18th BISOP

Belgrade International Symposium on Pain
May 20th 2023, Hotel Mona Plaza, Belgrade

Serbian
Pain
Society

ZBORNIK PREDAVANJA 18. BISOP

18. beogradski internacionalni simpozijum o bolu

Beograd 20. maj 2023.
Hotel Mona Plaza, Beograd

PROCEEDINGS 18th BISOP

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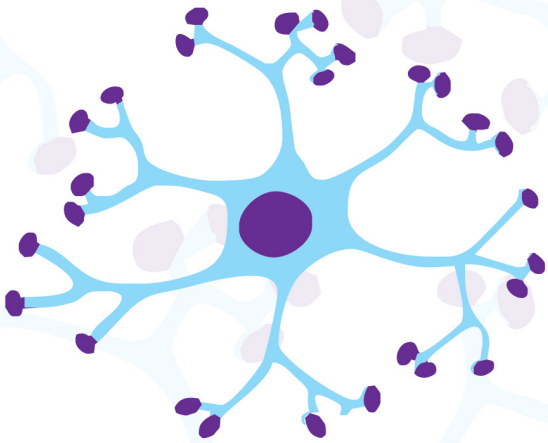

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Contents/Sadržaj

1 What the Editor Thinks

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ABSTRACT

The Editorial process is an integral, and often feared, part of scientific publishing. Rejection is common and this should not discourage Authors from resubmitting. Most scientific papers are unsolicited; many of them get eventually accepted with major or minor amendments. The most common reason for a straight rejection is a poor fit with the chosen journal audience. The most common issues that the Editor wants Authors to fix are a mixture of conceptual and style flaws in the submitted paper. Accepting the Editor and Reviewers' advice is essential to successful publication; the Authors need a degree of humility, knowing that they will hone their scientific writing skills in the process.

Key words: *Editor; Scientific publishing; Manuscripts; Peer review.*

INTRODUCTION

Every writer aims to publish and Editors need copy. While this sounds like a match made in Heaven, "Writing is a bloodsport", as writer Paul Theroux said[1] and scientific literature is no exception. In fact, paper rejection is common and there are published lists of sure-fire ways to be rejected[2,3]. Summary rejections are not entirely rare; unless the manuscript is of extraordinarily poor quality, straight rejections usually occur in case of a poor fit between the paper, the journal and its readership[4]. When the right journal is chosen and approached – and if the paper is already of a good standard at the first submission – the Editor will subject the paper to peer review.

The peer review process aims to filter manuscripts and offer constructive criticism[5]. Reviewers are experts in their field and usually give up their time for free[5]. Useful reviews are specific and 'forensic'; they also tend to address both substance and style, as well-written papers are easier to read and convey their message more effectively[5]. Authors have much to gain in the process and should leave their pride at the door; not accepting a suggestion should be an exceptional occurrence and the justification for doing so really thoroughly explained. Peer reviewers usually make a recommendation to the Editor for acceptance with minor changes, acceptance with major changes, or rejection; the final decision rests with the Editor.

The main reason for rejecting a paper based on substance is, first and foremost, an uninteresting research question with conclusions that do not introduce new knowledge, new insights in established knowledge or practice change[2,3,5,6], followed by bad and/or misused statistics[2,3,5,6]. Frequent style reasons for rejecting a paper are: ignoring journal-specific style instructions[2,3,5,6], poor text-checking for typos and grammar issues change[2,3,5,6], resubmitting a rejected paper without substantial changes change[2,3,5,6] and a paper with a convoluted style which makes it difficult to read change[2,3,5,6].

CONCLUSION

Publishing is the beginning of an ongoing feedback process and Authors should accept this fact gracefully. Rejections and requests from Editors for changes to submissions are the norm, usually because of a combination of conceptual and style issues.

The vast majority of respectable journal Editors genuinely want to improve the quality of submissions. Authors should respect the Editor and reviewers' work and always act on their suggestions; even if case of a disagreement, there is probably a grain of truth in every criticism they move to the paper. Finally, Authors should never forget the golden rule: one way or another, the Editor is always right.

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2 Quality indicators for a good paper

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ABSTRACT

There is plenty of available literature on what makes a scientific paper a good one. It should have a simple, unequivocal and, whenever possible, 'catchy' title. Its abstract, the most read part after the title, should be concise but clear. The Introduction should present a good research question, linked to previous knowledge. Its Methods section should allow reproducibility of the study and, ideally, of results. Results carry the factual answer to the research question, are clearly displayed and not repeated unnecessarily. The Discussion part explains the meaning of the study results and their wider significance within the subject area, pointing at future developments. Its Conclusions give one, max. two, strong and clear messages. Language and style should make reading easy and pleasant.

Key words: *Research; Publishing; Paper structure; Writing tips.*

INTRODUCTION

Scientific literature is full of advice for prospective writers on how to design a good paper with the highest chances of publication[1,2,3,4,5,6,7]; this advice is remarkably, if unsurprisingly, consistent across different articles and areas. Title and abstract are the most read parts of a scientific paper[4]; as such, the title should be crisp and able to catch the readers' attention, while the abstract should be able to 'stand alone' in giving the essentials about the paper[1,2,3,4,5,6,7] – the 'why', the 'what' and the 'so what'[4]. Its Introduction sets the scene, briefly linking the paper to past research and knowledge[1,2,3,5,6,7]; it should also very

clearly display the research question or the paper's main aim[1,2,3,5,6,7]. The Methods part is one of the most scrutinised sections as it is linked to reproducibility[1,2,3,5,6,7]; critical flaws in it are almost impossible to correct without changing the study layout and usually compromise the paper's chances of publication significantly[9,10,11]. Results should offer a factual answer to the study question(s) [1,2,3,4,5,6,7] (the 'what'4), with the most important findings reported first[1,2,3,4,5,6,7]; data should be displayed in the most effective way and unnecessary repetition should be avoided[1,2,3,4,5,6,7]. The Discussion should not simply repeat the results for readers; rather, it should give a stringently logical interpretation of them, explaining their meaning and relevance for the study and within the wider context of the subject area[1,2,3,4,5,6,7] (the 'so what'[4]). In so doing, it should also point to limitations and uncertain areas[1,2,3,4,5,6,7]. In the Conclusions, a clear and concise take-home message should be given, pointing to whether – and if so, how - current practice should change[1,2,3,4,5,6,7]. Usually, direction for future research is also suggested[1,2,3,4,5,6,7].

CONCLUSION

A good scientific paper is written with its prospective readers in mind. It answers an interesting scientific question in a language that is easy to read. It describes rigorous and reproducible methods, leading to well-analysed results and a tightly logical discussion of their meaning for current and future practice and research. In essence, every good scientific paper tells an exciting story.

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3 Perioperative pain management in patients with kidney dysfunction

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ABSTRACT

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) are increasingly prevalent global healthcare problems in patients undergoing surgery. Perioperative pain management in CKD- and ESRD patients is complex and preserving residual kidney function is key. Hyperkinetic circulation through arterio-venous fistulae for haemodialysis, decreased protein binding and decreased excretion of active metabolites are among the main reasons for changed drug pharmacokinetics in CKD and ESRD; there are also non-renal effects due to concomitant intestinal transport and hepatic metabolic changes. From the most advanced stages of kidney disease (CKD 3-4) before renal replacement therapy, non-steroidal anti-inflammatory drugs are probably best avoided in most cases, while antiepileptics need careful dose reduction. In general, alfentanil and fentanyl are the safest options among opioids, while codeine and meperidine are best avoided. Haemodialysis should not be assumed to be a panacea in case of drug toxicity. A multimodal approach to perioperative pain management in CKD and ESRD should include regional analgesia; however, platelet dysfunction from uraemia or medications and hypertrophic collateral circulation in patients with arteriovenous fistulae may increase bleeding risk. Careful planning and a holistic approach are essential in guiding the best perioperative pain management in these complex patients.

Key words: *Chronic; End-stage; Kidney disease; Pain management; Perioperative*

INTRODUCTION

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) are increasingly prevalent global healthcare problems, which also affect patients undergoing surgery[1,2,3,4]. Perioperative pain management in CKD- and ESRD patients is complex[1,2,3,4] and preserving residual kidney function is key[1,5]. Hyperkinetic circulation through arteriovenous fistulae for haemodialysis, decreased protein binding and decreased excretion of active metabolites are among the main reasons for altered drug pharmacokinetics in CKD and ESRD[1,2,3,4]; there are also non-renal effects due to concomitant intestinal transport and hepatic metabolic changes[6]. In the most advanced staged of kidney disease (CKD 3 to 5) non-steroidal anti-inflammatory drugs (NSAIDs) are probably best avoided in most cases[1]; through inhibition of prostanoid synthesis they can worsen medullary hypoxia via regional hypoperfusion and increased tubular transport activity[5]. They also expose patients to side effects, especially at more advanced CKD stages1. Among opioids, alfentanil and fentanyl are the safest options[1,2,3,4,7], while codeine and meperidine are to be avoided[1,2,3,4,7]. Hydromorphone is relatively safe[7,8] and oxycodone can also be used[7,9], especially in patient-controlled analgesia as an alternative to fentanyl and/or in patients already established on oxycodone. As oxycodone depends on cytochrome metabolism, clinicians should be mindful of possible genetic polymorphism modulating CYP2D6 and CYP3A activities[9,10,11], which may lead to changes in oxycodone pharmacokinetics[10,11]. Gabapentinoids do not undergo hepatic metabolism and are excreted exclusively by the kidney, requiring appropriate dose adjustment[1,12]. Haemodialysis does not help flush out larger molecules and should not be assumed to be a panacea in case of drug toxicity[7]. A multimodal approach to perioperative pain management in CKD and ESRD should include regional analgesia[1]; however, platelet dysfunction from uraemia or medications may increase bleeding risk1 and hypertrophic collateral circulation in patients with arteriovenous fistulae may make regional blocks more difficult, even in expert hands with ultrasound guidance.

CONCLUSION

Perioperative pain management in CKD- and ESRD patients is complex, while co-morbidities and drug metabolism issues create a narrow therapeutic window; drug nephrotoxicity also risks causing further renal damage. Avoiding/curtailing direct nephrotoxicity and preserving renal protective mechanisms are both key to limiting damage to residual function. A carefully planned, multimodal approach to perioperative pain management, taking into account changes in drug metabolism and excretion in CKD and ESRD, is essential in achieving the best results in these complex patients.

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4 Pediatric neuraxial blocks: adjunct analgesics to local anesthetics

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ABSTRACT

Pediatric regional anesthesia is developing rapidly. Using ultrasound improved the application of regional techniques in children and contributed to their safety. At present, peripheral blocks are more often used than central neuraxial blocks. However, local anesthetics in regional anesthesia in children have certain disadvantages. The combination of adjuvant anesthetics with local anesthetics has brought many benefits. Compared to adult patients, the choice of adjuvant anesthetics for pediatric neuraxial anesthesia is limited. Clonidine is the only proven safe additive anesthetic for neuraxial blocks. Morphine, ketamine, and dexmedetomidine may be used in certain circumstances.

