own (usually hematopoietic) cells, which are then subsequently then reintroduced into that individual.

Challenges to Gene Therapy-Mediated Chronic Pain Treatments

Several challenges can arise when considering gene therapy-mediated chronic pain treatments. The manufacturing of components needed in gene therapies can be

time consuming, difficult to produce in high yields, costly, and can take a long time to produce due to the increasing demand for gene therapy manufacturing, making the therapy inaccessible for many patients. In 2019, the FDA approved a $2.1 million gene therapy for pediatric patients with spinal muscular atrophy (10). Unfortunately, many patients may have a difficult time gaining access to these groundbreaking and life-saving treatments due to the aforementioned challenges. Immune responses against the systemic delivery of an adeno-associated virus (AAV) vector pose another challenge (10). To mitigate these effects, the AAV could be administered into the spinal intrathecal space, which would then bypass the blood-brain-barrier and target pain stimuli before it reaches the brain. This would ultimately decrease the possibility of systemic immunogenicity and may also reduce the dosage needed to achieve pain relief. The drug approval process is another possible challenge for gene therapy treatments. As with any prescription medication drug, the approval process for a novel gene therapy is not as straightforward and properly guided as with traditional small molecules or antibodies (10).

Conclusion

The number of non-responders to treatment among chronic pain patients is high, and one of the reasons for this is the large variability in the manifestations of chronic pain. Identifying the phenotypes of chronic pain could facilitate the development of tailored treatment approaches. A study of genetically independent components of chronic musculoskeletal pain phenotypes revealed that hereditary factors are shared by chronic back, neck/shoulder, hip, and knee pain. Additionally, this study supported the notion that neurological and psychological components are important contributors to chronic pain.

Several future perspectives can be made regarding gene therapy for chronic pain patients. This includes identifying which variables or factors can be used when developing phenotypes or subgroups, as well as which biological factors can be included. Identifying if social factors are reflected in our modelling is also an important consideration. Finally, identifying the treatments best matched to the subgroups and testing them in clinical trials may be performed.

Genetic markers can help us perform a variety of functions. They can not only help identify patients who are at risk for developing certain chronic pain conditions, but also can evaluate the efficacy of a particular treatment, thus minimizing healthcare costs. Genetic markers also help in determining the need for invasive treatment options such as surgery and aid in delivering more personalized drugs and medicine, which helps ultimately avoid polypharmacy-related adverse events.

Gene therapy has been applied to several CNS diseases including neurodegenerative and neurodevelopmental disorders, as well as chronic and neuropathic pain. Gene therapy products can be tailored to counter the pathophysiological mechanisms of particular diseases, including the use of gene replacement, gene silencing, transplicing, and

modulation of cellular pathways to improve phenotype or expression of suicide genes. Several targets that have been tested in preclinical studies of gene therapy for pain include channels (TRPVI, Kv1.2, Nav), enzymes (GAD), receptors (IL-1R, TNFR1), interleukins (IL-4, IL-10), proteins (GDNF), and more. Before these precision medicine therapies are accessible to the public, gene therapy manufacturing improvements, a better understanding of the immune responses, and the development of a clear regulatory pathway will be needed.

References

1. Knezevic NN, Tverdohleb T, Knezevic I, Candido KD. The Role of Genetic Polymorphisms in Chronic Pain Patients. Int J Mol Sci. 2018;19(6).
2. Gaskin DJ, Richard P. The economic costs of pain in the United States. J Pain. 2012;13(8):715-24.
3. Rudd RA, Seth P, David F, Scholl L. Increases in Drug and Opioid-Involved Overdose Deaths - United States, 2010-2015. MMWR Morb Mortal Wkly Rep. 2016;65(50-51):1445-52.
4. Obbarius A, Fischer F, Liegl G, Obbarius N, van Bebber J, Hofmann T, et al. A Step Towards a Better Understanding of Pain Phenotypes: Latent Class Analysis in Chronic Pain Patients Receiving Multimodal Inpatient Treatment. J Pain Res. 2020;13:1023-38.
5. Tsepilov YA, Freidin MB, Shadrina AS, Sharapov SZ, Elgaeva EE, Zundert JV, et al. Analysis of genetically independent phenotypes identifies shared genetic factors associated with chronic musculoskeletal pain conditions. Commun Biol. 2020;3(1):329.
6. Dimova V, Herrnberger MS, Escolano-Lozano F, Rittner HL, Vlckova E, Sommer C, et al. Clinical phenotypes and classification algorithm for complex regional pain syndrome. Neurology. 2020;94(4):e357-e67.
7. Meisingset I, Vasseljen O, Vollestad NK, Robinson HS, Woodhouse A, Engebretsen KB, et al. Novel approach towards musculoskeletal phenotypes. Eur J Pain. 2020;24(5):921-32.
8. Suri P, Palmer MR, Tsepilov YA, Freidin MB, Boer CG, Yau MS, et al. Genome-wide meta-analysis of 158,000 individuals of European ancestry identifies three loci associated with chronic back pain. PLoS Genet. 2018;14(9):e1007601.
9. Suntsov V, Jovanovic F, Knezevic E, Candido KD, Knezevic NN. Can Implementation of Genetics and Pharmacogenomics Improve Treatment of Chronic Low Back Pain? Pharmaceutics. 2020;12(9).
10. Vega-Loza A, Van C, A MM, Aleman F. Gene therapies to reduce chronic pain: are we there yet? Pain Manag. 2020;10(4):209-12.
11. Kariyawasam D, Alexander IE, Kurian M, Farrar MA. Great expectations: virus-mediated gene therapy in neurological disorders. J Neurol Neurosurg Psychiatry. 2020;91(8):849-60.

Suprascapular nerve block for non-specific shoulder pain – single center experience

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Abstract

Introduction.Chronic pain in the shoulder and arm is common in people over 50. Physical therapy and the use of nonsteroidal anti-inflammatory drugs are the basic therapies. In some cases, it is necessary to use a suprascapular block. Goal.Show our results in the treatment of chronic shoulder pain using suprascapular block. **Material and method** Patients who were treated for chronic shoulder pain from January 2014 to April 2022. These patients received suprascapular block using 7 mg betamethasone. **Result.** From January 2014 to April 2022, 19 patients were referred to a pain therapy clinic. They had different diagnoses, but the main diagnosis was chronic shoulder pain. Due to the pain of strong intensity, a suprascapular block was applied, using 7 mg betamethasone. After 24 hours, the pain was almost disappeared.

Conclusion This is a simple and effective block in the treatment of chronic shoulder pain. There were no complications.

Key words: suprascapular block, shoulder pain, chronic pain

Introduction

Pain in the shoulder and arm is common in the population of people over 40. It also occurs in younger people, but with age, the incidence and prevalence of this pain increase. The mean incidence of pain in the shoulder patient per 1000 person-years was 22.2 in the 18–44 age category and 37.1 in the 65 age category. The incidence was higher in women (1).

Symptoms commonly presenting with shoulder pain are: pain is often referred to the shoulder from other sources and, even in the case of pathological conditions of the shoulder, the location of the pain is often misleading. pain felt at night-time, radiation of pain into the arm, stiffness or loss of motion in that joint, weakness, numbness,

paraesthesiae and head aches (2). The pain causes structural or functional impairment and subsequently leads to disability and handicap.

Osteoarthritis is the most common cause of shoulder pain and functional disability. It may occur after trauma or be result repeated microtrauma. In general shoulder pain can be caused by musculoskeletal pathology (within the shoulder region) or by pathology of organ systems within the trunk. It is wise for clinicians to assess for all of these possibilities when a patient complains of shoulder pain (3,4).

In diagnosis of shoulder pain, it is important to start with a clinical examination. Then, that the clinical picture and clinical findings correlate with other diagnostic methods (ultrasound, radiological, MRI examination) (5,6).

Diagnosis and treatment of this pain should be multidisciplinary. Pain treatment includes a combination of nonsteroidal anti-inflammatory drugs or cyclooxygenase 2 inhibitors and physical therapy. Local anesthetic and steroid injections have marginal and short therm effect on pain. But it is reasonable next step (7,8) .

The use of corticosteroids in suprascapular block gives good results in the treatment of chronic shoulder pain (5,9). Suprascapular nerve blockade (SSNB) was first described in 1941. This block is used for therapy acute and chronic pain, neuropathic pain, pain in rheumatoid arthritis, osteoarthritis, various rotator cuff disorders including frozen shoulder, for therapy of moderate to severe postoperative pain after open and closed shoulder surgery (10).

N. suprascapularis is formed from the fibers of the spinal roots. It separates from the trunk of the superior brachial plexus and extends through the supraclavicular fossa along the lateral edge of the plexus all the way to the scapular incision. It further continues its way to the scapular neck and then passes under the ligamentum transversum to the fossa infraspinate. N suprascapularis innervates mm supraspinatus and infraspinatus and gives sensitive branches to the shoulder and acromioclavicular joint, as well as suprascapular blood vessels (Figure 1) (11,12).

Using surface landmarks, the SSNB may be localized via a posterior or superior approach. Applying the block is simple. The patient is sitting, his head is flexed forward, his arms are lowered between his legs. We palpate the spin of the scapula along its entire length, from the inner edge of the scapula to the acromion. Determine the junction of the middle and outer thirds of the scapula. 2 cm above that point we mark the place of the sting. Let's clean the puncture site. With a syringe containing 1 ml of betamethasone, and on which there is a 21G needle (0.8x 40 mm), we performed a puncture at the marked place, at an angle of 90^{o} to the skin until contact with the bone (2 to 3 cm in depth). (Figure 2) After contact, and after the trial aspiration, we move the tip of the needle medially, laterally until the loss of contact. Then we entered the suprascapular fossa. After re-aspiration, we inject the contents of the syringe. We pull out the needle. We recommended to the patient to use proton pump blockers for the next three days and on that day to use less the hand whose suprascapular nerve is blocked. Use

analgesics as needed and continue further physical treatment after two to three days. The control was scheduled for one month when it was possible to repeat the block with a corticosteroid. Potential advantages of this approach is extremely low risk of pneumothorax (10,11,12,13,14).

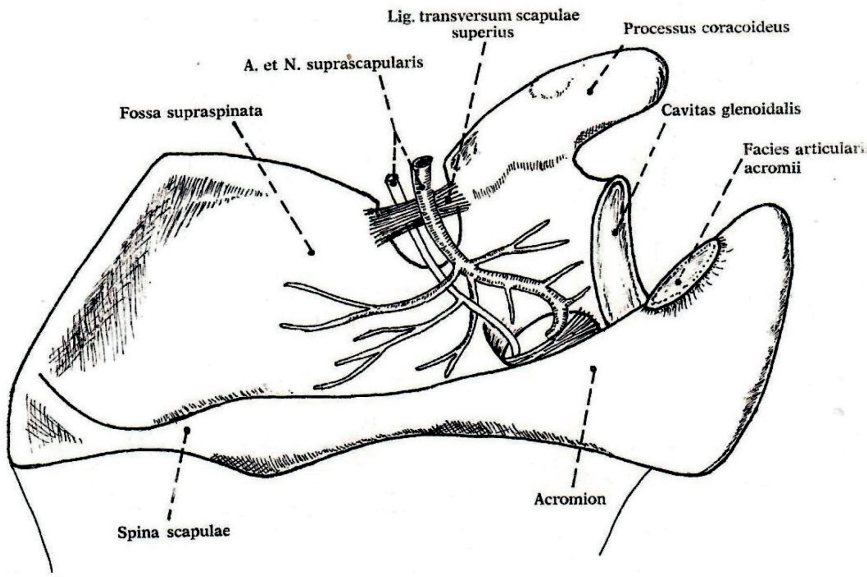

Figure 1. Right shoulder blade (Scapula), viewed from above (12).