Keywords: *neuraxial blocks; children adjuvants; local anesthetics*

INTRODUCTION

Regional anesthesia is the future of pediatric anesthesia. The use of peripheral blocks in children over three years is very popular. However, neuraxial blocks are still used in daily practice in all pediatric ages and mainly refer to caudal and epidural blocks and not very often for intrathecal application of local anesthetics (LA). Complications of neuraxial anesthesia in children are six times more frequent than with the application of peripheral blocks and cause caution in using adjuvant analgesics with LA for neuraxial blocks (1,2).

LIMITATION OF LOCAL ANESTHETICS

The limitation of LA is the insufficient length of action and side effects on the cardiovascular and central nervous systems. Extending the length of action of LA is possible by increasing the dose, using dual-shot techniques or continuous use, which increases the possibility of LA intoxication. In the case of continuous use of LA, there is an additional risk of catheter dislocation and infection (3). The danger of using long-acting LA or continuous block is that a motor block also develops in addition to the sensory block, which is undesirable in the postoperative course due to the increased frequency of complications. The typical analgesic effect of LA after a single application usually lasts 4-12 hours. However, acute surgical pain lasts longer, up to 72 hours. In children, the continuous use of LA approaches the toxic limits of the concentrations of these drugs.

ADJUVANT ANESTHETICS

The mentioned problems were partially solved by the use of drugs called adjuvant anesthetics or LA additives. By definition, adjuvants are drugs that increase the effectiveness or potency of other drugs when administered simultaneously and have a synergistic effect. In this sense, adjuvants prolong the action of LA - especially the sensory block, accelerate the onset of LA, reduce the possibility of unwanted effects of LA and enable the use of lower concentrations for continuous use. At the same time, they provide hemodynamic stability, have a sedative effect, and reduce the need for anesthetics; emergence from anesthesia is easy and calm without delirium, tremors and pain. A combination of LA and adjuvant anesthetics is ideal for one-day surgery (4).

Two basic requirements exist for an additive anesthetic to be used safely in combination with LA or another additive anesthetic. The first is that the formulation of the drug is preservative-free (morphine, alpha 2 adrenoceptors and ketamine S are preservative-free). Another requirement is that meta-analyses have proven the absence of neurotoxicity for a given drug. Animal studies have shown the absence of neurotoxicity for LA, preservative-free morphine and clonidine, but not for ketamine (5). The only proven safe additive, according to the mentioned standards, is clonidine. Under certain circumstances, it can be preservative-free morphine, ketamine and dexmedetomidine. In addition, the exact mechanism of action of the drug as an adjuvant must be known.

These drugs are divided into two large groups: non-opioid and opioid adjuvants. Non-opioid adjuvants are vasoconstrictors, alpha 2 adrenoceptor agonists, anti-inflammatory drugs, acetylcholine esterase inhibitors - neostigmine, adenosine, ketorolac, midazolam, magnesium sulfate and sodium bicarbonate. Opioids can be lipophilic and hydrophilic. It would be best to always use formulations without

preservatives (benzethonium chloride and chlorobutanol) because they are histotoxic. When choosing an adjuvant drug, the benefit should be weighed against potential risks, the child's age and the drug's effect on comorbidities. Only a few drugs from the group of adjuvant anesthetics used in adult patients are considered safe for use in the pediatric patient population (6). It should be emphasized that midazolam, neostigmine and buprenorphine were tested in children as off-label drugs without adequate preclinical tests, which limits their use as additives. The drug can be declared an additive anesthetic if it prolongs analgesia by 20 to 50% compared to LA and works at least 2 hours longer than the control group. Table 1 shows that there are recommendations, with levels of evidence for each adjuvant anesthetic concerning the applied techniques of neuraxial anesthesia in pediatric patients(1).

Table 1. Recommendations and levels of evidence for each adjuvant anesthetic concerning the applied techniques of neuraxial anesthesia in pediatric patients

NEUROAXIAL BLOCK	*DRUG*	*LEVEL OF EVIDENCE*	*DOSES OF DRUGS*
Spinal block (ex-premature baby, neonate)	*Clonidin*	A_2	*1-2μg/kg*
Spinal - older child	*Clonidin* *Morphine*	A_2 A_2	*1-2μg/kg* *10-30μg/kg*
Caudal block (ex-premature baby, neonate, infant)	*Clonidin*	A_1	*1 μg/kg*
Caudal block >1 year	*Clonidin* *Dexmedetomidin* *Morphin* *Racemic and S Ketamine (>4 years)*	A_1 A_2 A_2 B_3	*1-2 μg/kg* *1-2 μg/kg* *33-50μg/kg* *0,5mg/kg*
Continuous epidural with the right position of the tip of the catheter	*Clonidin*	A_3	*0,1 μg/kg/h*
Continuous epidural with the suboptimal position of the tip of the catheter	*Morphine* *Synthetic opioids*	A_3 A_3	*33-50μg/kg as interminttent bolus 1-3 x daily*

Opioids: have been used for 50 years for this purpose. Historically, they are considered the gold standard for evaluating the effectiveness of adjuvant anesthetics, especially morphine. Their action in combination with LA is at the level of the spinal

cord via opioid receptors, which are also affected by endogenous opioids. The most dominant action appears to be on μ receptors, whereby opioids selectively modulate the activity of A and C fibers. Enkephalins bind to δ receptors causing spinal analgesia. Dynorphin binds to k receptors, causing analgesia and sedation by hyperpolarizing afferent sensory neurons. It was estimated that they prolonged analgesia with LA from 4 to 24 hours. The optimal choice of opioids as an adjuvant is still controversial. Morphine, fentanyl, sufentanyl, buprenorphine, and diamorphine are used in children for neuraxial blocks based on models from clinical studies. Morphine is hydrophilic; compared to other opioids, it remains longer in the cerebrospinal fluid, spread cephalic which prolongs the exposure of rostral receptors to opioids and, thus, the appearance of side effects (nausea, vomiting, itching, urine retention, sedation, respiratory depression). It is used in spinal surgery in older children, sometimes without LA. Administration of morphine requires supervision of the child for the next 12-24 hours. Its benefit in the caudal block has been proven. Prolongs analgesia for up to 12 hours in 30-50 μg/kg pro doses. It is a good alternative when the tip of the epidural catheter is not in the ideal place. It is usually given as a 20-30μg/kg bolus and continuously 1 μg/kg/h (7). Fentanyl is lipophilic; even without LA, it shows local analgesic effects but in high concentrations. In combination with LA, it delays the onset of sensory and motor block and prolongs analgesia for 2-4 hours. It does not prolong the motor block to that extent. Fentanyl changes the pH of the solution in combination with LA, thus reducing penetration into the nerve fiber. There are works where neonates are given intrathecally/spinally, like sufentanyl. The benefit of epidural administration of synthetic opioids in combination with LA in children has not been proven(8). Sufentanyl is lipophilic and 6-10 times more potent than fentanyl. It is more liposoluble than other opioids, so its effect is faster and shorter, with many side effects. It causes drowsiness more than respiratory depression. Its action is fast but short (up to 3 hours). These properties of the drug make it popular for continuous epidural anesthesia and patient-control analgesia in children. In thoracic and abdominal pediatric surgery, doses of sufentanyl as adjuvant LA are initial bolus of 0.5-1μg/kg and infusion of 0.1-0.3μg/kg/h. Buprenorphine is a highly lipophilic partial opioid agonist. By blocking voltage-dependent Na channels, it exhibits a local anesthetic effect. Its metabolite norbuprenorphine also exhibits analgesic activity. Diamorphine is an analog of morphine. It has a faster and shorter action than morphine.

Vasoactive drugs: show the best effect in combination with lidocaine. The mechanism of action is vasoconstriction, which slows down the resorption of LA and antinociceptive action by presynaptic inhibition via alpha 2 adrenoceptors. Adrenaline is the first used vasoconstrictor adjuvant. Ischemic changes in the spinal cord can occur with the continuous action of adrenaline. In neonates, it prolongs analgesia twice as much as in older children, where it shows a minimal effect on analgesia. It is used for the test dose for the caudal block when bupivacaine is used in a dilution of (1:200000).

Alpha 2 adrenergic agonists: show sedative, analgesic and sympatholytic effects and hemodynamic stability of the patient. They have a central effect through receptors in the posterior horns of the spinal cord. Locally, they cause vasoconstriction, which reduces LA uptake. Clonidine and dexmedetomidine are given by intrathecal, epidural and caudal approaches. The effects are dose-dependent. Dexmedetomidine is seven times more selective than clonidine - it is more specific for alpha 2 than alpha 1 receptors. Both drugs delay the onset of sensory-motor block, prolong the duration of action of LA, and delay recovery from the motor blockade. Side effects are bradycardia and hypotension. Oral, intrathecal, and intravenous dexmedetomidine has also been shown to prolong the action of intrathecal LA. Clonidine and dexmedetomidine are given with LA in the caudal block and clonidine in continuous epidural in children (4). There are preservative-free formulations of clonidine. Doses of clonidine are 1-2 μg/kg. Larger doses cause sedation, bradycardia, and hypotension, and there is a risk of apnea, especially in neonates and infants. It can be given continuously at 0.1 μg/kg/h with bupivacaine or ropivacaine epidurally. Due to respiratory depression, it is not recommended for ex-premature babies and infants younger than 3 months (9).

Other medicines: ketamine is administered systemically and epidurally, as a preservative-free formulation, as racemic Ketamine and Ketamine S. This drug is not administered intrathecally, nor in neonates and infants, due to the described apoptotic effect on spinal cord neurons. It is used for caudal block in a 0,25-1 mg/kg pro dose and can cause sedation, hallucinations, nystagmus, nausea, and vomiting in larger doses. Racemic and S ketamine show a similar effect on the duration of analgesia (10). Midazolam acts as an indirect GABA agonist or via benzodiazepine receptors in the spinal cord. It is available in the preservative-free form and is added to 0.5% hyperbaric bupivacaine for subarachnoid block. Clinical studies on intrathecal and epidural administration of midazolam in children are described. Doses of midazolam is 50 μg/kg. Trodone: is a synthetic analog of codeine. Epidural use in children is controversial. According to some studies, it prolongs analgesia for up to 14 hours after abdominal procedures. Doses are 0.5-1 mg/kg. Neostigmine: acetylcholinesterase inhibitor acts through muscarinic receptors, increasing the acetylcholine at the terminal nerve endings and prolonging analgesia. It is given intrathecally and is accompanied by significant side effects: nausea and vomiting. Commercial preparations contain preservatives: paraben and methylparaben.