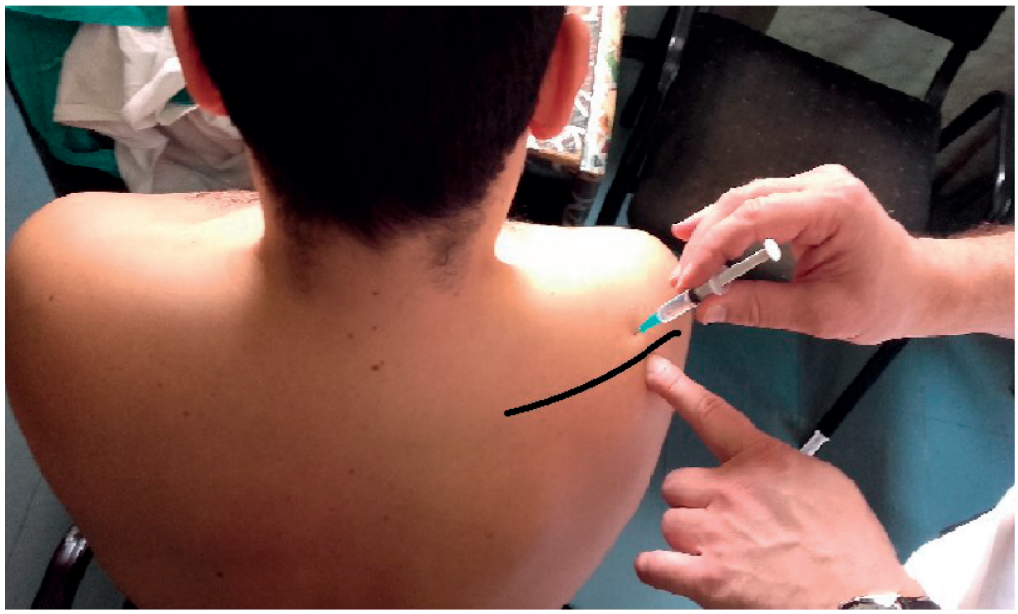

Figure 2. Display of the puncture site, or block, on the manikin (14)

Goal

Show our results in the treatment of chronic shoulder pain using suprascapular block.

Material and method

Patients who were treated for chronic shoulder pain from January 2014 to April 2022. These patients received suprascapular block using 7 mg betamethasone.

Results

From January 2014 to April 2022, 19 patients were referred to a pain therapy clinic. They had different diagnoses, but the main diagnosis was chronic shoulder pain (Table 1). The average age of our patients was 53.8 + 8.9 years (min 40, max 70 years). There were 10 men and 9 women. All patients were fully diagnosed. They were on physical therapy and used analgesics. The intensity of their pain is still high (VAS 7-8). For this reason, in the manner described above, suprascapular nerve block using 7 mg betamethasone, was applied in all patients. Three days after the block, patients were used proton pump inhibitors. The pain almost disappeared. The patients were stopped using analgesics. In three patients, the block was repeated after one month because the pain was still present. There were no complications.

Table 1. Diagnoses in our patients

Diagnosis	Number of patients and (%)
Contusio reg. omae	3 (15,8)
Painful shoulder syndrome	7 (36,8)
Radiculopathia cervicalis	4 (21)
Tendinitis humeri calcificata	3 (15,8)
Synovitis et tenosynovitis	1 (5,3)
Capsulitis humeroscapularis adhesiva	1 (5,3)
Total	19 (100%)

Discussion

As in Greving's study, our patients with chronic shoulder pain were in the sixth and seventh decades of life (1). Suprascapular block did not give good results in the treatment of postoperative shoulder pain, but it was effective in the treatment of chronic shoulder pain of other etiologies (10). We also obtained such results in pain therapy in our research for non-postoperative pain.

Imaging methods did not give an advantage over the topographic orientation for the application of the suprascapular block. The use of corticosteroids and local

anesthetics for suprascapular block significantly reduced pain compared to placebo (15,16). Suprascapular block with corticosteroids and physical treatment gave better results than the block without physical therapy and physical therapy without block (17).

Conclusion

According to our results, this is a simple and effective block in the treatment of chronic shoulder pain. There were no complications. An objective conclusion requires research on a large number of patients.

References

1. Greving K, Dorrestijn O, Winters JC, Groenhof F, van der Meer K, Sevens M, Diercks RL. Incidence, prevalence, and consultation rates of shoulder complaints ingeneral practice. Scand J Rheumatol 2012;41:150–155.
2. Dalton SE. Clinical examination of the painful shoulder. Baillière's Clinical Rheumatology.1989;3(1):453-474.
3. Petchkrua W, Harris SA. Shoulder pain as an unusual presentation of pneumonia in a stroke patient: a case report. Arch Phys Med Rehabil 2000; 81:827-9.
4. Foye P. CORRESPODENCE Arch Phys Med Rehabil 2000;81:1256
5. Allen GM. The diagnosis and management of shoulder pain. J Ultrason 2018; 18: 234–239.
6. Bradley MP, Tung G, Green A. Overutilization of shoulder magnetic resonance imaging as a diagnostic screening tool in patients with chronic shoulder pain. Journal of shoulder and elbow surgery. 2005 Jun 30;14(3):233-7.
7. Mitchell C, Adebajo A, Hay E, Carr A. Shoulder pain: diagnosis and management in primary care BMJ 2005;331:1124–8
8. Waldman SD. Atlas of Common Pain Syndromes. Philadelphia: Elsevier Saunders 2012
9. Taskaynatan MA, et al.The use of corticosteroids in suprascapular block gives good results in the treatment of chronic shoulder pain.Tohoku J. Exp. Med. 2005;205:19-25.
10. Chan CW, Peng PWH. Suprascapular Nerve Block A Narrative Review. Reg Anesth Pain Med 2011;36: 358-373.
11. Janković D. Regionalna nervna blokada i infiltraciona terapija bola, Beograd: Obeležja 2004
12. Jovanović S. Anatomski atlas. Beograd: Naučna knjiga 1983
13. Katz J.Atlas of Regional Anesthesia. APPLETON & LANGE, Norwalk, Connecticut, 1994.
14. Palibrk I, Veličković J, Barović S, Đukanović M, Miljković B. Suprascapular block in the therapy of chronic pain in the shoulder and the shoulder joint (suprascapular block). SJAIT 2016;(1-2):105-108.
15. Shanahan EM, et al. Suprascapular nerve block in chronic shoulder pain: are the radiologists better? Ann Rheum Dis 2004;63:1035–1040.

16. Shanahan EM, et al. Suprascapular nerve block (using bupivacaine and methylprednisolone acetate) in chronic shoulder pain. Ann Rheum Dis 2003;62:400–406.
17. Abdelshafi ME, et al.Relief of chronic shoulder pain: a comparative study of three approaches. Midle East J Anaesthesiol 2011;21(1):83-92.

POSTTRANSPLANTACIONI BOLNI SINDROM

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Abstrakt

Posttransplantacioni bolni sindrom je poremećaj koji se može javiti kod transplantiranih pacijenata, koji su na imunosupresivnoj terapiji kalcineurinskim inhibitorima (Takrolimusom i Ciklosporinom). Ovo stanje značajno narušava kvalitet života pacijenta, a terapija bola je uslovljena pravilno postavljenom dijagnozom, obzirom da klinička slika može podsećati na niz drugih poremećaja.

Ključne reči: Posttransplantacioni bolni sindrom, kalcineurinski inhibitori.

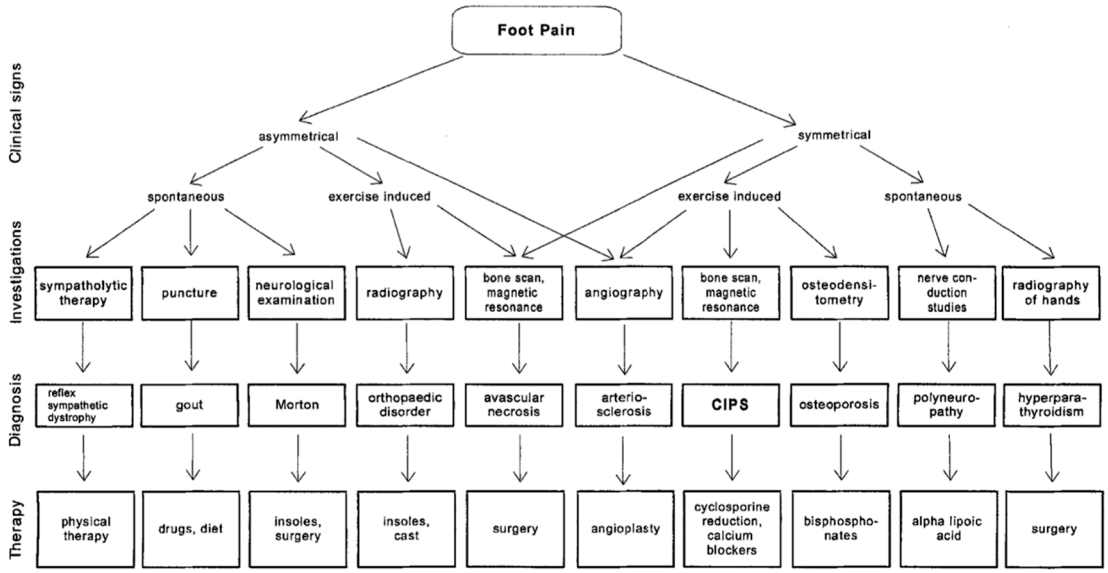
Uvod

Klinička slika posttransplantacionog bolnog sindroma se može razlikovati po težini I izgledu, tako da je ovaj sindrom opisivan u literaturi pod brojnim nazivima: 1) bol u kostima distalnih ekstremiteta nakon transplantacije; 2) sindrom refleksne simpatičke distrofije; 3) sindrom bola indukovanog inhibitorima kalcineurina; 4) edem koštane srži distalnih ekstremiteta nakon transplantacije (1).

Ovaj sindrom se javlja kod 5-10% pacijenata sa transplantiranim organom i to u prvih 3-18 meseci nakon transplantacije (1). Karakterišu ga epizode osteoartikularnog bola isključivo u donjim ekstremitetima (kičma i kukovi su pošteđeni). Bol je jak, onesposobljavajući, pogoršava se u uspravnom položaju i pri kretanju i često dovodi do imobilizacije pacijenta. Još jedna karakteristika ovog bola jeste da je simetričan.

Prilikom kliničkog pregleda, osim blagog edema, ne zapažaju se druge lokalne promene (crvenilo i trofičke promene kože). Pacijenti imaju hipertenziju. Od dodatne dijagnostike, od velike pomoći su scintigrafija i magnetna rezonanca (MR). Na scintigrafii se zapaža povećano nakupljanje radionuklida u tibijalnom platou i metatarzumu. MR pokazuje edem koštane srži u kondilusu femura i tibijalnom platou.

Šema 1. – Postavljanje dijagnoze posttransplantacionog bolnog sindroma (2)



Kamen temeljac terapije ovog bolnog sindroma je smanjivanje doze inhibitora kalcineurina ili njegova zamena. Od velike pomoći je i elevacija nogu iznad nivoa srca (minimiziranje venskog pritiska i smanjivanje edema koštane srži). Kalcitonin takođe može pomoći kod ublažavanja bolova (inhibiranjem osteolize). Analgetici nemaju veliki značaj

Zaključak

U kliničkoj praksi, u terapiji bola kod pacijenata kojima je transplantiran organ, važno je imati u vidu mogućnost pojave posttransplantacionog sindroma bola. Iako ćemo se sa ovim sindromom retko susretati, pravilna dijagnoza će nam pomoći da izbegnemo bespotrebnu upotrebu opioida, a pacijentu će poboljšati kvalitet života.