CONCLUSION

In pediatric patients, clonidine is the only proven safe additive anesthetic for neuraxial blocks. Morphine, ketamine, and dexmedetomidine may be used in certain circumstances. Other off-label drugs and the newer generation of additive anesthetics require additional research to use neuraxial blocks in children safely.

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5 Cancer pain: modern pharmacoterapy management

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ABSTRACT

Pain is an unpleasant feeling and emotional experience associated with real or possible tissue impairment or described as such impairment. One of the first methods for diagnosis and the basis of further adequate therapy is pain history and pain anamnesis. The simplest unidimensional tool for pain measuring is the Numerical Pain Scale (NSB). In the assessment of neuropathic pain component, two multidimensional assessment tools help us quickly and efficiently in daily clinical work: Pain Detect and DN4 questionnaire. An individual approach to each patient is an imperative of personalized and precise medicine, which we strive for in modern pharmacotherapy of cancer pain. The step-by-step approach to cancer pain therapy, has today been replaced by the use of an analgesic elevator. There is great fear of prescribing opioid analgesics due to their possible side-effect of respiratory depression, opioid-induced constipation, tolerance and addiction. Adjuvant analgesics recommended for combination with basal opioid analgesia are: tricyclic antidepressants, gabapentinoides, selective inhibitors of noradrenaline and serotonin uptake, long-acting corticosteroids, bisphosphonates (zolendronic acid). Palmitoylethanolamide (PEA) has found its place in the pharmacotherapy of mixed cancer pain along with administered coanalgesics and of course basal opioid analgesia.

Key words: *cancer pain, pharmacotherapy, analgesics, adjuvant analgesics, supplements.*

INTRODUCTION

Pain is an unpleasant feeling and emotional experience associated with real or possible tissue impairment or described as such impairment (1).

Brevik's study talks about inadequate treatment of cancer pain. Even half of the practicing doctors do not consider the patient's quality of life, given that he is suffering from an oncological disease. A smaller part of the ordinary doctors does not recognize pain as a problem that endangers the patient's health, while some, treating the basic disease itself, think that there is no need to give this type of symptomatic therapy. Some doctors do not have time to discuss with the patient about his complaints, while some do not even dare to ask the patient about the pain because they do not know an adequate pharmacotherapeutic solution for the treatment of their cancer pain (2).

During the step towards pain relief, the patient's pain history was taken correctly. Pain anamnesis - The pain is subjective feeling so it measured pain hard, but there are principles for pain evaluation. It is necessary for the patient to believe when he claims to have pain, especially if he is suffering from a malignant disease!!! Estimate the weight of pain using the appropriate tools is recommened (3).

The doctor must collect the following data from the pain history of each patient and from pain ananesis:

- Localization and spread of pain intensity and quality of pain (pressure, anneal-ing, ignition, stabbing);
- Duration of pain (occasional and constant pain);
- Factors that mitigate and reinforce pain.

One of the first methods for diagnosis and the basis of further adequate therapy is pain history. As already mentioned, it is necessary to find out information about: the localization and spread of the patient's pain, the intensity and quality of the pain (pressure, burning, burning, burning, stabbing, tingling, tingling), the duration of the pain (occasional and constant pain) and the factors that lead to relief or enhancing the patient's pain. Pain is a subjective feeling and we must believe the patient when he says that he feels pain, but in addition there are principles of pain evaluation in terms of evaluating the severity of pain using appropriate tools (4).

The simplest unidimensional tool is the Numerical Pain Scale (NSB) - when the patient is asked to state on a scale of 1-10 how much he feels pain. Of course, due to possible abuse, the patient should be emphasized to be realistic in giving this assessment, because the adequacy of his further treatment of that painful condition will depend on it. Based on these pain values, pain can be classified by intensity into:

- Mild (weak) pain – NSB values = 1-3;
- Moderate pain - NSB values = 4-6;
- Strong (severe) pain – NSB values = 7-10.

In addition to this scale, this group of tools also includes the Visual Analogue Scale, which is suitable for monitoring and therapeutic pain control, the Verbal Scale, the Facial Scale (5).

In the assessment of neuropathic pain component in the patient's total cancer mixed pain, two multidimensional assessment tools help us quickly and efficiently in daily clinical work, namely:

1. Pain Detect questionnaire - allows the ordinary to have a clear picture after surveying and examining the patient, whether the patient's pain is only of nociceptive origin or has a neuropathic component, which is very important because of the modality of future pharmacotherapy that the ordinary will decide to prescribe to the given patient. This questionnaire was validated and translated into Serbian, on the basis of which the patient's total score is calculated and a conclusion is drawn about the presence of a neuropathic component of his pain. If the patient's score is 1-12, for that patient it is unlikely (< 15%) that his pain has a neuropathic component so that it is mainly based on the nociceptive component which is dominant. The patient's score 13-18 is an unclear zone, ie. a neuropathic pain component may be present and leaves the ordinarius to assess the patient's pain type using other methods. If the patient has a score of 19-38, it is clear that his pain has a predominantly neuropathic component (6).
2. Neuropathic Pain Diagnostic Questionnaire (DN4 questionnaire) - by anamnestically surveying the patient, it enables a quick and easy orientation to the prescribing doctor about the neuropathic component of pain using 4 simple questions with 10 response modalities, on which further pharmacotherapy of the patient's pain condition will be based. The total score that a patient can achieve is 10, and a value of 4 or more is taken with high statistical significance for the presence of a neuropathic pain component of that patient (7).

If, by applying all the mentioned tools, it is not possible to clearly differentiate the type of pain of the patient, it is necessary to apply one of the supplementary diagnostic methods.

MAIN LECTURE TEXT

The concept of total pain was developed by Cicely Sounders, which includes - physical, social, mental and psychological pain (8). Consequently, objectives of pharmacological treatment of the chronic cancer pain are:

- Reduction of pain intensity;
- Removal of insomnia - improvement of sleep;
- Removal of joint depression and anxiety;
- Improving the quality of life (social and emotional).

Drug choice dependens on individual approach. In the style of new trends in pharmacotherapy, an individual approach to each patient is an imperative of personalized and precise medicine, which we strive for in modern pharmacotherapy of all diseases.

Accordingly, it is necessary to introduce the patient with a therapy plan and installing realistic expectations! When choosing the medicine, take care of:

- The effectiveness of the drug;
- Security / Tolerance of the drug;
- Method of drug application;
- Interactions with other drugs;
- Potential side effects;
- Risk of overdose and abuse;
- Patient adherents and prices (9).

WHO recommendations for pharmacological treatment of cancer pain include five basic settings (10):

- Peroral analgesics application;
- Application in properly prescribed intervals;
- Choosing analgesics according to analgesic ladder;
- Individual approach;
- Careful medical documentation.

The WHO analgesic scales imply that non-opioid analgesics are prescribed for mild pain, weak opioids in combination with non-opioids and co-analgesics for moderate pain, and strong opioids in combination with non-opioids and adjuvant drugs for severe pain (11). A more recent revision of these recommendations includes a fourth analgesic step, which includes parenteral (spinal or epidural) application of opioids within the so-called Patient-controlled analgesia (12).

The latest recommendations today imply the very safe and clinically effective use of an analgesic elevator instead of a step-by-step approach within the analgesic ladder. Analgesic lift implies that the second analgesic step is skipped and that it is safe and with an adequate analgesic response to transfer the patient immediately from non-opioid analgesics to gradual titration with smaller doses of opiates in cancer pain (13).

For this therapeutic indication (cancer pain) - extended-release (long-acting) opioids are recommended because they have: prolonged time until maximum drug plasma concentration is reached, decreased fluctuations of drug concentration, prolonged analgesia within therapeutic response, decreased risk of potential toxicity and respiratory depression, decreased potential abuse, dosing is less frequent and it makes patient adherence to the treatment better, as well as stable plasma drug concentration in correlation of analgesia duration.

Initial opioid dose should be low and long-acting opioid dose should be gradually increased and titrated considering daily requirements of short-acting opioid formulation due to pain breakthrough (1/6 of long-acting opioid total daily dose). It is mandatory for patients on long-acting opioid treatment to be provided with fast-acting medication for breakthrough pain treatment (13).

The following long-acting strong opioids formulations are available in Serbia – oxycodone, oxycodone/naloxone fixed combination, hydromorphone, tapentadol, fentanyl. From imidiate realise (IR) strong opioids for breakthrough pain pharmacotherapy, in Serbia are available: oral formulations of morphine sulfate and oxycodone IR capsules. Out of weak analgesics in Serbia, tramadol is available for independent use or as fixed dose non-opioid combination tramadol/paracetamol – indicated for moderate pain treatment. Treatment of moderate cancer pain starts with tramadol as a weak opioid analgesics relative to pain intensity.

The common characteristic of all opioid analgesics is that in addition to the therapeutic effect - analgesia in the central nervous system (CNS), they also lead to unwanted (side) effects by agonizing opioid receptors located outside the CNS. This primarily refers to receptors in the gastrointestinal system. The agonization of that receptors, all opioids lead to the only side effect to which tolerance is not established over time, which is opioid-induced constipation which is a part of Opioid-induced bowel dysfunction (OIBD) (14). The basis of this dysfunction is – affected longitudinal propulsive peristalsis, sphincter tone has been increased and liquid content has been changed due to increased absorption and reduced secretion. This is the only side-effect of opioids that does not develop tolerance and that is a huge problem in clinical oncology practice. Prophylactic laxatives that should be prescribed concurrently with opioid analgesics, do not eliminate the cause of opioid-induced bowel function disorder. They are mostly ineffective and may result in additional side-effects, and their only target is colon. For this type of constipation use of macrogol is recommended (15).

There is great fear of prescribing opioid analgesics due to their possible side-effect of respiratory depression (reduced sensitivity of the respiratory center to carbon-dioxide), however, it has been shown in clinical practice that tolerance this effect occurs rapidly.

It is well known that administration of morphine (and other opioids) may lead to the development of tolerance and addiction. Withdrawal syndrome may occur after sudden cessation of therapy, or at administration of opioid antagonist, such as naloxone. Use of opioid analgesics may be accompanied by physical and/or psychological dependence and tolerance development. Symptoms may be relieved by dose reduction, or change in dosage form, as well as by gradual morphine withdrawal (16).

According to all aforementioned, characteristics of an ideal opioid would be: short half-life, long-acting effects, predictable pharmacokinetics, no clinically significant metabolites, rapid-onset, easy titration, without 'plateau' drug dose, with minimum side effects.

Given that the majority of oncology patients with cancer pain have not only a nociceptive but also a neuropathic component of pain (which is validated by the mentioned questionnaires) within mixed cancer pain, ESMO recommendations for adequate pharmacotherapy of this entity imply the inevitable combination of adjuvant analgesics with opioids (10).