Reference

1. Frank-Peter Tillmann, Marcus Ja ̈ger, Dirk Blondin, Martin Oels, Lars-Christian Rump, Bernd Grabenseeband Gerd-Ru ̈diger Hetzel : Post-transplant distal limb syndrome: clinical diagnosis and long-term outcome in 37 renal transplant recipients. Transplant International (2008.) 0934-0874
2. W.Grotz, M.K.Breitenfeldt, S.W.Braune, K-H.Allmann, T.M.Krause, J.A. Rump, P.J. Schollumeyer: Calcineuron-inhibitor induced pain syndrome (CIPS): a severe disabling complication after organ transplantation
3. C.G.Gevirtz: Menaging posttransplantation pain syndromes. Nursing (2009.)
4. A.Meyrier: Calcineurin inhibitor-induced pain syndrome after kidney transplantation -a rare but disabling condition. NDT Plus (2011.)4:63-66
5. L.Gurin, R.Gohh, P.Evangelista: Pain syndrome with stress fractures in transplanted patients treated with calcineurin inhibitors. CKJ (2012) 5:13-16

Perioperativna analgezija za karotidnu endarterektomiju/ Perioperative analgesia in carotid endarterectomy

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Uvod

Karotidna bolest se najčešće manifestuje kao aterosklerotična stenoza karotidne arterije, koja može dovesti do ishemijskog moždanog udara. Moždani udar predstavlja važan uzrok trajne invalidnosti i treći je uzrok smrti u razvijenim zemljama, odmah posle bolesti srca i malignih bolesti. Dijagnoza karotidne arterijske bolesti postavlja se na osnovu anamnestičkih podataka, fizikalnog pregleda, duplex ultrasonografije, angiografije, transkranijalne Doppler ultrasonografije i kompjuterizovane tomografije s angiografijom.

Karotidna endarterektomija

Karotidna endarterektomija je najčešći operativni zahvat u vaskularnoj hirurgiji. To je hirurška procedura koja podrazumeva odstranjenje aterosklerotske intime i medije koji izazivaju kritičnu stenozu, a izvodi se u cilju restitucije karotidnog krvnog protoka i smanjenja incidencije embolijskog i trombotičkog moždanog udara. Operativno lečenje karotidne stenoze apsolutno je indikovano kod simpomatskih pacijenata sa stenozom većom od 70% (Nivo dokaza A). Glavni ciljevi kod ove operacije su: adekvatna preoperativna priprema, pravilan izbor anestetika i izbor anestezije kako bi odmah postoperativno moglo da se uradi procenjivanje neurološke funkcije i perioperativna analgezija.

Specifičnosti anestezije za karotidnu endarterektomiju

Nakon pažljivo sprovedene preoperativne pripreme , izbor hipnotika i analgezije je ključna stvar za uspeh operacije. Takođe, intraoperativni ciljevi tokom operacije na karotidnim arterijama jesu istovremeno postizanje protekcije srca i mozga. Pacijenti kojima je indikovana ova intervencija uglavnom imaju generalizovanu aterosklerozu i neke pridružene bolesti , najčešće DM, HBI, HOBP ili neko neurološko oboljenje.

Kod bolesnika intraoperativno treba održavati normokapniju. Hipokapnija može dovesti do smanjenja cerebralne perfuzije na strani ishemije, dok hiperkapnija može da uzrokuje „fenomen krađe“ kontralateralne strane od strane gde postoji ishemija. Skoro svi uobičajeno korišćeni anestetici smanjuju cerebralni metabolizam, čime ispoljavaju cerebralni protektivni efekat. Pokazano je da i propofol i etomidat smanjuju moždanu električnu aktivnost i bazalni cerebralni metabolizam kiseonika. Barbiturati ispoljavaju neuroprotektivan efekat tokom perioda regionalne ishemije, ipak nije pokazano da barbiturati u značajnoj meri poboljšavaju neurološki ishod posle karotidne hirurgije, a dovode do značajnog odlaganja ekstubacije bolesnika.

Od inhalacionih anestetika, sevofluran je inhalacioni anestetik izbora kod ovakvih intervencija.

Opšta anestezija u karotidnoj hirurgiji je komfornija kako za pacijenta, tako i za hirurga , ali je monitoring neurološke funkcije manje pouzdan. Prednosti opšte anestezije nad regionalnom anestezijom jesu sigurnost i bezbednost disajnog puta, kontrolisana oksigenacija i ventilacija s održavanjem koncentracije ugljen-dioksida u arterijskoj krvi u opsegu referentnih vrednosti i neuroprotektivno dejstvo primenjenih anestetika. Nedostaci opšte anestezije su uobičajene komplikacije opšte anestezije (otežan disajni put, glavobolja, bol u grlu), zaostali efekat anestetika u neposrednom postoperativnom periodu koji može da maskira znake i simptome ranog neurološkog deficita. Neposredno postoperativno neurološki deficit mogao bi pogrešno da se protumači kao efekat anestezije s obzirom na to da se u početku prvenstveno manifestuje kao sedacija, agitacija ili konfuzija bolesnika, a ne kao klinički jasan motorni deficit.

Regionalna anestezija se postiže analgezijom dermatoma od C2 do C4 na strani vrata koji se operiše. Osnovna prednost primene regionalne anestezije jeste bolja mogućnost procene neurološkog statusa bolesnika tokom klemovanja karotidne arterije. Bolesnik je tokom operacije budan , čime se obezbeđuje egzaktan monitoring neurološke funkcije, veća je stabilnost arterijskog krvnog pritiska, smanjena primena vazopresorne terapije, niža cena lečenja, skraćena dužina lečenja i odsustvo neželjenih efekata primene opšte anestezije.

Osnovni nedostaci primene regionalne anestezije jesu što budan bolesnik mora mirno da leži na leđima, sve vreme operacije , zbog čega je potrebno da bude kooperativan i neklaustrofobičan. Primena regionalne anestezije se ne preporučuje kod bolesnika sa neurološkim i reumatološkim bolestima, kod anksioznih i agitiranih bolesnika i kod bolesnika sa tremorom i kratkim i debelim vratom. Ukoliko je potrebno da se bolesnik intubira intraoperativno, uspostavljanje disajnog puta može biti tehnički otežano i praćeno značajnom hemodinamskom nestabilnošću. Incidencija konverzije regionalne anestezije u opštu anesteziju u karotidnoj hirurgiji je od 0,1 do 11,6%.

Intraoperativna regionalna anestezija može se izvesti površnim ili dubokim cervikalnim blokom.

Blokada cervikalnog pleksusa

Površni blok cervikalnog pleksusa tehnički se lakše izvodi od bloka dubokog cervikalnog pleksusa. Ubrizgavanjem od 25 do 30ml rastvora lokalnog anestetika (bupivakain 0,375%, maksimalna doza 1,4mg/kg), na sredini i duž zadnje ivice sternokleidomastoidnog mišića, na oko 1,5cm ispod kože, postiže se adekvatna analgezija za površne strukture vrata.

Brojnim kliničkim studijama je pokušano da se utvrdi da li karotidna endarterektomija urađena u regionalnoj anesteziji daje bolje rezultate od one koja je urađena u opštoj anesteziji. Rezultati GALA studije pokazali su da nema statistički značajne razlike u incidenciji moždanog udara,infarkta miokarda i smrtnog ishoda nakon primene opšte ili regionalne anestezije.Naš stav je da se koristi kombinovana primena opšte anestezije i površnog bloka cervikalnog pleksusa, čime se obezbeđuju prednosti opšte anestezije sa potenciranom intraoperativnom analgezijom.

Naše iskustvo u primeni tapentadol u terapiji postoperativnog bola nakon karotidne endarterektomije

Kako ova operacija uzrokuje bol srednjeg intenziteta, obično se za postoperativnu analgeziju koriste minimalne ili umerene doze analgetika. Korišćenjem intraoperativno površnog cervikalnog bloka, analgezija je obezbeđena i nekoliko sati posle operacije. Imajući u vidu da ceo anesteziološki menadžment ima za cilj ranu ekstubaciju i procenu neurološkog statusa, a pacijenti mogu da uzimaju odmah terapiju per os, pored aktuelnih analgetika koji se najčešće koriste u JIL, ideja nam je bila da procenimo efikasnost upotrebe tapentadola u obezbeđivanju adekvatne analgezije kod bolesnika kojima je rađena karotidna endarterektomija.

Istraživanje je sprovedeno kao prospektivna studija na Klinici za Kardiohirurgiju tokom 2020. i 2021. godine.Istraživanjem je obuhvaćeno ukupno 90 pacijenata, 60% muškaraca i 40% žena, kojima je indikovana karotidna endarterektomija. Korišćena je opšta anestezija uz površni blok cervikalnog pleksusa. Za lečenje postoperativnog bola kod 30 pacijenata je korišćen tapentadol, u dozi 50mg/12h. Za procenu intenziteta bola korišćena je vizuelna skala bola. Pacijenti su ocenjivali 3 puta dnevno jačinu boli , i zatim je srednja vrednost tog dana korišćena za analizu. Merenje je vršeno u 8,14 i 20h.

Dominantni komorbiditeti su bili hipertenzija i DM tip 2, ali nije bilo razlike u učestalosti različitih komorbiditeta između grupe lečene tapentadolom i grupe kojoj je propisan drugi analgetik.Intenzitet bola, procenjivan vizuelnom skalom bola, se nije razlikovao u 1, 2. i 3. danu nakon operacije. Međutim, uočen je statistički značajan bolji odgovor na analgetsku terapiju tapentadolom u 4. danu ($p<0,05$) i 5. danu ($p<0,001$). Petog dana nakon operacije, tapentadolom je postignuto potpuno obezboljavanje kod većine pacijenata.

Učinak tapentadola je naročito bio značajan u grupi pacijenata sa DM tip 2. Statistički značajna razlika u sniženju intenziteta bola između pacijenta lečenih tapentadolom

i drugim analgetikom je uočena već 2. dana nakon operacije ($p<0,05$) koja je bila sve izražnije do 5. dana kada je tapentadolom najčešće postignuto potpuno odsustvo bola, dok je u grupi pacijenata lečenih drugim analgetikom i dalje bio prisutan blag bol.

Tapentadol je snažan analgetik, svoje dejstvo postiže kao agonista na mi-opioidnim receptorima i dodatnom inhibicijom ponovnog preuzimanja noradrenalina. Tapentadol svoje analgetičko dejstvo vrši direktno, bez farmakološki aktivnog metabolita. Maksimalne koncentracije tapentadola u serumu se beleže između 3 i 6 sati posle uzimanja tableta sa produženim delovanjem. Metaboliše se u jetri a izlučuje putem bubrega. Doziranje 50mg na 12 sati.

Efikasnost je potvrđena u kliničkim ispitivanjima, gde su bila obuhvaćena stanja ne malignog nociceptivnog bola i neuropatskog hroničnog bola kao i kod hroničnog bola povezanog sa tumorima.

ABSTRACTS

17th Belgrade International Symposium on Pain

ORIGINAL WORKS

OW.1.BISOP.2022.

Interfascial Plane Blocks for Postoperative Pain Management Following Breast Surgery

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Introduction: Breast surgeries are some of the most painful procedures. If perioperative pain is not well controlled, chronic postoperative pain could become serious problem. Regional analgesic techniques take central place in multimodal pain management plan. Interfascial plane blocks (IPBs) are important part of the multimodal pain management following breast surgery.1,2 Thanks to the international Kybele program,3 IPBs were introduced in everyday clinical practice in Leskovac General Hospital (LGH).

Methods: All breast surgery cases that had IPB as a part of a multimodal perioperative pain management plan, done during the period October 2017 – February 2020 were obtained from the anesthesia databases of LGH. IPB was performed in operating room either before or at the end of surgery. All patients that had IPB were checked for pain relief.

Results: In LGH, IPB was performed in 64 patients. Pectoralis block type 2 (Pecs II) was performed in 43 patients, and erector spinae plane block (ESPB) in 3 patients undergoing breast-conserving surgery. IPB was performed in 18 patients undergoing mastectomy with axillary dissection (Pecs II in 1 patient, serratus anterior plane block (SAPB) in 5 patients, and ESPB in 12 patients). Catheter for continuous local anesthetic infusion in ESP was placed in 2 patients before mastectomy and axillary dissection, and was used for two days. Bupivacaine or levobupivacaine 0.25% with dexamethasone 4 mg were injected under ultrasound guidance. We performed Pecs II block with the single needle pass at the level of the 3rd – 4th rib in the anterior axillary line using 20 ml of local anesthetic solution (LA) in fascial plane deeper to the pectoralis minor muscle, and 10 ml in fascial plane superficially to the pectoralis minor muscle. SAPB was performed using 20 ml of LA at the level of the 4th – 5th rib between anterior and posterior axillary line superficially to the serratus anterior muscle. ESPB was performed using 20 ml of LA between erector spinae muscle and transverse process of the 4th – 5th thoracic vertebra. All patients had a surgery under general anesthesia. Acetaminophen and NSAID were available postoperatively for breakthrough pain. All patients had satisfying pain control, 0 to 3/10 on a numeric rating scale. Patients who had IPB as a part

of pain management did not use opioids postoperatively. No complications regarding block performance were noticed.