Adjuvant analgesics recommended for combination with basal opioid analgesia are:

- ❖ Tricyclic antidepressants (TCA);
- ❖ Anticonvulsive (gabapentinoides);
- ❖ Selective inhibitors of noradrenaline and serotonin uptake (SNRI);
- ❖ Long-acting corticosteroids (dexamethasone);
- ❖ Bisphosphonates (zolendronic acid).

An effective drug from the TCA drugs for this therapeutic indication is amitriptyline, which is rarely used today (at least in oncology patients) due to its cardiotoxicity as it leads to prolongation of the QT interval (17).

From the group of gabapentinoids, the use of pregabalin and gabapentin is recommended in patients with good creatinine clearance. The mechanism of their action is binding to calcium channels and in this way they prevent the influx of calcium ions, which consequently leads to disruption of potential conduction. Adequately explained their use with opioid analgesics leads to adequate relief of the neuropathic component of their pain and the absence of interactions and side effects of therapy, which leads to good compliance (18). The most common side effect of these drugs is the appearance of dizziness, which is tolerable after the first week of drug administration, then the following can occur less often: drowsiness, headache, weight gain, dry mouth, fatigue.

Duloxetine belongs to group of selective inhibitors of noradrenaline and serotonin uptake. Serotonin (5-HT) and noradrenaline are key modulatory transmitters on descending inhibitory roads pain. In an animal model has been proven to duloxetine dose-depending increases extracellular levels 5HT and on the different parts of the brain, normalizations of the pain tolerance and reduces persistent pain, and it does not lead to neurological deficit. Even duloxetine can be safely combined with pregabalin for more effective treatment of the neuropathic component of pain in mixed cancer pain (19). In addition to duloxetine, this group of antidepressants also includes venlafaxine, but it is prescribed less because of its potential to cause hypertension, while duloxetine has side effects only in the form of gastrointestinal complaints and is safer to use.

The use of corticosteroids is also justified for this therapeutic indication. The advantage and recommendation is to use only long-acting cortico preparations, i.e. dexamethasone because it has: minimum mineralcortic activity, better analgesic and antiinflammatory response from the other cortico drugs, longer action, antiedematous effect, it is indicated also for nausea, vomiting and loss of appetite as part of palliative care for cancer patients (20).

Bisphosphonates are also very useful coanalgesics due to the inhibition of osteoclast activity. Patients suffering from breast cancer, prostate cancer and lung cancer have the highest prevalence of metastases on the skeletal system as part of metastatic disease. Parenteral administration of third-generation bisphosphonates - zolendronic acid suppresses osteoclast activity in oncology patients with bone metastases, reduces the pool of proinflammatory cytokines, and thus prevention of potential pathological fractures in these patients is carried out. One of the rare side effects of its use is osteonecrosis of the lower jaw. It is necessary for patients who are on bisphosphonate therapy to regularly check the values of nitrogenous products before therapy due to the elimination of bisphosphonates from the body (21).

In addition to the standard supplements in pain therapy that have been used so far, the new molecule palmitoylethanolamide (PEA) has found its place in the pharmacotherapy of mixed cancer pain along with administered coanalgesics and of course basal opioid analgesia. PEA is endocanabinoid anandamide amide, endogenous amide. The interest in PEA increased after the discovery that this substance has the ability to inhibit the release of inflammatory mediators from activated mastocities and reduce infiltration and activation at the site of injury to nerves. The concept that lipid N-acylethanolamines as PEA act on autocoid mechanism for the first time she proposed Rita Levi-Montalćini, Nobel Prize winner (Rita Levi-Montalcini).

According to this mechanism, PEA is synthesized as a result of injury or inflammation in order to focus on this pathological condition. PEA manifests its effects by reducing migration and degranulation of mastocities, attracting neutrophils and excessive activation of astrocytes and glial cells. In this way, under the action of PEA, mastocities and glial cells are transformed from activated immune cells in the resting cells (22).

CONCLISION

The pain is difficult to measure - what for one person it can be unbearable, it can be treasures for the other. The pain can be nocyceptive, neuropathic or mixed!!! It is not only important to the intensity of pain, but as pain affects the patient's life! Many oncology patients have more comorbids and use more drugs, which makes the pain treatment even more complex. The rational choice of analgesics and dose is crucial. Chronic cancer pain is a biopsychosocial phenomenon with a multitude of factors that operate mutually, which requires interdisciplinary multimodal pain therapy.

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6 Paravertebral block for the prevention of chronic postsurgical pain after breast cancer surgery

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ABSTRACT

Chronic postsurgical pain after breast cancer surgery is a major reason for physical disability and deterioration of the quality of life. Different patient and treatment related factors are associated with persistent pain, lasting more than 3 months, after breast cancer surgery. There are a multiple approaches in prevention of this kind of pain. There is increasing interest in the role of paravertebral block as a part of strategy in chronic pain prevention.

Key words: *PMPS, PVB*

INTRODUCTION

Chronic pain, the most troubling symptom after breast surgery, is common and leading cause of disability and suffering and almost always this pain is resistant to treatment (1). It is frequently reported by patients undergoing breast cancer surgery, with a prevalence of up to 35% (2). According to a Finnish study (3), more than half of women who have breast cancer surgery have continuing pain a year after surgery. This prospective study found that 50% of patients had mild pain and 16% had moderate to severe pain 1 year after breast cancer surgery.

FACTORS RELATED WITH CHRONIC PAIN AFTER BREAST SURGERY

Factors associated with persistent pain are chronic preoperative pain, axillary lymph node dissection, radiotherapy, and adjuvant chemotherapy. It is well-known that

the most morbid procedure performed in breast cancer surgery is the axillary lymph node dissection. According to this, the most painful procedures is radical mastectomy. Also patient-reported lymphedema at 6 months corresponded to a higher pain score. Beside treatment related risk factors for chronic pain, there are some patient related factors. Younger age and higher BMI are associated with greater pain (4,5,6). Importantly, patients' degree of anxiety and depression before surgery are correlated to the amount of pain they experience at 6 months.

POSTMASTECTOMY PAIN SYNDROME

Definition of post-breast surgery pain syndrome (PBSPS) is pain of at least moderate severity, present for at least six months, located in the ipsilateral breast/chest wall, axilla, or arm, possesses neuropathic qualities, present at least 50% of the time, and may worsen with shoulder girdle movement (7). Postmastectomy pain syndrome (PMPS) is a subset of PBSPS. PMPS is a type of neuropathic pain, a complex chronic pain state that is typically associated with nerve fiber injury. This chronic pain is believed to be related to injury of the sensory nerves to the breast, chest, and upper arm/axilla. The definition of PMPS has not been standardized. The current definition for PMPS used by the International Association for Study of Pain is "chronic pain in the anterior aspect of the thorax, axilla, and/or upper half of the arm beginning after mastectomy or quadrantectomy and persisting for more than three months after surgery" (8). The important distinction that neuropathic pain does not only arise following oncologic breast cancer treatments, but rather, all breast surgeries, including breast reconstruction, cosmetic breast surgery, and breast reductions (9). There is a new classification system for neuropathic pain following breast surgery (10). The neuropathic pain is devided into phantom breast pain (PBP), injury to the intercostobrachial nerve, neuroma formation (from direct injury or from entrapment of nerve in scar), and other nerve injury pain that does not fall into any of the preceding categories. The symptoms of PBP are similar to those of postmastectomy pain syndrome (PMPS) although the patients with PBP report the persistence of sensations within their amputated breast. PBP is characterized by disturbing and painful sensations in the nipple area alone or involving the entire breast or segment that was resected. These sensations may persist for years after the operation. The etiology includes central nervous system sensitization and cortical reorganization, which are associated with nerve damage and are considered to have a role in pain chronification (11). The injury to neurons results in spontaneous and evoked hyperexcitability.

Postmastectomy pain syndrome (PMPS) can be caused by direct nerve injury (eg, transection, compression, ischemia, stretching, and retraction) during the breast cancer operation or from subsequent formation of a traumatic neuroma or scar tissue (12,13,14). Alternatively, indirect nerve injury can occur intraoperatively or

postoperatively. Intraoperatively, retraction and poor arm positioning can stress and compress peripheral nerves (15). Postoperatively, stretch and compression injuries can occur from hematoma, seroma, and scarring (16). Different types of sensory disturbances (eg, tingling, burning, numbness) can then result from nerve injury (17).

BREAST INERVATION

The breast parenchyma and overlying skin are innervated by the anterior and lateral cutaneous branches of intercostal nerves T3 to T6. The ICBN is most frequently injured during axillary dissection, which is a major risk factor for PMPS (9). Breast cancer operations can damage the brachial plexus, ICBN, lateral cutaneous branch of the second intercostal, and long thoracic and medial and lateral pectoral nerves that innervate the breast, chest wall, and ipsilateral extremity (13). In particular, surgical procedures in the upper outer quadrant of the breast and axilla, where major nerves traverse the operative field, are particularly vulnerable to nerve injury (18). In addition, local radiation treatments and neurotoxic systemic therapy (eg, taxanes, plati-num agents, vinca alkaloids) may also exacerbate PMPS (19,20) .

PARAVERTEBRAL BLOCKS

Chronic post-surgery neuropathic pain (PSNP) involves specific mechanisms, such as nerve trauma (intercostobrachial neuralgia, injury to the nerves innervating the breast and armpit), leading to the spontaneous generation of ectopic impulses and exaggerated excitability, affecting the injured and even uninjured neighboring sensory afferents. The profound analgesic effect of regional anesthesia, such as para-vertebral block (PVB), may reduce the sensitization underlying CPSNP, therefore accounting for the specific preventive effect on CPSNP (21). Regional anesthesia may prevent CPSP by limiting the nervous system remodeling that occurs when a persistent nociceptive stimulus is applied, resulting in hyperalgesia, allodynia, and sustained wound pain.

This preventive effect may be of potential interest because the prevalence of CPSNP is high after breast surgery, exposing patients to a specific disease burden. Unfortunately, most studies evaluating the incidence of CPSP after breast surgery do not monitor neuropathic characteristics or use very heterogeneous evaluation tools.

The perioperative pain management appeared as a major point to reduce the risk of chronification of pain after surgical trauma. The possibility of preventing CPSP by specific interventions, such as regional analgesia (RA), has been reviewed.

The most recent literature reviews in two meta-analysis, authors have concluded that PVB can limit the incidence of CPSP 6 months after BCS (22,23). The most recent

and largest RCT, which was not primarily designed for the CPSP outcome, reported no protective effect of PVB in the prevention of CPSP at 12 months. In the larger meta-analysis, from 2020 they found no clinical effect of PVB on CPSP after breast surgery at 3, 6, or 12 months (24). The results of this meta-analysis suggest that the incidence of CPSNP 6 months after BCS may be 52% lower in the PVB group, with a low quality of evidence. The number needed to treat estimates suggested that 12 (7–56) patients would need to be treated by PVB to prevent CPSNP in one patient . These results are consistent with published findings suggesting that prolonged afferent interruption by intercostal blocks or thoracic epidurals may reduce the risk of CPSNP (24). In another study from 2014, it was described a lower incidence of pain in association with a multi-day continious PVB, as well as a decrease in pain-related physical and emotional dysfunction 1 year after mastectomy (25). A different prospective study investigated the effect of continuous PVB for 3 days after surgery (25). The continuous ropivacaine infusion in the experimental group reduced the pain intensity and provided better physical and emotional function at 12 months after the surgery compared to control group which received only a single shot PVB.

A single-center, double-blind study showed that ultrasound-guided multilevel paravertebral block lowered the incidence of chronic pain 3 months and 6 months after partial mastectomy with or without axillary lymph node dissection. Cochrane review (26) on chronic pain also found that paravertebral block reduced chronic pain after breast surgery but graded the evidence as low (23). Another recent review and meta-analysis concluded that the data on chronic pain for PVB are too scarce to be conclusive. The quality of evidence was considered to be low, mainly due to a lack of adequate blinding. Nonetheless, although the existing evidence is weak and conflicting, there is increasing interest in the role of paravertebral block in preventing chronic pain after breast cancer surgery (23).

Reacently published observational study investigated interaction between the effect of catastrophizing and regional anesthesia (RA) on chronic PMBP. Specifically, RA was associated with reduced pain severity and pain impact 3, 6, and 12 months postoperatively, but only among those with high baseline catastrophizing scores. In addition, both RA and lower catastrophizing scores were associated with lower incidence of persistent opioid use (27).

CONCLUSION

Paravertebral blockade is an excellent regional anesthetic technique for primary or adjunct anesthesia and analgesia. Appropriate patient selection, anatomic knowledge, and proper technique are essential to patient safety. According to evidences from literature there are still conflicting data. Patients undergoing breast cancer surgery, have benefit

from preoperative multilevel single-shot thoracic PVB at six months. This block also improves postoperative analgesia and reduces neuropathic pain within one year after surgery.

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7 Chronic and recurrent pain in patients on hemodialysis: causes and therapeutic approaches

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ABSTRACT

Hemodialysis (HD) is the most prevalent type of renal replacement therapy globally. HD population is ageing and experiencing multiple comorbid conditions. Pain is a common symptom in HD patients with a prevalence ranging from 21% to 92%. It may be associated with underlying renal disease, comorbid conditions commonly related with HD (carpal tunnel syndrome caused by dialysis-related amyloidosis, calciphylaxis, pruritus), or linked to HD procedure itself (hemodialysis headache, muscular cramps, intestinal/cardiac ischemic pain secondary to intradialytic hypotension, pain related to vascular access cannulation). Pain has profound negative effect on patients' psychological well-being, mobility, quality of life and survival. Despite its importance and frequency, data on this issue is limited in the available literature. Also, reported results vary substantially due to inconsistent methodology. Besides insufficient awareness of the problem, poor medical education and fear of possible side effects to drugs preclude adequate pain management in this distinct population. Hopefully in the future more knowledge about pathophysiolical mechanisms of certain types of HD-related pain and expanded involvement of pain specialists with this population shall improve its management and outcomes.

Key words: hemodialysis, pain, hemodialysis headache, calciphylaxis, vascular access, analgesics

INTRODUCTION

Chronic kidney disease (CKD) has emerged as one of the most prominent causes of death and suffering in the last decades (1). It is associated with numerous

comorbidities and detrimental effect on the quality of life, thus presenting a substantial burden for the healthcare system (2).

Hemodialysis (HD) is still the most prevalent type of renal replacement therapy globally (3). The procedure has evolved remarkably in the last two decades related to technical improvements, new treatment options for anemia and secondary hyperparathyroidism, and novel evidence in the areas of iron therapy, diabetes management and physical exercise (4). Nevertheless, these advancements have still failed to translate into desired clinical benefits.

Analogous to the general population, HD population is ageing and longer survival is only contributing to the development and presentation of new comorbidities which adversely affect patients' quality of life and add to their discomfort. One of the most important qualitative parameters when evaluating patient's quality of life is bodily pain (5). This lecture shall examine the available and most recent data related to pain prevalence, origin, severity, outcomes and treatment options in this complex population.

PAIN PREVALENCE IN HD POPULATION

The reported prevalence of chronic pain in the HD population ranges from 33% to 82%, while the prevalence of acute or recurrent pain ranges from 21% to 92% (5). Such high variability may be related to the inconsistent methodology which hampers the comparison of the results. The prevalence of headache ranges from 4% to 76.1%, presence of chronic musculoskeletal pain from 57% to 77%, neuropathic pain from 2% to 62%, abdominal pain from 13.5% to 15.7%, back pain from 14.3% to 52%, chest pain from 2.6% to 44%, bone pain from 37% to 96.5% (6). Some studies reported significant association between the presence and severity of pain and female gender, lack of spouse, Caucasian ethnicity, unemployment, low income, higher number of comorbidities, longer dialysis vintage, Charson Comorbidity Index, absence of diabetes, and presence of depression in HD patients (7, 8). Nevertheless, the results are highly variable and there are more recent studies with contradictory conclusions (9, 10).

PAIN ORIGIN AND PAIN SEVERITY IN HD POPULATION

Pain in HD population is multifactorial and multidimensional. Primary renal disease (e.g. polycystic renal disease, amyloidosis, calculosis) itself may cause painful reaction. Comorbid conditions that are associated with pain, such as ischemic peripheral artery disease, diabetic neuropathy, age-related osteopenia/osteoporosis, CKD-mineral bone disease, and peripheral uremic neuropathy are also commonly present in this population. Certain types of pain are related to HD procedure, such as dialysis headache

(DH), muscular cramps, intestinal/cardiac ischemic pain secondary to intradialytic hypotension, or are caused by comorbidities or treatments which are commonly associated with prolonged HD therapy (carpal tunnel syndrome caused by dialysis-related amyloidosis, calciphylaxis, pruritus, or erythropoietin injections). Finally, vascular accesses are a commonly overlooked treatment-specific source of pain in HD population. Central catheters can result in osteomyelitis and discitis, and arteriovenous fistulae can be associated with acute pain related to cannulation or lead to painful ischemic neuropathies (11, 12).

SOME SPECIFIC CAUSES OF PAIN IN HD POPULATION

According to the International Headache Society criteria, DH has no specific characteristics, occurs during or is caused by HD and resolves sponetaneously within 72 hours after the HD session has ended. Evidence of causation is demonstrated by at least two of the following: headache develops during HD sessions, headache ceases after successful kidney transplantation, and headache worsens during dialysis and/or headache resolves within 72 hours after the end of the HD session (13). Previous studies have reported the prevalence of DH from 6.6% to 70% (14), but despite such high burden DH has been poorly studied (15).

The pathophysiology of DH is still unresolved. Possible causes include large water and electrolyte shifts during the procedure as part of the dysequilibrium syndrome, accelerated coffeine withdrawal, presence of hypertension and certain biochemical alterations (16). DH is more common in HD than in PD patients, while other features of this condition may vary (16). The diagnosis and management of DH remain a challenge for nephrologists, neurologists and pain specialists.

Pain during vascular access cannulation is another distinctive HD-related problem. According to the limited sources in literature its prevalence varies from 12% to even 80%, depending on definition and pain-assessment tools used (17). It is significantly associated with stress and anxiety, while application of topical analgesic cream, as an uncommon prophylactic measure, returned inconsistent results in alevieting the discomfort (18). Cetain cannulation techniques appear to be associated with less pain, but are, unfortunately, correlated with adverse events and technique failure. Listening to music has also been explored as a possible pain relief intervention in this setting (19).

Calciphylaxis is a deadly, painful disease with a 1-year mortality of up to 50% (20). It is commonly seen in patients undergoing HD with an estimated prevalence from 0.04% to 4% (20). The progressive arterial calcification in this condition can affect multiple body organs. In cutaneous calciphylaxis, extremely painful and non-healing nodules, plaques, and ulcers may appear. Diagnosis can be difficult and skin biopsy with histological analysis is currently the most reliable method. Treatment is challenging and

with variable success. Besides analgesic options, wound care and modification of risk factors should also be employed. Several clinical trials are currently underway that are studying targeted therapies for this condition.

PAIN ASSESSMENT IN HD POPULATION

Adequate assessment of pain for its location, severity, character and duration is the initial step in the management since the choice of initial analgesic therapy depends on the type of pain (21, 22). Elucidating neuropathic, nociceptive and mixed-origin pain in HD patients relies on the "PQRST" approach: Provokes and Palliates, Quality, Region and Radiation, Severity, and Time. Most studies which addressed pain in HD population used the visual analogue scale (VAS) to assess it, but other instruments, such as McGill Pain Questionnaire, Brief Pain Inventory, Pain Management Index, International Classification of Diseases 9 – Chronic Musculosceletal, Euroqol-5D, 6-point Likert scale and Wong-Baker scale, have also been employed.

CONSEQUENCES OF PAIN IN HD POPULATION

Pain has profound negative effects on patients receiving HD and is associated with up to a 1.5-fold increase in mortality compared with HD patients without chronic pain (23). Pain which limits daily activities is associated with functional impairment, low physical activity, poor social functioning, sleep disturbance and premature mortality (6, 24). Pain frequency and intensity also correlate with poor health outcomes in HD population, that can be partially explained by the tendency to skip or shorten HD treatments when experiencing pain, especially related to HD procedure itself (25). Furthermore, patients who suffer from pain have a higher age-comorbidity index than those who do not (26). Pain and psychological disturbances easily get involved in a vicious cycle. Depression or anxiety can intensify the perception of pain, and pain can worsen the symptoms of depression and anxiety (9). Finally, pain has profound negative impact on the quality of life of HD patients, similar to other population groups (27).

PAIN MANAGEMENT IN HD POPULATION

Adequate control of pain is extremely important to improve quality of life. Nevertheless, pain is generally poorly managed in HD population. This symptom is often neglected and considered an inevitable companion of CKD and dialysis treatment. Besides insufficient awareness of the problem, other barriers to the adequate treatment

of pain in this population include lack of medical education and fear of possible side effects to drugs.