Conclusions: IPB are local anesthetic injection in the space between two muscles under ultrasound control. IPB are relatively simple to perform and technically straightforward to learn. In comparison to neuraxial techniques and thoracic paravertebral block (TPVB), they provide similar analgesia, and have better benefit – risk ratio. We need new studies that will show which IPB is the best analgesic option for different type of breast surgery.

References:

1. Versyck B, van Geffen GJ, Chin KJ. Analgesic efficacy of the Pecs II block: a systematic review and meta-analysis. Anaesthesia. 2019;74: 663-73. doi: 10.1111/anae.14607
2. Gürkan Y, Aksu C, Kuş A, Yörükoğlu UH, Kılıç CT. Ultrasound guided erector spinae plane block reduces postoperative opioid consumption following breast surgery: A randomized controlled study. J Clin Anesth. 2018; 50:65-8. doi: 10.1016/j.jclinane.2018.06.033.
3. Pejčić N, Mitić R, Veličković I. Quadratus lumborum blok – metod postoperativne analgezije stiže u Srbiju kroz vrata OB Leskovac. Apollinem medicum et aesculapium. 2017; 15:16–20.

OW.2.BISOP.2022.

THE BEST POSTER PRESENTATION-THE THIRD PLACE

Treatment of the knee chronic pain by radiofrequency ablation

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Introduction: Chronic pain is common in patients with knee joint osteoarthritis. General practitioner, orthopedic surgeon, and physiatrist diagnose a knee osteoarthritis after conducting physical and radiological exams. Treatment includes a non-pharmacological, pharmacological and surgical approach. If patients have contraindications for knee surgery or medicament therapy, conventional radiofrequency ablation (RFA) is a minimal invasive pain-relieving option for the treatment of moderate and severe pain. It is performed after a positive genicular nerves block, defined by a threshold of ≥ 50% reduction in baseline pain intensity, concordant with the local anesthetic duration of action. RFA is performed under fluoroscopic guidance through electrodes placed at knee articular nerves (branches of saphenous and femoral nerve). They create thermal lesion causing sensory or sympathetic denervation without motor deficits.

Methods: This paper is a retrospective analysis of radiofrequency ablations of genicular nerves performed at the University Hospital Osijek, Croatia during 2019. We measured pain intensity before and after the procedure (by using a visual analog scale, the interval from 0 to 10); duration of pain relief measured in months; patient's average age; patients sex distribution. Statistical processing was done in SPSS 23.0. The normality of the distribution of numerical data was tested by the Shapiro-Wilks test. When comparing nominal with numerical variables, Student's T-test was used in the case of the normal distribution, while a Mann-Whitney test was used in case of abnormal distribution. In the case of dependent numerical variables, a T-test of differentiation was used for testing.

Results: We performed diagnostic genicular nerve blocks in a total of 39 patients. Five patients had a negative diagnostic blockade. Five patients went to cryo genicular nerves ablation instead of radiofrequency ablation. Two patients with a positive diagnostic test did not arrive at an appointment for the radiofrequency lesion. Five patients did not come to control meeting, so data were not available for analysis. In the end, we analyzed 22 patients. Five of them were men and 17 women. The median of the patient's

age was 72 years (IQR 66, 5-79). Pain intensity before the procedure has a mean of 7.59 (SD 1.297). Pain intensity after the procedure has a mean of 4.09 (SD 2.022). We have a statistically important decrease in pain intensity after the procedure ($p<0,001$, T-test differentiation). The median of pain relief was 3 months (IQR 0, 75-6, 0). There was no statistically important difference in parameters between sexes. Men and women were the same age, had the same duration, and decrease of pain intensity after the procedure.

Conclusion: Treatment of the knee chronic pain by radiofrequency ablation results in statistically important decrease in pain intensity during three months after the procedure.

Keywords: Knee osteoarthritis, genicular nerves, radiofrequency, ablation, chronic pain.

References:

1.Choi EJ, Choi YM, Jang EJ, Kim JY, Kim TK, Kim KH. Neural Ablation and Regeneration in Pain Practice. Korean J Pain. 2016; 29(1):3–11. doi:10.3344/kjp.2016.29.1.3

2.Jamison DE, Cohen SP. Radiofrequency techniques to treat chronic knee pain: a comprehensive review of anatomy, effectiveness, treatment parameters, and patient selection. J Pain Res. 2018; 11:1879–1888. Published 2018 Sep 18. doi:10.2147/JPR.S144633

OW.3.BISOP.2022

THE BEST POSTER PRESENTATION-THE SECOND PLACE

Percutaneous laser disc decompression in treatment of lumbar radicular pain

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Introduction: Percutaneous laser disc decompression (PLDD) is minimal invasive procedure for treatment of lumbar radicular pain caused by disc herniations. The laser fiber is introduced through a needle inserted in nucleus pulposus. Laser energy evaporise small amount of water in nucleus pulposus wich cause great fall in intradiscal pressure. The aim of this study is to present our clinical experience and to show the benefits of this procedure.

Methods: A total of 62 patients who met the criteria of PLDD underwent procedure in 2019. The data was reviewed retrospectively. The patients had symptomatic lumbar radicular pain, image documented.

Results: Among them, 25(40.3%) patients was male and 37(59.7%) patients was female. The mean age was 49.29. Reduction in pain mesured with Numeric Rate Scale (NRS) was statisticaly singificant. Among the 62 patients, PLDD was done in 49 of them and at the 13 of them PLDD could not be done. Out of 62 patients, 42 came for a regular control exam. Before surgery NRS was 4-6 in 21 patients, in 31 patients NRS was 7-8 and in 10 patients was 9-10. After surgery pain intensity was 0-3 in 12 patients, 4-6 in 21 patients, 7-8 in 7 patients and 9-10 in 2 patients. Complication rate was 0.

Conclusion: Percutaneous laser disc decompression is safe and effective procedure for treatment of lumbar radicular pain caused by disc herniations. If performed by experienced clinicians, the reduction of pain is significant and with a minimal complication rate.

References:

1. Daniel S J Choy, Johannes Hellinger, Stefan Hellinger, Gian Paolo Tassi, Sang-Ho Lee. 23rd Anniversary of Percutaneous Laser Disc Decompression (PLDD).Photomed Laser Surg. 27 (4),535-8;Aug 2009. DOI: 10.1089/pho.2009.2512

2. Momenzadeh S, Koosha A , Monfared MK ,Bairamil J , Zali A, Ommi D, Hosseini B, Hashemi M, Sayadi S, Aryani R. JOURNAL OF LASERS IN MEDICAL SCIENCES The Effect of Percutaneous Laser Disc Decompression on Reducing Pain and Disability in Patients With Lumbar Disc Herniation. Journal of lasers in medical sciences. 10,29-32;2019. DOI: 10.15171/jlms.2019.04

OW.4.BISOP.2022

Nurses' knowledge and attitudes regarding pain

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Introduction: Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. In health care, "Pain is everything who experiences it says it is and exists however person says it exists."

Aim: The aim of the study was to determine the knowledge and attitudes of nurses about pain, as well as differences in knowledge and attitudes about pain in relation to their age, work experience, level of education and type of department in which they work.

Material and methods: The research was conducted as a descriptive cross-sectional study, in December 2021 and January 2022. The sample consisted of nurses working at the Institute of Oncology of Vojvodina. The KASRP questionnaire includes 43 questions, which referred to general socio-demographic data, as well as knowledge and attitudes about pain.

Results: Nurses showed low knowledge and inadequate attitude towards pain, as no nurse had a total score value of more than 80%. According to the values of the total score, nurses older than 46, who have over 16 years of work experience, who have completed master's academic studies in health care, as well as those working in the Department of Anesthesiology and Intensive Care still have slightly better knowledge and a more positive attitude towards pain.

Conclusion: Nurses have low knowledge and inadequate attitude towards pain. No statistically significant difference was found in the knowledge and attitudes in relation to their age, work experience, level of education and department in which they work.

Keywords: attitudes; kasrp; knowledge; nurse; pain

References:

1. European Pain Federation. What is the definition of pain? EFIC, Brussels, 2022. [Internet] [Cited 15.02.2022.] Available from: https://europeanpainfederation.eu/history/what-is-pain/
2. Williams ACC, Craig KD. Updating the definition of pain. Pain. 2016 Nov;157(11):2420-23.
3. Pjević M. Hronični bol : mehanizmi, dijagnostika i lečenje. Novi Sad: Medicinski fakultet u Novom Sadu, 2017.

OW.5.BISOP.2022.

THE BEST POSTER PRESENTATION–THE SECOND PLACE

Prediction of the distance from skin to epidural space for thoracic epidural catheter insertion by BMI and computed tomography

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Introduction: Thoracic epidural analgesia (TEA) in thoracoabdominal surgery provides good perioperative analgesia, reduce usage of opioids and enable better splanchnic perfusion. TEA is the gold standard for postoperative pain control, lead to attenuated postoperative stress response, faster recovery, reduced length of hospitalization. For successful TEA correct identification of epidural space and insertion of the epidural catheter is required. Correlation between measured distance from skin to epidural space on preoperative CT scanner with obtained actual distance during placement of thoracic epidural catheter could be helpful anesthesiologists, especially residents in performing this procedure. The objectives of this study were to show correlation between the actual distance from skin to epidural space (actual insertion length -AIL) using the median or paramedian approach and estimated insertion length (EIL) measured on preoperative CT scanner. The second goal of this study was to investigate the correlation between the patient's BMI and AIL.

Methods: This prospective study included 61 adult patients which were scheduled for elective major thoracoabdominal and abdominal surgery with inserted epidural catheter prior to the induction of general anesthesia. In 43 patients a preoperative CT thoracic and abdominal scanner was performed and the distance from the skin to the epidural space was measured at different thoracic level (from Th 6-7 to Th 10-11), for medial or paramedial approach. After monitoring the patients, all were placed in the traditional sitting position, with neck flexion and feet resting on the stool. Entry of the needle into the epidural space was identified using the loss of resistance (LOR) technique.

Results: There was a statistically significant difference in the mean value in depth of the epidural space measured on CT scanner and the AIL (4±0.1 cm vs. 2.8±0.1 cm,

p<0.001). A statistical difference was observed at all levels of thoracic epidural catheter insertion. The mean depth at deferent level on CT scanner vs. AIL was respectively Th6-7: 4.2±0.1 vs. 3.1±0.6 cm, Th7-8: 3.9±0.8 vs.2.5±0.8 cm, Th8-9: 4±0.9 vs. 3±0.9cm, Th9-10: 4.2±0.9 vs.2.8±0.7 cm (p<0.001). Despite a positive correlation between EIL and AIL (r=0.319, p=0.037), nonlinear regression models have shown that the CT scanner measurements cannot be used as a good predictor for AIL (p>0.001). A strong positive correlation between the patients BMI and both EIL vs. AIL were observed (r=0.724 vs. 0.282). Regardless, BMI like EIL cannot be used as a predictor for AIL.

Conclusion: In our study the preoperative abdominal CT is not helpful in prediction of the distance for thoracic epidural insertion. Heterogeneity of thoracic level insertion and small number of patients could be reason for these results. For definite conclusion further studies are needed.

References:

1.Soltani Mohammadi S, Piri M, Khajehnasiri A. Comparing Three Different Modified Sitting Positions for Ease of Spinal Needle Insertion in Patients Undergoing Spinal Anesthesia. Anesth Pain Med. 2017;7(5):e55932.

2.Ravi, K. K., Kaul, T. K., Kathuria, S., Gupta, S., & Khurana, S. (2011). Distance from Skin to Epidural Space: Correlation with Body Mass Index (BMI). Journal of anaesthesiology, clinical pharmacology, *27*(1), 39–42.