Experts in the field recommend a holistic, stepwise and multidisciplinary approach to treating pain, starting with a thorough assessment of the symptom, its cause, and reversibility (22). Palliative care specialists and/or pain specialists should be mobilized in the team approach to treat pain in HD population. The treatment options should then be presented to and discussed with the patient and his/her family or caregivers (6). When pain medications are necessary, the World Health Organization three-step ladder approach should be followed. The most common medication used for intradialytic pain is IV paracetamol, however many patients report little benefit (28, 29). Hopefully in the future, concerns about the use of NSAIDs and increased knowledge about pathophysiology of chronic pain will contribute to practitioners' confidence with the use of major analgesics and opioid prescriptions. Alternative, non-drug therapies are also gaining popularity and might be beneficial in some circumstances. These include physical therapy, exercise, cognitive behavioural therapy, meditation, yoga, massage, acupuncture and aromatherapy.

CONCLUSION

Pain is a common and undertreated symptom in HD patients which is significantly associated with patients' quality of life, morbidity and survival. More studies are needed to elucidate the pathophysiological mechanisms and evaluate different treatment options for painful conditions in this distinct population. These observations reflect the urgent need for medical education in dialysis providers and more involvement from pain specialists in the treatment of HD patients.

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8 The role of histamine in pain in children, what do we know?

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INTRODUCTION

Histamine was traditionally examined for its involvement in mast cell activation pathways or as a catalyst for vascular alterations when its level was elevated, as in allergies, anaphylaxis, etc. However, histamine's role is not just for allergy or anaphylaxis, as many studies and academics have attempted to prove over the past 20 years, but also as a "local hormone." Neurogenic inflammation has a significant role in the pathophysiology of pain and works through many mechanisms (1-4). In this context, several studies now stress that histamine intolerance (HIT) may contribute to chronic stomach pain, head migraines, or acute and chronic neuropathic pain and may worsen attention-deficit/hyperactivity disorder (ADHD) in children. (5–7). The HIT prevalence is approximately 1% worldwide, and about 80% of those patients are adults. A lower diagnosis rate is possible in children, as children most likely do not consume as much fish, cheese, or fermented sausages as adults, and the symptoms may not be displayed clearly enough to diagnose HIT (1). Even if histamine's function in this article is not thoroughly explored, we assess the information provided and highlight histamine's contribution to pain and HIT in children.

DEFINITION

The 2008 definition of neurogenic pain was "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system," but the "Neuropathic Pain Special Interest Group of the International Association for the Study of Pain" does not accept this definition, primarily due to the two terminology differences. Treede RD et al. specifically separated terminology into two categories: disease (which can affect any

organ system) and somatosensory system (formally defined as either the peripheral or central nervous system) (8–10). The bottom line is that, depending on the lesion or condition being experienced, neuropathic pain can be split into two subgroups: peripheral or central, depending on the lesion or disease undergoing.

INCIDENCE OF NEUROPATHIC PAIN

The overall incidence of neuropathic pain worldwide in the general population is estimated to be between 7-10% (10, 11). Unfortunately, this incidence is different depending on the burdens each country faces. It is reported that over 40% of Europeans cannot control their neuropathic pain (12). The incidence of pain in children has similarly been reported at different percentages (13). Furthermore, Laney et al. and Hopkins et al. have reported that acroparesthesia in children is noticed after two years of age and occurs in 59% of boys and 41% of girls, with the median ages 7-9 years, respectively (14,15).

PAIN, HISTAMINE, AND RECEPTORS

Histamine is present in the body's two main types of immune cells (basophils and mast cells). Mast cells can be located in connective tissues, mucosal linings, the GIT, the lung, the brain, surrounding nerve terminals, and the skin, whereas basophils circulate in the vasculature (16). Both cells can produce substances that function as defenses against invaders. Histamine is a neurotransmitter that is produced by histaminic neurons in the posterior hypothalamus (17).

Pathophysiologically, the human body contains four distinct varieties of histamine receptors. Activation of these receptors can result in different symptoms based on the amount of histamine released, which is determined genetically by when or how the stimulus occurs. Receptors are seven-transmembrane G-proteins: H1, H2, H3, and H4. They modulate physiological and pathophysiological actions, such as pain (17, 18).

Astonishing is that individuals have elevated histamine levels due to activating their immune systems by substances such as cortisol (stress), inflammation, etc. Histamine is primarily degraded by the enzymes histamine N-methyltransferase (HNMT) and Diamine Oxidase (DAO). HNMT requires proper methylation to function, and DAO involves many parameters to operate appropriately (17). If HNMT and DAO (GIT) are not acting quickly (typically aren't), the body becomes overwhelmed with histamine, and reactions begin.

We must be aware that an excess of histamine does not result in an allergic reaction but rather in the breakdown of enzymes and the production of non-functioning essential compounds, injuring tissues and producing a vicious cycle of histamine release.

According to this perspective, histamine is a neurotransmitter and an essential mediator of nociceptive information in the CNS. Histamine, on the other hand, sensitizes nociceptor signals and produces hypersensitivity when it is produced due to infection, injury, or damage. Histamine is the most potent requisitioning agent for mast cells. As mentioned, technically, it is not histamine overload but HNMT and DAO overload that keeps pain in a magical loop. Because these enzymes are the most significant molecules in the human body, they cause pain to the cells on their own (18).

H3 receptors are considered entirely presynaptic, with no evidence of postsynaptic expression. They have H4 receptors, which are more sensitive to histamine than H1 and H2. The function of H4 still needs to be better known. All receptors have the same fundamental structure. They create distinct ligands on presynaptic or postsynaptic locations, which resemble the kinds of other pain signaling peptides to a significant extent. Pain perception from ligands and the area of CNS or PNS is determined by variations in underlying signaling peptides (17).

When discussing histamine, it is essential to remember that it interacts with non-neuronal cells, particularly in neuropathic pain. Interactions between these two systems are crucial in progressing inflammation and persistent neuropathic pain. Overall, non-neuronal cells have little effect on neuroglial pain, but when combined with histamine, they symbiotically enhance pain, most likely due to mast cells activating microglia (17-19).

As a result, depending on the location of the receptor, histamine receptors signal in distinct nociceptive pathways, resulting in more significant pain; their function and influence on pain are varied. Presynaptic or postsynaptic receptors can exist. H1 and H2 subtypes are mostly recognized post-synaptically. Both are excitatory receptors and complex modules that, in the case of H1, block potassium-voltage-gated channels and, in the case of H2, activate calcium channels (17, 18).

H3 receptors are considered exclusively presynaptic, but postsynaptic expression is still not elevated. They with H4 receptors express a higher affinity for histamine than H1 and H2. The role of H4 still needs to be understood. The basics of all receptors form different ligands on presynaptic or postsynaptic places that, to a great extent, the type of other pain signalizing peptides. The differences in underlying signalizing peptides determine the pain perception from the ligands and the place of CNS or PNS (17).

We must remember that histamine interacts with non-neuronal cells, especially in neuropathic pain. Interactions of these two systems play a vital role in developing inflammation and chronic neuropathic pain. Overall, non-neuronal cells do not have a high impact on neuroglial pain. Still, when coupled with histamine, they symbiotically increase the pain, probably due to mast cells triggering microglial activation (17-19).

What is very interesting is the fact that in neurological pain, pharmacological tolerance to opioids occurs very fast. This leads to an opinion that opiodogenic and histaminic systems interact on different bases. Firstly, all opioids are strong histamine liberators, and as a result, the level of histamine and degradation enzymes is increased.

Secondly, it is suggested that opioids and histamine form ligands (formally explained) that induce increased pain (20). Animal studies have confirmed that when H1, H2, and H3 receptors are blocked in combination and giving morphine has a better effect on analgesia and lowers the histamine's endogenic system (21).

CONCLUSION

From the preceding discussion, it is evident that histamine acts as a pain initiator at the level of cells and signaling pathways. Although this has received much attention over the past two decades, it needs to be better understood and requires further research. The selective pharmacological antagonism of neurons that express H receptors could provide novel therapeutic benefits for pain treatment. H receptors' antagonistic and agonistic properties are comparable to those of medications like pregabalin. This permits researchers and clinicians to rationalize and alter the future treatment strategy for neuropathic pain.

WHERE HISTORY AND THE FUTURE INTERSECT

Typically, histamine is associated with classic allergy symptoms such as a congested nose, wheezing, coughing, eczema, inflamed eyes, edema, skin rash, etc. These are considered "classic histamine symptoms"; unfortunately, many others exist. Histamine is a neurotransmitter that causes pain in the joints, connective tissues (fibromyalgia), musculoskeletal tissue, bloating, various GIT symptoms (diarrhea, constipation), hypotension, tachycardia, dizziness, painful menstruations, estrogen dominance, insomnia, brain fog, difficulty concentrating, or multitasking. It has been demonstrated that elevated histamine levels and histamine intolerance are associated with worsening ADHA in children. Histamine intolerance is due to mast cell activation issues, the lack of the DAO enzyme, high-histamine foods, stress, or other reasons. Consequently, the future lies somewhere between historical knowledge and inventive methods of altering historical knowledge. Several medical measures can be taken to resolve these issues, beginning with preventing the release of histamine and progressing to immune system homeostasis. However, this only applies to patients who are not undergoing surgery or experiencing pain and not those who are experiencing tension, trauma, or acute or chronic pain.

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9 Sciatica: disc surgery versus minimally invasive procedures

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ABSTRACT

The author presents a critique of the established treatment of sciatica where disc surgery is considered the gold standard and minimally-invasive interventions are underused.

Key words: *sciatica, radicular pain, disc surgery, epidural*

INTRODUCTION

This article attempts to expose the flaws in the treatment of sciatica caused by lumbar disc herniation. It is established practice that the cases of new onset sciatica that do not resolve with pain medication and physiotherapy are referred for surgical opinion. They are typically offered a microdiscectomy when there is a surgical target - nerve root compromise secondary to lumbar disc herniation, concordant in side and level with the distribution of pain. It seems that microdiscectomy is regarded as the [unstated] gold standard, and the treatment pathways in the UK, where the author works, are grounded in this view. Patients with a new onset sciatica are often unable to engage in physiotherapy because of acute leg pain. Somewhat perversely, failure of physiotherapy supports resort to surgery - in effect, as a means of pain management. Here we argue that less invasive but aggressive pain management in the form of epidural steroid injections should be routinely offered before surgery. This approach will likely have a surgery-sparing effect and result in fewer spinal operations and better long-term outcomes.

Imagine a medicolegal case where the claimant had had lumbar disc surgery for sciatica and suffered an unspecified bad outcome. It can be a lack of benefit from the

operation, early recurrence of spinal complaints, and in some cases sustained neurological deficit. We have seen at least two cases of serious port-surgical pelvic organ disfunction requiring permanent self-catheterisation and colostomy in the absence of preoperative cauda equina syndrome. The claimant files a clinical negligence complaint. The claimant's point is not the bad outcome per se, but the fact that he was not fully informed about alternative treatment options.

The claimant argues that during the consent process he was not made to understand that surgery can be avoided with the same outcome and less risk. He did not know that sciatica has a high rate of spontaneous recovery and that in clinical trials the 5-year outcome is not significantly different with or without surgery. Importantly, he was not told that if he fails to recovery spontaneously, he still can choose to have disc surgery later (1).

The claimant asserts that as the first step he could have an epidural injection and that the minimally-invasive transforaminal epidural injections (TFE) are effective (2), achieve an outcome that is non-inferior to surgery in 60 - 78% of cases, allow to avoid surgery and has less risk of serious adverse events. Again, those who fail to recover without surgery can have an operation later, and the delay of surgery seems to be without detriment (3, 4).

The claimant states that it was negligent to fail to tell him that after disc surgery, up to 54% of patients suffer recurrence of leg pain and up to 65% - recurrence of back pain at 3 years (5). Even worse, he was unaware of the term 'failed back surgery syndrome (FBSS)' defined as persistent or recurring low back pain, with or without sciatica following spine surgery (6). People with FBSS continue to have back and/or leg pain despite anatomically successful lumbar spine surgery (7). The claimant was surprised to learn that, unlike new onset sciatica, FBSS does not respond to physiotherapy or epidural injections, and that the treatment with proven efficacy - spinal cord stimulation (7) is highly invasive, expensive, not suited for all cases of FBSS and does not have a 100% success rate.

The claimant believes that when he was offered surgery, it was especially negligent to fail to address the broader subject of disc herniation. He was allowed to suffer the common misunderstanding that unless the disc bulge shown on his MRI scan is surgically removed, his sciatica will not resolve. He had no grasp of the fact that generally the correlation between the MRI and the clinical picture is relatively poor (8, 9, 10), and, in particular, when studied in a mixed group of patients randomly assigned to disc surgery versus conservative treatment, the MRI findings at 12 months had no correlation with the clinical outcome at all (11).

Before his operation, the claimant was convinced that once a disc bulge has occurred it will not change with time by itself. In fact, according to a recent systematic review, new disc herniations undergo spontaneous regression and decrease in size by half at 12 months in 63% of cases (12).

Spontaneous resolution of sciatica is common.

As an illustration of the claimant's argument, below is a personal observation of a symptomatic disc herniation with concordant MRI findings (Figure 1) where the symptoms of sciatica have fully resolved spontaneously within 6 months.

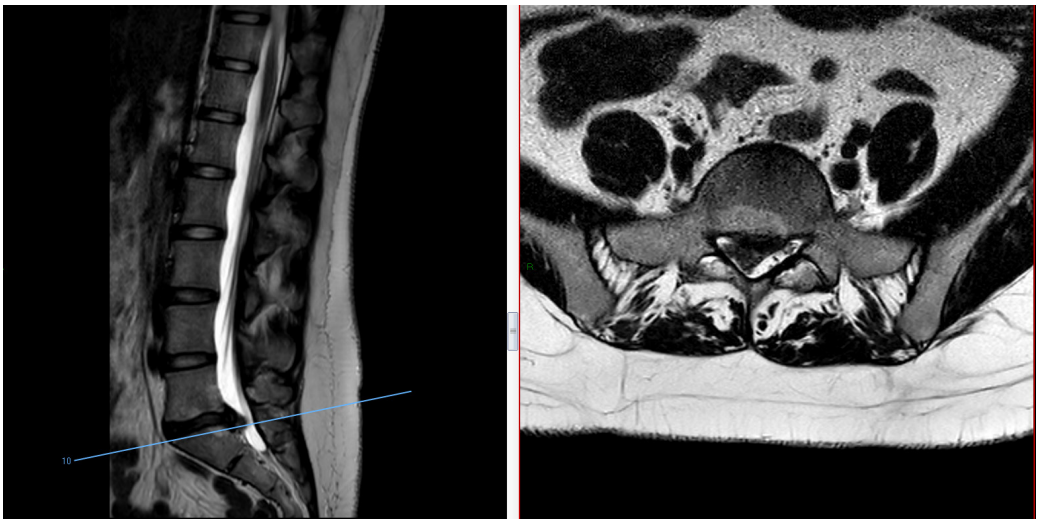

Figure 1. MRI scan of a right-sided L5/S1 disc herniation with full clinical correlation.

The claimant asserted earlier that TFE has a surgery-sparing effect. The assertion is made with the reference to two clinical trials.

First, a 2014 Dutch study compared TFE with disc surgery by offering a TFE to patients who were selected for surgery - to see what proportion could be spared surgery (3). Of the 69 patients who received TFE, only 22% went on to have an operation. The remaining 78% recovered sufficiently without surgery. It is implicit in the study that disc surgery is the current gold standard. The study's logic is this: if TFE spares surgery, it means non-inferiority.

Remarkably, the critics of the Dutch study dismiss its data as 'unscientific' on the grounds that, among other weaknesses, it is not a randomised controlled trial (RCT) and, therefore, does not provide strong evidence base. What they seem not to notice is that disc surgery, the current gold standard, is not evidence-based either.

Second, a 2021 multi-centre RCT form the UK (NERVES) directly compared surgical discectomy with TFE and showed no significant difference in outcome, except for a number of serious adverse events in the surgical group (4). The non-surgical patients were allowed crossover to surgery at a later stage, but 60% have made a good recovery without surgery. Patients with the cauda equina syndrome or serious motor deficit such as a foot drop were excluded from the trial. The NERVES trial has finally answered the 'not-an-RCT' objection and is a major contribution to the TFE evidence base.

CONCLUSION

The claimant summarises his case by stating that he suffers neuropathic leg pain similar to his original pain before surgery, but the fact that he had had surgery makes his long-term prognosis significantly worse. He believes that he should have been given a chance to recover without surgery, using early invasive pain control by means of TFE, and that this approach is supported by published evidence. It is especially true since the guideline NG59 from the UK National Institute for Health and Care Excellence (NICE) recommends epidural injections followed by surgical decompression, in this order - epidural first (13).

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10 Interventional Modalities for Refractory Migraines

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ABSTRACT

Migraines are a complex disorder characterized by episodes of moderate-to-severe headaches which may unfold over hours to days. Despite following conventional treatment strategies, many patients continue to experience disabling headache, making them "refractory" or "intractable" to standard treatment. In this case, interventional pain management is often the appropriate course of action. Two of the best-researched, and most effective nerve blocks for refractory migraines are the greater occipital nerve block and the sphenopalatine ganglion block. Several neuromodulation strategies are also available for treating refractory migraines, including transcranial magnetic stimulation, remote electrical neuromodulation, transcutaneous electrical nerve stimulation, and peripheral nerve stimulation (PNS) targeting structures such as the external trigeminal nerve, vagal nerve and occipital nerve. Interventional treatment options that target the inhibition of painful nerves constitute a promising avenue for patients with refractory headache disorders, and more, large RCTs are needed to clearly demonstrate their efficacy.

Key words: *acute migraine, chronic migraine, refractory migraine, intractable migraine, nerve block, neuromodulation, interventional pain management*

INTRODUCTION

Migraines are a complex disorder characterized by episodes of moderate-to-severe headaches which may unfold over hours to days. They constitute the second leading cause of disability worldwide (1). Their presentation is typically unilateral and often

associated with nausea and increased sensitivity to light and sound. A retrospective study found that 76% of migraine patients report triggers, the most common of which are stress, hormonal changes, skipped meals, and weather changes (2). Migraines are a highly prevalent condition, affecting approximately 12% of the population, and two to three times more prevalent in women than in men. Furthermore, women report longer attack duration, increased risk of headache recurrence, greater disability, and a longer period of time required to recover. For both men and women, the prevalence grows throughout puberty and peaks in their thirties, then continues to decline through life (3).

Migraines are classified into subtypes according to the headache classification committee of the International Headache Society (4). The most common subtype is migraines with aura, which account for 75% of migraines. These are recurrent attacks lasting 4 to 72 hours, typically unilateral and pulsating. Migraines without aura are typically fully reversible, and last minutes. Migraines that occur on at least 15 days in a month, for more than three months, are categorized as chronic.

REFRACTORY MIGRAINES

Many patients continue to experience disabling headache despite optimal treatment, making them "refractory" or "intractable" to standard treatment (5). More specifically, refractory migraines are characterized by failure to respond to 5 classes of preventive treatments including topiramate, onabotulinumtoxin A, CGRP pathway monoclonal antibodies, beta-blockers, tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors, and sodium valproate/divalproex sodium. A failed trial is defined as less than 50% reduction in frequency and/or severity of monthly migraine days, intolerance to adverse effects, or contraindication of use.

Treatment options for refractory migraine should provide acute, preventive or transitional relief, and may be oral/nasal or interventional in nature (5). For instance, nerve blocks may provide transitional relief via an injectable route, and neuromodulation may provide acute or preventive relief.

NERVE BLOCKS FOR REFRACTORY MIGRAINES

One of the best-researched nerve blocks for refractory migraines is the greater occipital nerve (GON) block. One randomized controlled trial (RCT) conducted on 60 patients with acute migraine headaches found that GON blockade with bupivacaine was as effective as an intravenous dexketoprofen and metoclopramide treatment, and superior to placebo (injection of normal saline into the GON area), at treating acute migraine for at least 45 minutes (6). GON blockade has also shown efficacy in treating

chronic migraines. One RCT compared a series of 4 weekly GON blocks with bupivacaine or saline in 44 patients, showing that bupivacaine was superior to placebo, had a longer lasting effect than placebo (up to 3 months), and was effective at preventing chronic migraines (7). Another RCT followed a similar protocol to compare GON blocks with lidocaine and saline in 44 patients (8). This study also found that GON with lidocaine was superior to placebo in decreasing the average number of headache and migraine days for at least 12 weeks.

Looking to compare GON to supra orbital nerve (SON) blockade using lidocaine in acute migraine treatment, a large RCT was conducted in 128 patients (9). Here, the patients were divided into 4 groups: GON, SON, combined, and placebo (saline). All patients who received blockades with lidocaine showed effective relief in acute migraine attacks. Among them, GON and combined blockades led to greater pain reduction than SON blockade alone.

Another nerve block which has shown efficacy in treating acute and chronic migraines is the sphenopalatine ganglion (SPG) block. This intervention can be delivered subzygomally, a more accurate but invasive approach, or transnasally, a simpler and safer approach (10). In the treatment of acute migraines, one RCT with 38 patients found that, compared to saline, SPG blocks with bupivacaine delivered repetitively for 6 week provided significant headache relief, sustained at 24 hours (11). Headache relief for 24 hours was also noted in a another study, in 55 patients with acute migraines who received SPG blocks with lidocaine (12). The efficacy of SPG blocks on chronic migraines was also assessed in a placebo-controlled RCT in 38 patients (13). The results of this exploratory study suggested long-term clinical benefits with the use of repetitive SPG blockades with bupivacaine, in terms of a reduction of headache days and improvements in quality of life.