3.Kao MC, Tsai SK, Chang WK, Liu HT, Hsieh YC, Hu JS, Mok MS. Prediction of the distance from skin to epidural space for low-thoracic epidural catheter insertion by computed tomography. Br J Anaesth. 2004 Feb;92(2):271-3. doi: 10.1093/bja/aeh053. PMID: 14722181.

OW.6.BISOP.2022.

THE BEST POSTER PRESENTATION-THE FIRST PLACE

Is thoracic epidural analgesia still better choice following esophagectomy?

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Introduction: Thoracic epidural analgesia (TEA) is a gold standard following esophagectomy. Adequate postoperative pain control is a key item of enhanced recovery after surgery (ERAS) programs, fostering faster mobilization and early recovery. Pain relief with epidural analgesia is superior compared to systemic opioid analgesia following esophagectomy. Non-analgetic benefits of epidural analgesia include reduce central sympathetic stimulation, with subsequent favorable effects on coagulation and homeostasis and on gastrointestinal, metabolic, and immune function. This study primarily aims to compare the postoperative quality of pain control between TEA versus parenteral opioids, time of mobilization, postoperative pneumonia and length of hospital stay in patients following esophagectomy.

Methods: This prospective study included 118 adult patients which were scheduled for elective esophageal cancer surgery. All patients undergo esophagectomy with two-field lymphadenectomy. We observed two groups of patients. The first group included patients with placed thoracic epidural catheter at an intervertebral level between T5 and T8 prior to the induction of general anesthesia. After anesthesia induction, continuous epidural analgesia was started (0.125% chirocaine, 2mcg/ml fentanyl) in a dose of 5-12ml/h. The second group was represented by patients without TEA and opioid analgesia (fentanyl) was obtained. In our study, we observed the postoperative quality of pain control patients until the second postoperative day. In terms of pain monitoring, we used topographic (anatomic) localization of pain, The Visual Analogue Scale (VAS) and the type and amount of systemically administered analgesics. We evaluated demographic characteristics of patients, type of operation (open vs. laparoscopic or hybrid esophagectomy). Also we evaluated time of mobilization, postoperative pneumonia and length of hospital stay between these two groups.

Results: TEA was placed in 51 of 118 patients (43.22%). 53 (45.76%) patients underwent minimally invasive esophagectomy, 40(33.9%) Hibrid Ivor Lewis and 24

(20.34%) patients open esophagectomy. There was a statistically significant difference in the existence of pain between the group of patients with and without TEA on the operative day. Patients without TEA had more severe pain on arrival at the intensive care unit (ICU) according to the VAS scale ($p<0.001$; 7.27±1.88 vs. 2.49±1.56). In the observed period, the use of systemic analgesics was higher globally in patients without TEA ($p<0.001$). The use of opioid analgesics is statistically significantly higher in patients without TEA ($p=0.003$; 273.88±86.75 vs. 17.65± 51.79mg, morphine 0.72± 2.66 vs. 0 mg). Group of patients with TEA had a statistical significance in mobilization on the first postoperative day ($p<0.001$). There is significant statistical difference between TEA and without TEA groups in development of postoperative pneumonia ($p<0.001$; 1 vs. 23) and in the length of hospital stay ($p<0.001$; 11.75±2.51 vs. 15.96±7.61days).

Conclusion: In our study, patients with TEA had a less pronounced degree of pain in the early postoperative period. A much smaller amount of systemically administered analgesics was used in patients with TEA. Also, patients with TEA, were mobilized faster, which were prevented postoperative pneumonia and reduced length of hospital stay.

References:

1.Cheong Chung JNg, Kamarajah SK, Mohammed AA, Sinclair RCF, Saunders D , Navid M, Immanuel A , Phillips AW. Comparison of multimodal analgesia with thoracic epidural after transthoracic oesophagectomy. Br J Surg. 2021;108(1):58-65

2.Windisch O, Heidegger CP, Giraud R, Morel P, Bühler L. Thoracic epidural analgesia: a new approach for the treatment of acute pancreatitis? Crit Care. 2016 May 4;20(1):116

3.Deana C, Vetrugno L, Bignami E, Bassi F. Peri-operative approach to esophagectomy: a narrative review from the anesthesiological standpoint. J Thorac Dis. 2021; 13(10):6037-6051.

OW.7.BISOP.2022.

Preoperative carbohydrate load and the level of postoperative pain, anxiety and nausea in patients undergoing breast surgery

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Background: Preoperative caloric load, 3 hours before the surgery has been debated in relation to major surgeries and as a part of the Enhanced Recovery After Surgery Protocols (ERAS) during the last decades[1]. Its influence on the postoperative complications and unwanted events has been elaborated and proved in several studies[1,2]. However, its influence in nondiabetic patients and its correlation to postoperative pain and anxiety in breast surgery has still not become a part of the protocols. The aim of our study was to analyze the occurrence of postoperative pain, anxiety, nausea and glycemia in patients undergoing breast surgery.

Method and material: In a prospective study 40 female patients, aged 40-60, non-diabetic (preoperative Hb A1c<5.7mmol/l), ASA I, II, scheduled for radical mastectomy at the University Clinic for thoracic surgery, Skopje from January 2022 to April 2022 were included in the study. In the study patient with diabetes melitus, EF<50%, after hemotherapy, with renal or endocrine diseases were not included in the study. Patients, with computer-based randomization were divided into two groups. Patients in Group A received 3 hours preoperatively carbohydrate drink* of 200 ml, whereas patients in group B received an equal amount of tap water. All patients underwent standardized anesthesia and post-operative analgesia protocol. In all patients we analyzed the demographic data, the level of glycemia, and according to the Visual Analog Scale (VAS in mm) the level of pain, anxiety, and nausea 12 and 24 h postoperatively. Furthermore, we analyzed the level of additional analgesia needed postoperatively with tramadol.

Results: Preoperative demographic characteristic in the groups were homogenic. Mean age in group A was 56.3 years + 4.7 SD, while in group B was 56.7 years + 2.9 SD. Level of anxiety was moderate in both groups preoperatively (after the drink), but not significantly lower in the patients in the first group (6.3 vs 7.7) while pain and nausea were low for that time measurements for both groups. On the other hand, 12h

postoperatively pain was on average 2.3 vs 4.5; anxiety was 5.3 vs 5.7 and nausea occurred with average score of 5.2 and 2.7 and glycemia was significantly higher in the group B in respect to the groups. 24 h after the operation was no significant difference in the VAS score for all three parameters between the groups. In the group B 50% of the patients needed additional analgesia during the first 12 h.

Conclusion: Carbohydrate loading with 200ml of solution 3h preoperatively lowers the pain and the need for additional analgesia during the first 12 h postoperatively. Furthermore, it influences on lowering the postoperative glycemia, nausea and anxiety in female patients undergoing breast surgery. However, more randomized studies are needed.

*the content of the solution was: water, maltodextrin, fructose, sodium citrate, aroma with osmolarity of 240mOsmol/L.

Key words: preoperative, carbohydrate load, anxiety, pain.

References:

1.Forero M, Adhikary SD, Lopez H, et al. The erector spinae planeblock: a novel analgesic technique in thoracic neuropathic pain.Reg Anesth Pain Med. 2016;41:621---7.5.

2.Forero M, Rajarathinam M, Adhikary S, Chin KJ. Continuous erector spinae plane block for rescue analgesia in thoracotomy after epidural failure: a case report. A A Case Rep. 2017;8:254-256

3.Hernandez, Maria A., et al. Erector spinae plane block for inguinal hernia repair in preterm infants. Pediatric Anesthesia, 2018, 28.3: 298-299.

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Occurrence of pain after Video assisted thoracotomy (VATS) for lung resection done in different anesthesia combinations

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Background: Lung surgeries done with Video assisted thoracoscopy (VATS) have been reported as more suitable, less invasive approach that results in overall less postoperative pain, less postoperative complications and shorter hospitalization[1]. Even though the differences of pain treatment in thoracic surgery are still a debate going on (due to the fact of different technics), rarely considered fact is the occurrence of pain and pain relief in patients undergoing VATS[2,3]. The aim of our study was to evaluate the occurrence of pain in patients undergoing lung resection in general anesthesia (GA), in combination with intercostal block (IB), and epidural anesthesia.

Material and method: in a retrospective manner, recorded data from 45 patients undergoing treatment of pneumothorax with VATS at the University Clinic for Thoracic Surgery in Skopje (for one-year 2021) were evaluated. Inclusion criteria were, age 30-60 years, BMI<30 m^2, EF> 50%, first time pneumothorax, no malignant, endocrinological and renal disease present, general anesthesia (GA) given. According to the anesthesia regime given in combination to GA patients were divided in three groups; group EA+-GA (n=15) where epidural analgesia was in combination with GA; group ICNB+GA (n=15) intercostal nerve block in combination with GA and group GA (n=15) where no only general anesthesia was given. In all patients we evaluated the demographic characteristics and occurrence of postoperative pain during the 1,3,6,12 and 24 hours postoperatively assessed by visual analogue scale (VAS).

Results: All groups were homogenous. The pain was significantly lower in the first 1,3,6 and 12 h in the groups where patients received general anesthesia and combination of epidural analgesia or ICNB when compared to GA group. Furthermore, patients who were in the group ICNB + GA had significantly lower pain compared to EP + GA in the 6,12 and 24 hours.

Conclusion: Our study has confirmed that after VATS pain occurs and that the combination of general anesthesia with epidural analgesia or ICNB shows reduction in

its intensity. However, when patients that receive ICNB have significantly lower pain for the 6,12 and 24 hours postoperatively so maybe this combination is better alternative for postoperative pain treatment after VATS. Larger studies are needed.

Key words: video-assisted thoracoscopy, postoperative pain, epidural, intercostal nerve block

References:

1. Landreneau RJ, Hazelrigg SR, Mack MJ, Dowling RD, Burke D, Gavlick J, et al. Postoperative pain-related morbidity: Video-assisted thoracic surgery versus thoracotomy. *Ann Thorac Surg.* 1993;56:1285–9.
2. Soto RG, Fu ES. Acute pain management for patients undergoing thoracotomy. *Ann Thorac Surg.* 2003;75:1349–57.
3. Taylor R, Massey S, Stuart-Smith K. Postoperative analgesia in video-assisted thoracoscopy: The role of intercostal blockade. *J Cardiothorac Vasc Anesth.* 2004;18:317–21.

OW.9.BISOP.2022.

The advantage of ketamine in laser treatments for children

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Background: The use of lasers in pediatric anesthesia and surgery is a relatively recent aspect of the field. In the last 20 years, improvements in medicine have led to an increase in the number of different types of lasers, and the indications for their use on the skin have broadened, starting with vasculitis, scars, keloids, and tattoo removal. Pulsed dye laser and CO2 laser treatments for children are uncomfortable and must be performed multiple times. Procedural analgosedation (PSA) is recommended for younger children who are afraid and unable to communicate, as well as older children if the laser needs to treat a larger area of skin with uneven surfaces, such as the skin of the ears, the skin between the fingers, the eyes, and the nose, where local anesthetic penetration is insufficient. The goal of this prospective, blinded study was to look at ketamin and propofol's respiratory and cardiovascular stability, clinical efficacy, and pain management during and after PSA for skin changes using Pulse dye or CO2 lasers.

Methods: Before the laser intervention, all patients have premedicated with midazolam syrup at a dose of 0.5 mg/kg (maximum dose was 10 mg), and received fentanyl at a dose of 1 μg/kg, which was increased based on the intensity of the painful stimuli and the duration of the intervention. The participants in this trial were 310 children aged 1 to 18, with ASA-PS scores of I to II, who were randomly assigned to the ketamin or propofol groups. We use a Visually-analog scale and a Facial pain score to monitor pain immediately after laser intervention.

Results: The difference in total fentanyl consumption between the groups was highly statistically significant ($t = 4.090$, $DF = 308$, $p<0.01$). The average Visual-analog scale score in the propofol group was significantly higher than the ketamine (2.61 ± 0.97 vs 2.17 ± 0.45, $t = 5.079$, $DF = 308$, $p <0.01$). In addition, the mean Facies pain scale score was significantly higher in the propofol group than in the ketamine group (2.61 ± 0.97 vs 2.36 ± 0.49, $t = 15{,}631$, $DF = 308$, $p <0.01$). The propofol group had a substantially higher score on the Facies pain scale after laser treatment than the ketamine group (1.32 ± 0.54 vs 1, $t = 7.295$, $DF = 308$, $p <0.01$).

Discussion: In our study, there are no statistically significant differences in the study between the groups related to gender, body weight and age of the subjects, diagnosis and type of lasers used. The average age in both groups was four years. The lower dose of fentanyl administered in the ketamine group, can be explained by the analgesic effect of ketamine alone, thus reducing the total amount of opioid analgesic administered. The European Association of Pediatric Anesthesiologists has included ketamine in the official protocol of multimodal intraoperative and postoperative analgesia for various surgical interventions in children since 2018.

Conclusion: Children who received ketamine needed less opiates and had less pain during and after PSA, according to our findings.

References:

1. Chayapathi V, Kalra M, Bakshi AS, Mahajan A. A comparison of ketamine + midazolam to propofol for procedural sedation for lumbar puncture in pediatric oncology by nonanesthesiologists-a randomized comparative trial. Pediatr Blood Cancer. 2018 Aug;65(8):e27108.
2. Stevic M, Ristic N, Budic I, Ladjevic N, Trifunovic B, Rakic I, Majstorovic M, Burazor I, Simic D. Comparison of ketamine and ketofol for deep sedation and analgesia in children undergoing laser procedure. Lasers Med Sci. 2017 Sep;32(7):1525-1533.

OW.10.BISOP.2022.

Is general anesthesia necessity for subdural hematoma drainage?

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Introduction. Neurosurgery and anesthesia have made amazing advancements in recent years. Despite this, in nations with limited resources, chronic subdural hematoma (CSDH) is usually treated surgically. Burr hole craniotomy under general anesthesia is the most common procedure for its removal. However, because this group of patients is typically older and has several comorbidities, local anesthetic with sedation will improve recovery while reducing complications. The goal of this study is to assess the prognosis of using a local anesthetic potentiate with sedative for CSDH management.

Material and methods. Five patients with CSDH were operated on under sedation and local anesthetic from June to December 2020. Patients were enrolled in this study after receiving written consent from them. All patients under the age of 19, those with multilocular hematomas, and those who were unwilling to cooperate were eliminated from this study. The patient was given local anesthetic by injecting 10ml Lidocaine 2% subperiosteally and subcutaneously. Sedation was provided by boluses of midazolam and continuous propofol on an infusion pump. The CSDH was emptied after a burr hole craniotomy was done. All patients were evaluated for clinical appearance, hemodynamic stability, complications, and satisfaction. The neurological state of patients was graded on admission and discharge using Markwalder's neurologic grading system.

Results. Patients' demographic data ranged from 54 to 85 years old (mean 72). There were two females (40%) and three males (60 %). Trauma was the cause of all of the cases of CSDH. One patient had a disturbed state of consciousness, and all of the patients had a headache as a symptom. Markwalder's neurologic grading method identified grade 1 in four cases (80%) and grade 2 in one (20%). Markwalder's neurologic grading system improved after the evacuation. Grade 0 was classified in four patients (80%), and grade 1 was noticed in one patient (20%). During in the perioperative and postoperative periods, all patients were hemodynamically stable. In the two weeks following surgery, no bad outcomes or deaths had happened. There were no complaints from any of the patients.

Discussion: It is vital to define the safest, simplest, and most successful surgical method, especially for developing nations. The gold standard for surgical therapy of persistent subdural hematoma is burr hole craniotomy. During CSDH surgery, a local anesthetic is usually chosen for patients with concomitant complicated systemic illness. Many studies have shown that both general and local anesthesia are safe in chronic subdural hematomas with a modest consequence. Furthermore, general anesthesia may affect the return to preoperative levels of awareness after such procedures, which must be evaluated early postoperatively to rule out the need for redoing due to early postoperative remembrance.

Conclusion: Under local anesthetic with sedation, the treatment of CSDH is successful, adequate, and safe. It will reduce the length of stay in the hospital, as well as the cost and complication rates.

References:

1.Regan JM, Worley E, Shelburne C, Pullarkat R, Watson JC (2015) Burr hole washout versus craniotomy for chronic subdural hematoma: patient outcome and cost analysis. PLoS One 10(1):e0115085. https://doi.org/10.1371/journal.pone.0115085

2.Kim S., Jung S., Won Y., Choi C., Young Yang J. A Comparative Study of Local versus General Anesthesia for Chronic Subdural Hematoma in Elderly Patients Over 60 Years. Korean J Neurotrauma 2013;9:47-51. doi.org/10.13004/kjnt.2013.9.2.47

CASE REPORTS

CR.1.BISOP.2022.

Treatment of trigeminal neuralgia by radiofrequency neuromodulation

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Introduction: Trigeminal neuralgia (TN) is one of the most common causes of facial pain. The prevalence of TN in the general population is 0.01-0.3%. It affects women more often and usually occurs in older age. Sometimes medical treatment is not effective enough and may have unacceptable side effects. Other treatment options include surgical interventions and minimally invasive techniques such as percutaneous rhizotomy with glycerol, percutaneous balloon decompression, and percutaneous radiofrequency thermocoagulation (CRF). CRF is widely used for TN treatment, but high temperatures > 70° C can cause serious complications, while lower temperatures are inefficient. Pulsed radiofrequency (PRF) uses the current in short, high-power pulses, while the "silent" phase allows heat elimination and the temperature of the tissue generally does not exceed 42° C.

Case report: 63-year-old women was referred to our Pain Clinic with exacerbation of trigeminal pain in the distribution of second and third division of her right trigeminal nerve. For the last 40 year she had episodes of trigeminal pain 3-4 times per year, but for the last six months they occurred 3-4 times per week. Because of the side effects carbamazepine was discontinued, and she was taking pregabalin 2x150 mg/d which was insufficient. MR angiography showed neurovascular conflict, but she was not prone to surgery. After diagnostic block of Gasserian ganglion with levobupivacaine which resolved her pain for 24 hours we preformed PRF on second and third branch of the trigeminal nerve. She was pain free for six month after the procedure.

Conclusion: The mechanism by which PRF leads to pain reduction without thermal damage of the tissue is not fully understood, but rapid changes in the electrical field are assumed to result in the altered transmission of pain signals. According to available literature, compared to CRF, efficacy is lower, but with significantly less complications. However, the prolongation of PRF time from 2 to 6 to 8 minutes can significantly increase the efficiency of this method.

References:

1. Van Zundert J, Brabant S, Van de Kelft E, Vercruyssen A, Van Buyten JP. Pulsed radiofrequency treatment of the Gasserian ganglion in patients with idiopathic trigeminal neuralgia. Pain. 2003;104(3):449-52.

2.Erdine S, Ozyalcin NS, Cimen A, Celik M, Talu GK, Disci R. Comparison of pulsed radiofrequency with conventional radiofrequency in the treatment of idiopathic trigeminal neuralgia. Eur J Pain. 2007;11(3):309-13.
3.Luo F, Meng L, Wang T, et al. Pulsed radiofrequency treatment for idiopathic trigeminal neuralgia: a retrospective analysis of the causes for ineffective pain relief. Eur J Pain 2013;17:1189–92.

CR.2.BISOP.2022.

Ultrasound-guided percutaneous cryoneurolysis as an interventional pain management method for frozen shoulder syndrome: case report

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Introduction: The term known as the frozen shoulder has been associated with several underlying conditions: calcifying tendinitis, subacromial bursitis, rotator cuff tendon rupture, and adhesive capsulitis. Patients complain of shoulder pain, stiffness of the shoulder and restriction of active and passive movements. The average age in which these symptoms occur is 40 to 60 years, with a prevalence of 2-5% in the general population. Shoulder pain causes a significant work disability in this working age population and represents a burden on the health system due to sick leave. The conservative treatment approach includes pharmacological and physical therapy, intra-articular and perineural administration of local anesthetics and corticosteroids. Cryo-analgesia is a method that uses cryoprobes which deliver low temperature (nitrous oxide: −88 °C; carbon dioxide: −79 °C), in order to prevent the conduction of nerve impulses and thus lead to analgesia.

Case report: A 64 year old female patient who underwent ultrasound-guided percutaneous cryoneurolysis due to right sided shoulder pain after a positive diagnostic infiltration of the suprascapular nerve with local anesthetic and corticosteroid, evaluated pain on the NRS rating scale, duration of analgesia (in weeks), as well as abduction movement of the arm (expressed in degrees) before and after performing diagnostic infiltration and cryoneurolysis. She has a coronary disease, had a myocardial infarction 6 months ago, so she has a contraindication for pharmacological treatment with non-steroidal anti-inflammatory drugs. She also has a significant side effects due to opioids and therefore limited treatment options. Ultrasound guided suprascapular nerve infiltration led to pain reduction from NRS 10 to 4, abduction of the arm changed from 25 degrees before the infiltration to 80 degrees after the infiltration. Duration of analgesia was 4 weeks, after which followed the ultrasound guided cryoneurolysis of the right suprascapular nerve. The patient evaluated pain with 1-2 on the NRS rating scale and abduction of the arm improved to 90 degrees. Analgesia was effective for approximately 9 months (36 weeks).

Conclusion: Cryoneurolysis is a valuable interventional pain management method in the multimodal treatment of patients with shoulder pain, which brings relief, long-term analgesia, and reduces the need for pharmacological therapy, especially for patients with significant co-morbidities.

References:

1.Trescot AM. Cryoanalgesia in interventional pain management. Pain Physician. 2003;6(3):345-60.
2.Bellini M, Barbieri M. Percutaneous cryoanalgesia in pain management: a case-series. Anaesthesiol Intensive Ther. 2015;47(4):333-5. doi: 10.5603/AIT.2015.0045.
3.Smiley A, McGuire J. Cryoneurolysis for the Treatment of Sensory Nerve Pain. AANA J. 2018;86(6):495-503.

CR.3.BISOP.2022.

Erector spinae block and implantation of the perineural catheter for extravesical uretheral reimplantation in pediatric patient-case report

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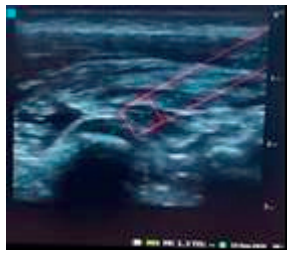
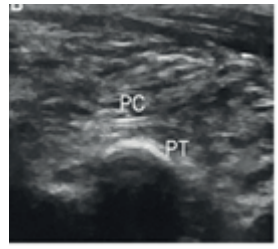
Introduction: ESP block (m. erector spinae block) is a newer method of regional anesthesia, first described in 2016 by Dr. Forero et al, when it is used to treat chronic thoracic neuropathic pain (1). The muscle erector spinae consists of multiple muscles and tendons that extend along the spinal column from the cervical to the lumbosacral segment.

Methods: In this case report; we will discuss a pediatric patient who underwent extravesical ureteral reimplantation by continuing spontaneous breathing under sedation after ESP block and catheter placement at the lumbar level.

Results: At the end of the operation, the patient woke spontaneously and without pain. At the ward, we administered Levobupivacaine 0.25% continuously through the perineural catheter with an infusion pump, 2-4 ml / h for the next 48 hours. Complications like pneumothorax, paravertebral hematoma, leg muscle weakness, nausea or vomiting did not occurred. After 48 hours, we removed the catheter and for analgesia prescribed Metamizole-Na^+ a 3.0 ml i.v. as needed. On the seventh postoperative day the patient was discharged home in good general condition.

Conclusion: Although ESP block is a new technique with still insufficient data, in this particular case, it has proven to be an potential excellent method for urological surgery procedures in children, as it provides high-quality intraoperative analgesia, which allows us to perform the intervention in analgo-sedation on spontaneous breathing. Also, continuous analgesia through the perineural catheter gave an excellent results.





References:

1.Forero M, Adhikary SD, Lopez H, et al. The erector spinae planeblock: a novel analgesic technique in thoracic neuropathic pain.Reg Anesth Pain Med. 2016;41:621--7.5.

2.Forero M, Rajarathinam M, Adhikary S, Chin KJ. Continuous erector spinae plane block for rescue analgesia in thoracotomy after epidural failure: a case report. A A Case Rep. 2017;8:254-256

3.Hernandez, Maria A., et al. Erector spinae plane block for inguinal hernia repair in preterm infants. Pediatric Anesthesia, 2018, 28.3: 298-299.

CR.4.BISOP.2022.

THE BEST POSTER PRESENTATION CASE REPORT-THE THIRD PLACE

Role of regional anesthesia for pediatric surgical patients with congenital syndromes

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Introduction: Special perioperative care is needed in children scheduled for surgical procedure and presented with congenital syndromes. The complexity of syndromes and potential complications might compromise perioperative flow and postoperative recovery.

Methods: These syndromes are characterized by multiple anomalies of the central nervous system, cardiovascular system, respiratory system, gastroesophageal reflux, musculoskeletal system. Regional anesthesia provided by and expert offers solution in case where the potential for difficult intubation, problems with ventilation and risks of aspiration, bronchospasm, laryngospasm, nausea, vomiting, pneumonia exists. We present regional anesthesia techniques applied for pediatric patients with Shprintzen-Goldberg Sy, Larsen Sy and Kabuki Sy.

Results: In three cases, we performed peripheral blocks including popliteal, lumbosacral, PENG, femoral, dual TAP in real time ultrasonography. All techniques were performed under sterile conditions and patients were under analgo-sedation. Perioperative course was uneventful and the patients were with stable hemodynamic parametars and respiratory function. None of these patients required perioperative use of opioids. During postoperative follow up children were awake, with normal respiratpry function, comfortable without pain, nausea and vomiting, and spontaneous diuresis.

Conclusion: Regional anesthesia, peripheral nerve and plane blocks might play a crucial role in the perioperative care of patients with congenital syndromes in whom the risk for potential complications exists.

References:

1.Pätau K, Smith DW, Therman E, et al. Multiple congenital anomaly caused by an extra autosome. Lancet. 1960; 1: 790-3.

2.Kosaki K, Takahashi D, Udaka T, Kosaki R, Matsumoto M, Ibe S, et al. Molecular pathology of Shprintzen-Goldberg syndrome. Am J Med Genet A 2006; 140: 104-8.
3.Sajnani AK, Yiu CK, King NM. Larsen syndrome: a review of the literature and case report. Spec Care Dentist. 2010 Nov-Dec;30(6):255-60.

CR.5.BISOP.2022.

Pneumothorax after erector spinae plane block for nephrectomy: complication or coincidence: a case report

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Introduction: Erector Spinae Plane block (ESPB) can be used to provide regional analgesia for a wide range of surgical procedures, and it has been widely used at different levels for different indications. This is a technique in which local anesthetic (LA) is injected between the erector spinae muscle and transverse process under ultrasound guidance, blocking the dorsal and ventral rami of the thoracic and abdominal spinal nerves. LA spreads on several neurotomes. The risk of serious complications is low, but amount of LA that will spread in the epidural space is not predictable, motor block and hemodynamic instability can occur.

Case report: We describe the case of 57-year-old male patient with a renal cell carcinoma scheduled for right nephrectomy. The patient was morbidly obese, weighing 145 kg (BMI 40,98 kg/m2). His comorbidity was arterial hypertension. We chose combining general anesthesia (GA) and ESPB. After induction of general anesthesia the patient was placed in the left lateral decubitus position. Lungs were ventilated using volume-controlled ventilation. Under all aseptic precautions we have identified the spine of the eighth thoracic vertebrae (T8). We placed the probe in a transverse orientation to identify the spinous process, then the probe was moved 3 cm laterally until the transverse process was identified. Visualisation was very difficult all the time due to the patient's obesity. Then the probe was moved to a sagittal plane to visualize the erector spinae muscles. A 16-gauge, 8 cm needle was inserted medially in-plane relative to the ultrasound probe and directed towards the transverse process. When the needle came into contact with the transverse process, correct tip position was confirmed by hydro-dissection with 3ml of 0.9% saline and 20 ml of 0.5% Levobupivacaine were injected. The surgery began and lasted 110 minutes. There were no complications during the surgery. The patient was awakened and transferred to intensive care unit. Pain intensity during the first 24h was VAS<3 and patient reserved only Acetaminophen 1g. Eight hours after surgery the patient has a decrease in saturation value to 91% and the partial pressure of oxygen (pO2) in blood gas analysis was 6.8 kPa. He complained of dyspnea and severe pain in his right shoulder and forearm. Computed tomography (CT) scan of

the chest and pulmonary angiography were performed and imaging showed the existence of partial pneumothorax of the right lobe and existence of pulmonary thromboembolism excluded. A thoracic surgeon was consulted and he observed the patient until discharge. The patient was discharged home after 8 days.

Conclusion: ESPB seems to be an effective analgesic technique. But, the development of pneumothorax after thoracic ESPB is possible. Some authors suggest to consider an alternative approach when performing ESPB in thoracic vertebral level (T9-T12) in obese patients, where the structures to visualize could be deeper and the risk of pleural puncture can be higher as the needle tip could be difficult to see. It may be that the incidence of pneumothorax will be higher if the procedure is carried out in patients undergoing positive pressure ventilation. Also, other reasons should be considered such as rupture bullae of lung parenchyma.

References:

1.Lopes MB, Cadorniga AG et al. Erector spinae block. A narrative review. Central Eur J Clin Res 2018;1(1):28-39

2.Coviello A, Golino L, Maresca A, Vargas M. Erector spinae plane block in laparoscopic nephrectomy as a cause of involuntary hemodynamic instability: A case report. Clin Case Rep. 2021;9:e04026.

3.Pirracini E, Poggi P, Maitan S. An alternative approach to reduce the risk of pneumothorax during erector spinae plane block in low thoracic vertebral levels. J Clin Anesth. 2020;59:14-15.

CR.6.BISOP.2022.

THE BEST POSTER PRESENTATION CASE REPORT-THE FIRST PLACE

Analgesia of postherpetic neuralgia using ketamine

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Introduction: The aim of this case report is to show the possibilities of pain treatment in postherpetic neuralgia by parenteral and epidural administration of ketamine.

Case report: A 70 year old male patient has been treated for multiple myeloma since 2008. He had had a bone marrow autotransplantation and a built-in pacemaker due to tachy-brady syndrome and he was on anticoagulation for atrial fibrillation. In 2016, herpes zoster appeared in the left hemithorax region. Despite the use of antivirals, severe neuropathic pain remained in the region of left Th4 and Th5 dermatomes, from the midline of the spine to the sternum. The patient scored 10 on the VAS pain scale with pronounced allodynia. He took numerous analgesic medications: NSAIDs, acetaminophen, tramadol, local lidocaine label, tapentadol, oxycodone, buprenorphine, morphine sulfate, amitriptyline, pregabalin, duloxetine. Over the years of treatment, the pain was partially reduced to 7 on the VAS scale. The patient was admitted and treated with continuous intravenous infusion of ketamine, 0.25 mg/kg/hour for three days, with midazolam sedation. On the third day, epidural administration of 25 mg of ketamine, 4 ml 0.25% levobupivacaine, and 40 mg Depo Medrol at the Th4/Th5 level was performed. He was discharged, continued on duloxetine, and only occasionally, a tramadol. There was no pain during i.v ketamine administration. Twenty four hours after cessation of ketamine, the pain was reduced to VAS 4, with hardly any signs of allodynia. The third day after epidural administration, pain was 3 on VAS. After three months there was a new exacerbation of pain.

Conclusion: Continuous administration of ketamine intravenously plus epidurally administered ketamine, methylprednisolone and levobupivacaine,led to satisfactory analgesia in postherpetic neuralgia, decreased allodynia, and significantly reduced need for oral analgesia for three months.

References:

1. Hocking G, Cousins MJ. Ketamine in chronic pain management: an evidence-based review. Anesth Analg. 2003;97(6):1730-1739.
2. Mizuno J, Sugimoto S, Ikeda M, Ikeda M, Machida K, Mikawa Y. [Usefulness of epidural administration of ketamine for relief of postherpetic neuralgia]. Masui. 2001 Aug;50(8):904-7.

CR.7.BISOP.2022.

Chronic Postsurgical Pain-new important issue in everyday medical practice in the developing country

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Introduction: Development of chronic pain is typically a result of peripheral and central sensitization, with chronic post-surgical pain (CPSP) being one of the most common presentations with 20% of average incidence. CPSP is defined as pain that develops after a surgical procedure and persists for at least 3 months. All other causes of pain as well as pain from a pre-existing pain problem must have been excluded 1. CPSP is not limited to major surgeries and can develop after smaller procedures such as hernia repairs 2. Consequently, the entity has become a separate category in the latest IASP classification of pain syndromes, to be included in the ICD-11 3.

Case report: Female 45 years old, unmarried, primary care doctor, previously healthy was examined at the Outpatient Pain Clinic UCCS. Six months after multiple surgical gynecological procedures followed with incisional hernia repair with mesh insertion, the patient was examined at the outpatient pain clinic. She complained on constant severe pain in the area of the infraumbilical surgical scare 7/10 NRS followed with tingling and burning with extensive alodinia and hyperalgesia mostly juring activities. Recently, she became tearful and anxious, impaired quality of life. Therapy with pregabalin 150 mg and duloxetine 30 mg was started followed with progressive increase of pregabalin dose to maximum 600 mg with topical lidocaine administration. Pain intensity was reduced by 25%: the patient was in a better mood, more active during the day, but still work absent. NMR examination showed multicystics of the right ovary with hemorrhagic content highly suspicious to malignancy. Another surgical procedure was performed by expanded medial incision. Endometrioid adenocarcinoma was confirmed, hysterectomy and right adnexectomy were performed followed with anterior abdominal wall repair by mesh insertion of larger dimension. The postoperative wound heals properly. During the entire perioperative period, the patient was treated with pregabalin 375 mg. At another pain control check, the patient complained of tingling in the supraumbilical part of the incision scare 3/10 NRS. Pregabalin dose was reduced with satisfied pain control and the patient was returned to work. Subsequent NMR examination did not show tumor recurrence. A year after the surgery, the pain became intensive again just after prescribed anterior abdominal wall muscles strengthening exercises. The patient became anxious, reported intense allodynia and hyperalgesia in the

supraumbilical part of the incision scare. Treatment was continued with pregabalin 600 mg and duloxetine 90 mg, topical lidocaine which provided reduced pain score by 30% over a 6-hour period of time. The patient was no longer able to be absent from work.

Conclusion: The presented case is good example of difficulties in diagnostic and treatment of CPSP. Also, this is good example of the major cause of prolonged suffering and disability in postoperative period suggesting the need for preoperative screening and perioperative multimodal therapy approach for prevention of CPSP.

Key words: CPSP, alodinia, hyperalgesia, pregabalin

References

1.Pak D, Jason YR, Kaye AD, Urman RD. Chronification of pain: mechanisam, current understanding and clinical implications.Current Pain and Headache Reports 2018;22:1-9.

2.Thapa P, Euasobhon P. Chronic postsurgical pain: current evidence for prevention and management. Korean J Pain 2018; 31:155-173.

3.Schug S, Lavandhomme P, Barke A, et al. The IASP classification of chronic pain for ICD-11: chronic postsurgical and posttraumatic pain. Pain 2019; 160: 45-52.

CR.8.BISOP.2022.

Is there adeqate analgesia for pain management in the setting of surgical complication

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Introduction: Ankle fractures are one of the most common orthopedic injuries which treatment can be surgical or conservative, depending on the stability of an ankle joint. Followed by severe postoperative pain its management requires a multimodal concept of analgesia in order to reduce postoperative complications, provide early rehabilitation and to increase patient's satisfaction.

Case Report: We describe the case of a 30-year-old female patient (BMI 21.63 kg / m2). The patient got an ankle fracture while skiing. She denied comorbidities, medicationes and previous surgeries. Because of the patient's refusal of spinal anesthesia, general anesthesia (GA) was induced with midazolam 0.05 mg/kg, fentanyl 3 μg/kg, propofol 1.5–2.0 mg/kg and rocuronium 0.6 mg / kg as a muscle relaxant. Using pressure-controlled ventilation anesthesia was maintained with inhalation of sevoflurane vapor in a mixture of O2/air gasses by achieving a minimum alveolar concentration of 1 with a bolus doses of fentanyl and rocuronium. The surgery lasted for 63 minutes with no complications during that time. In the postoperative period the patient was constantly upset, reporting severe pain 8-10 on VAS scale. She refused offered regional blok for pain management due to fear of the neadle. The patient was given tapentadol 100mg and acetaminophen 1g intermittenly every 4 hour and a bolus dose of Morphine 1 mg i.v., after which she reported lesser pain intesity, 5 on VAS scale. In a total of 24 hours, the patient recived 300 mg of tapentadol, 3000 mg of acetaminophen, 90 mg of ketorolac and morphine 7 mg. The next day, after a control X-ray and proved transposition of osteosynthetic material, revision surgery was done in general anesthesia.This time, postoperatively, guided by previous experience the patient accepted the ischiadic nerve block (Levobupivacaine 0,33%, 10 ml) and the adductor canal block (Levobupivacaine 0,33%, 10 ml), using an ultrasound guided technique. The ischiadic nerve was blocked above the popliteal region. The greatest pain that the patient reported during active exercise wasj VAS 3-5, at rest from VAS 0-3. Most of the day the patient denied pain. This time in a 24 hours period the patient recived 100 mg of tapentadol, 2000 mg of acetaminophen and 30 mg of ketorolac.

Conclusion: In orthopedic surgery transposition of ostheosynthetic material causes a great deal of pain and discomfort to the patient, and can not be easily managed without surgical reintervention. But every surgical reintervention is another stress to the already hurt tissue and to the patient as well. So multimodal analgesia aproach, preferably using regional anesthesia as a part of it, is the best solution.

References:

1. Miller R. Miller's anesthesia. 9th edition, Philadelphia, Elsevier; 2019.
2.Tengberg PT, Ban I. [Treatment of ankle fractures]. Ugeskr Laeger. 2018;180(41).
3.Joshi G, Gandhi K, Shah N, Gadsden J, Corman SL. Peripheral nerve blocks in the management of postoperative pain: challenges and opportunities. J Clin Anesth. 2016;35:524-529.

CR.9.BISOP.2022.

Opioid free anesthesia technique for laparoscopic cholecystectomy: a case report

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Introduction: For years, opioids have been the essence of the therapeutic approach in general anesthesia due to their analgesic and sedative effects.But, in some cases their use is contraindicated, and it is up to the anesthesiologist to find alternative techniques to provide sufficient analgesia during surgery.

Case report: A 41-year-old male patient (180 cm, 106 kg, BMI 32.7) was admitted to the surgery department as an emergency due to severe pain below the right costal arch. After the diagnostic procedures, it was determined that the cause of pain was acute inflammation of the gallbladder and he was scheduled for urgent surgery. The patient is former heroin addict who is receiving extended – release injections of opioid antagonist Nalmefene. For this reason, we have decided to perform opioid free anesthesia technique. General anesthesia was induced using Dexmedetomidine (0.3 mcg/kg), Lidocaine (1.5 mg/kg), Propofol (2 mg/kg)), and Rocuronium (1 mg/kg); and was maintained with Sevoflurane in an air/oxygen mixture with an inspired oxygen concentration (FIO_2) of 50%, in addition to a continuous infusion of IV Ketamine (5 μg/kg/min), Magnesium sulfate (2.5-10 mg /kg IBW/h), Dexmedetomidine (0.5-1 mcg/kg/h) and Lidocaine (1-3 mg/kg/h).A bilateral transversus abdominis plane block (TAP) was performed after induction of anesthesia. A total of 40 mL of 0.25% Bupivacaine was injected (20 mL per side). During the entire laparoscopic cholecystectomy operation, the patient was hemodynamically stable. The average value of the MAP was about 80 mmHg. After waking up from anesthesia, VAS score was 1. Postoperative analgesia was successfully continued with nonsteroid anti-inflammatory drugs and Acetaminophen.

Conclusion: Opioid free anesthesia is an alternative to the classic opioid-guided anesthesia technique, which can be successfully used both for elective and emergency surgery. It shows best results in gastrointestinal surgery due to the rapid postoperative onset of peristalsis. However, further researches are needed in this field.

References:

1.Matthes K, Gromski MA, Schneider BE, Spiegel JE. Opioid-free single-incision laparoscopic (SIL) cholecystectomy using bilateral TAP blocks. *J Clin Anesth*. 2012. doi:10.1016/j.jclinane.2011.04.014

2.Tekeli AE, Eker E, Bartin MK, Öner MÖ. The efficacy of transversus abdominis plane block for postoperative analgesia in laparoscopic cholecystectomy cases: a retrospective evaluation of 515 patients. *J Int Med Res*. 2020. doi:10.1177/0300060520944058
3.Beloeil H. Opioid-free anesthesia. *Best Pract Res Clin Anaesthesiol*. 2019. doi:10.1016/j.bpa.2019.09.002

CR.10.BISOP.2022.

THE BEST POSTER PRESENTATION CASE REPORT-THE SECOND PLACE

Different modalities of treating painful stump neuroma-what is next?

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Introduction: Trauma or iatrogenic injury induced neuromas are the result of proliferation during disorganized regeneration of an injured nerve. (1) Symptomatic neuromas can cause significant chronic pain and negatively impact quality of life. Symptoms often persist despite medications and non-operative interventions, which are largely ineffective and due to opioid crisis, treatments for chronic pain that limit narcotics are needed. Traditional surgical options may result in neuroma recurrence. (2) Spinal cord stimulation (SCS) as an evidence-based interventional treatment that has been used and approved for clinical use in a variety of pathological states including peripheral neuropathic pain. (3)

Case report: Male patient, 57 years old, faced traumatic amputation of both legs in 1992. due to mine; left-above knee and right-below knee. Before injury he was a karate representative sportsman and several years after the accident he became paralympic champion in table tennis. He used to wear both leg prosthesis and to have an active life. During the training and movement he felt no pain, but in rest, he suffered intermittent sharp stabbing severe pain of left stump on NRS scale of 9-10. From 2006 to nowadays he tried variety of different medications (NSAIDs, opioids, corticosteroids, antiepileptic drugs, antidepressants) but with limited pain relief (NRS 5). Acupuncture was unsuccessful too. Also, he underwent multiple procedures such as neurolysis of left sciatic nerve with local anesthetic, ultrasound-guided injection of dehydrate alcohol into the stump neuroma, surgical resections of neuroma of left sciatic nerve, implantation of fasciculi of sciatic nerve to the muscle, suture of peroneal and tibial nerve component. In December 2021. he was implanted spinal cord stimulator. During five-hour operation, the electrodes are placed between the spinal cord and the vertebrae (the epidural space) and the generator is placed under the skin. Some short period after operation he felt combination of pain and prickling to both legs and perineum. During the lying on bed he has no pain but when he moves, his actual pain score varys on NRS scale from 10 with feeling of tissue tearing apart from bones to 0 after the usage of Oxycodone 10 mg IR 4 times a day with Bromazepam 3 mg, twice a day. His frequencies on spinal cord

stimulator are adjusted every 2-3 weeks. It is left to see whether it will be some improvement in pain relief.

Conclusion: Neuroma's induced neuropathic pain is often resistant to medical treatments and conventional pharmacotherapy. Spinal cord stimulator is recommended according to literature data for selected indications related to periphery neuropathic pain-like patients who experience refractory pain. Despite role of SCS, technological advances in stimulator design and treatment protocols have not correlated with significant improvements in clinical outcomes. The reason may be cause of incomplete understanding of the mechanisms underlying SCS.

References:

1.Ashkar L, Omeroglu A, Halwani F et al. Post-traumatic neuroma following breast surgery. Breast J. 2013; 19:671–672.

2.Ducic I, Yoon J, Eberlin KR. Treatment of Neuroma-induced Chronic Pain and Management of Nerve Defects with Processed Nerve Allografts. Plast Reconstr SurgS Glob Open 2019; Dec 19;7(12):e2467.

3.Sun L , Peng C, Joosten E et al. Spinal Cord Stimulation and Treatment of Peripheral or Central Neuropathic Pain: Mechanisms and Clinical Application. Neural Plasticity Volume 2021 Oct 21; 2021:5607898.

CR.11.BISOP.2022.

Acute critical ischemia masked by epidural analgesia after radical cystectomy - a case report

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Introduction:Patients with bladder cancer are at high risk of developing both venous and arterial thromboembolic event contributing to hypercoagulable state.[1] Latest data revealed that the risk of developing any VTE event among patients undergoing radical cystectomy is 4.9%.[2] Although epidural analgesia has been recommended by ERAS protocol as an effective analgesic technique for abdominal surgery, latest studies showed that epidural use at time of radical cystectomy is associated with increased risk of perioperative complications[3]. In addition, the sensory loss produced by the anesthetic may mask the signs and symptoms of acute vascular occlusion.

Case report: A 72years-old man diagnosed with bladder cancer was scheduled to undergo radical cystectomy. The patient had a history of hypertension, rheumatoid arthritis, hypothyroidism and Hepatitis B. Preoperatively, patient was evaluated by vascular surgeon because of aortobifemoral bypass graft performed 6 years earlier, and after computed tomography angiography was performed, he concluded that graft patency was maintained. Preoperatively prophylactics dose of LMWH was administered. Surgery was performed under combined general-epidural anesthesia. Before induction of GA, epidural puncture was performed at the L3–L4 interspace, using a 17-gauge Tuohy needle. A catheter was then inserted 4 or 5 cm cephalad into the epidural space. After a test dose of 3 ml lidocaine, 1%, 10ml of Bupivacaine 0,25% was administered. After achieving a sensory anesthesia level at T8, general anesthesia was induced with propofol and Fentanyl. Paralysis was achieved with Cysatracurium. There were no complications during the surgery. After the operation, the patient was awakened and transferred to the intensive care unit, where an extradural infusion of bupivacaine 0.125% with 0.05mg Fentanyl, at a rate of 4 ml/h was administered. Lately in the evening, patient complained of tingling in his left leg, which was thought to be caused by the action of peridural analgesia and hence the rate was firstly reduced to 2 ml/h, and later was discontinued. Both legs were warm, the circumference of the legs was the same, femoral, popliteal pulses were palpable, only a slight weakness of the left leg and further tingling were noted. On the following day, the patient was better, complaining only of discreet paresthesia , so he got up and took a walk as part of physical rehabilitation. Early In the morning, on the

second postoperative day, the left leg was slightly colder, with decreased motor skills and sensibility, and the femoral pulse on the left was non-palpable. The patient was urgently transferred to the Clinic for Vascular Surgery, where an above-knee amputation was performed due to irreversible ischemia of the left leg caused by occlusion of left graft.

Conclusion: Thus, epidural analgesia provides an effective pain relief, complications must be closely observed. Epidural anesthesia could mask ischemic pain and delay diagnosis and treatment, which can be fatal. Any increasing demands for analgesia should drive an attention and trigger clinical neurological review. Epidural anesthesia may not be uniformly beneficial for patients with higher risk of thromboembolic complications. Additionally, implementing a bedside ultrasonography in postoperative care protocol could be helpful.

References:

1.Zareba P, Duivenvoorden W and Pinthusa J. Thromboembolism in Patients with Bladder Cancer: Incidence, Risk Factors and Prevention. Bladder Cancer. 2018; 4(2): 139–147.

2.De Martino RR, Goodney PP, Spangler EL, Wallaert JB, Corriere MA, Rzucidlo EM, et al. Variation in thromboembolic complications among patients undergoing commonly performed cancer operations. J Vasc Surg. 2012;55(4):1035–40.

3.Lassen K, Soop M, Nygren J et al. Consensus review of optimal perioperative care in colorectal surgery: Enhanced Recovery After Surgery (ERAS) Group recommendations. Arch Surg. 2009;144(10):961–969.

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