NEUROMODULATION FOR REFRACTORY MIGRAINES

Several neuromodulation strategies are available for treating refractory migraines, including transcranial magnetic stimulation, remote electrical neuromodulation, transcutaneous electrical nerve stimulation, and peripheral nerve stimulation (PNS) targeting structures such as the external trigeminal nerve, vagal nerve and occipital nerve. PNS, for instance, has shown significant efficacy in various forms of refractory headaches, via mechanisms of action which may involve activation of central endogenous pain modulation networks (14). One-hour treatment with external trigeminal nerve stimulation has also shown safety and efficacy compared to sham stimulation in a multicentre RCT with 109 patients who suffer from acute migraines (15).

In the treatment of acute migraines, remote electrical neuromodulation (REN) has also demonstrated efficacy. One large multicentre study including 252 patients found that REN provides a safe and clinically meaningful relief of pain and most bothersome

symptoms compared to placebo (16). A post-hoc analysis of a subgroup of 99 patients from the previously-described study found that REN also shows non-inferior efficacy compared with current standard of care acute migraine therapies (17).

Transcutaneous electrical nerve stimulation (TENS) devices can be very convenient to patients, for being portable and self-applied. An RCT with 74 patients found that although both the TENS and the sham groups demonstrated lower pain scores during migraine attacks, the reduction was statistically significant in the neuromodulation group (17).

approach, single-pulse transcranial magnetic stimulation (TMS), was studied in a meta-analysis including 5 studies, and 313 patients (18). The results showed that is effective for the acute treatment of migraine with aura after the first attack. However, TMS did not exhibit significant efficacy on chronic migraine. A recent, large RCT with 153 patients, however, suggested that single-pulse TMS may constitute an effective, well-tolerated treatment option for the long-term prevention of difficult-to-treat chronic migraines (19). Indeed, 45% of participants reported a sustained response to single-pulse TMS after 12 month.

Further on the topic of migraine prophylaxis, a recent network meta-analysis aiming to compare neurostimulation strategies included 19 RCTs, and 1493 patients (20). The results revealed that high frequency repetitive TMS over C3 yielded the most decreased monthly migraine days (mean difference of 8.7 days compared to sham) of all the interventions included. Meanwhile, only alternating frequency (2/100Hz) transcutaneous occipital nerve stimulation over the Oz yielded a significantly lower drop-out rate than the sham groups.

CONCLUSION

Treatment options for migraine headaches that are refractory to conventional treatment include interventional pain modalities such as nerve blocks (with targets including the occipital nerve or the sphenopalatine ganglion) and neuromodulation approaches such as stimulation targeting the peripheral or trigeminal nerves, transcranial magnetic stimulation, and remote electrical neuromodulation. Interventional treatment options that target the inhibition of painful nerves constitute a promising avenue for patients with refractory headache disorders, and large RCTs are needed to clearly demonstrate their efficacy.

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The Use of Regenerative Medicine in Treating Chronic Pain

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ABSTRACT

Regenerative medicine consists in supplementing the body's innate repair mechanisms with homologous or autologous biologic agents. For the management of spinal pain, guidelines have been developed for the responsible, safe and effective use of platelet-rich plasma (PRP) and mesenchymal stem cell (MSC) injections. PRP is obtained through centrifugation of a patients' blood with the aim of concentrating growth factors, which affords efficacy most evident in the treatment of inflammatory conditions. MSCs can be derived from various tissues, and can give rise to specialized cell types. Unlike PRP, MSCs are considered to be most effective in degenerative diseases, in environments with lower local levels of inflammation. Both strategies have so far shown evidence in being effective and safe options for musculoskeletal interventional pain management. Higher quality trials remain needed to provide more robust data on long-term effectiveness, to help determine the place of regenerative medicine in the pain management algorithm.

Key words: *regenerative medicine, platelet-rich plasma, mesenchymal stem cells, bone marrow concentrate, pain, osteoarthritis*

INTRODUCTION

Despite the variety of therapeutic techniques available for the management of chronic pain, from pharmacological to surgical approaches, low back and neck pain, and musculoskeletal pain remain responsible for the third and fourth highest health-care costs among disease categories (1). This is largely due to treatment complications, poor outcomes, and persisting disabilities.

A newer strategy to garner attention is regenerative medicine, which harnesses the body's essential ability to heal itself, by replacing, engineering or regenerating human cells, tissues or organs. Regenerative medicine consists in supplementing the body's innate repair mechanisms with homologous or autologous biologic agents. Guidelines have been developed for the responsible, safe and effective use of platelet-rich plasma (PRP) and mesenchymal stem cell (MSC) injections in the musculoskeletal system, in the management of spinal pain, (1).

PLATELET-RICH PLASMA

Platelet-rich plasma (PRP) is obtained through centrifugation of a patients' blood with the aim of achieving a platelet concentration at least 2.5 times higher than in peripheral plasma (2). This leads to the accumulation of growth factors, which affords efficacy most evident in the treatment of inflammatory conditions. Several types of PRP can be achieved, based on the presence of white blood cells and fibrin density.

One randomized controlled trial (RCT) aimed to compare the efficacy and safety of ultrasound-guided transforaminal injections of PRP or steroid in 124 patients with radicular pain due to lumbar disc herniation (3). Pain and function outcomes were significant in both groups and maintained for at least one year, suggesting that PRP may be a safer alternative to steroids. A 2023 single-arm meta-analysis included 6 studies on the use of intradiscal injection of PRP for the treatment of discogenic low back pain (4). The results showed that PRP is an effective and safe treatment, and no significant change in the patient's pain occurred 1, 2 and 6 months after PRP injection.

To study PRP in osteoarthritis (OA), a large RCT conducted in 288 adults with mild to moderate radiographic knee OA compared 3 intra-articular injections at weekly intervals of either leukocyte-poor PRP or saline (5). Despite slight decreases in pain scores, neither group demonstrated a significant difference in symptoms or joint structure at the one year follow-up. A similar, albeit larger and longer placebo-controlled trial compared pure PRP and saline for the treatment of knee OA in 610 patients (6). The results showed that both groups had comparable safety profiles, but the PRP group achieved at least 24 months of symptomatic relief as well as slowed OA progress.

Another large, active-controlled RCT in 238 patients with mild to moderate knee OA compared intra-articular injections of PRP, plasma rich in growth factor (PRGF), hyaluronic acid (HA), and ozone (7). Although the ozone group demonstrated better short-term results after 2 months, the PRP, PRGF and HA groups showed better results after 6 months. In terms of long-term pain management, at the one year follow-up, only the PRP and PRGF groups showed persistent improved symptoms. One study was further interested in comparing HA and PRP, and assigned 122 osteoarthritic knees into HA, PRP and HA+PRP groups (8). They found level II evidence that combining HA and

PRP was more effective than either treatment alone at inhibiting synovial inflammation, improving pain and function, and reducing adverse events.

A 2023 systematic review and meta-analysis included 40 studies, and 3035 participants, to evaluate the effects of intra-articular PRP injections compared to HA, corticosteroid and saline, in the treatment of knee OA (9). The results showed that, at 6 months follow-up, PRP was as effective and, in some studies, more effective than the other treatment modalities in terms of pain, function, stiffness, and safety. However, the evidence was judged to be of low or very low quality, with serious limitations in terms of risk of bias and heterogeneity. As a result, no recommendations were made for clinical practice.

MESENCHYMAL STEM CELLS

Mesenchymal stem cells (MSCs) can be derived from various tissues, such as bone marrow, adipose tissue, synovium, and human umbilical cord blood (10). These cells are capable of division and self-renewal for long periods of time, are unspecialized but can give rise to specialized cell types. Unlike PRP, MSCs are considered to be most effective in degenerative diseases, in environments with lower local levels of inflammation, in order to achieve their desired anabolic regenerative effects.

Another cell-based therapy is bone marrow concentrate (BMC), a more minimally manipulated autologous cell preparation, typically composed of mixed cell populations, with a lower prevalence of stem or progenitor cells, and more highly variable biological attributes and function (11). Safety and feasibility was shown in a study with a 3-year follow up, where 26 patients suffering from degenerative disc disease received autologous BMC into the nucleus pulposus of treated lumbar discs (12). The 20 patients who did not progress to surgery showed improvements in pain and function, and no radiographic worsening of clinical features.

Bone marrow MSCs have been shown to differentiate into nucleus pulposus-like cells, and stimulate the production of new cell matrix, which is promising in the treatment of degenerative disc disease (13). A long-term study treated 33 patients with lower back pain and disc degeneration with a posterior disc bulge with culture-expanded, autologous, bone marrow-derived MSCs (14). The patients reported significant improvements in pain, function and overall subjective improvement through 6 years of follow-up, along with minor adverse events.

Some evidence has shown that bone marrow MSCs can cause cartilage repair in osteoarthritis, leading to improvements in pain and function. A phase I/II RCT was conducted in 30 patients with knee OA, comparing increasing doses of a single intra-articular injection of in vitro expanded autologous bone marrow mesenchymal stromal cells in combination with HA (15). The results show that it is a safe procedure, resulting

in a clinical and functional improvement of knee OA, sustained for at least one year. A systematic review and network meta-analysis conducted on intra-articular cell-based therapy for OA included 13 studies, with follow-up of up to 12 months (16). The results indicate that cell-based therapy led to significant improvements in pain and some OA scores. Among the treatments included, high-dosage adipose-derived MSCs showed the most promising long-term effects.

An RCT aimed to compare BMC to PRP, in 90 patients with knee OA, (17). The results showed significant improvements in both groups, with level II evidence that both treatments performed similarly for 24 months. Furthermore, a recent meta-analysis included 6 RCTs, with 495 cases, on the combination of MSCs and PRP, for the treatment of knee OA (18). This combination showed good clinical efficacy in improving pain and joint function for at least one year, as well as a similar safety profile to MSCs alone.

Of note, potential adverse consequences of biologics include risk of infection, tissue rejection, and initial or transient worsening of pain (1). Several important contraindications remain, such as hematologic blood dyscrasias, platelet dysfunction, septicaemia or fever, cutaneous infection, anemia, malignancy, allergies, and genetic abnormalities in host cells when using autologous therapy.

CONCLUSION

Regenerative medicine, and the therapeutic use of biologics, have shown evidence in being a safe and cost-effective option for musculoskeletal interventional pain management. More specifically, platelet-rich plasma and mesenchymal stem cell injections have demonstrated efficacy in supplementing the body's innate healing process in several large trials, particularly for improving pain and function in patients with degenerative disc disease and osteoarthritis who failed standard of care treatments. Higher quality trials remain needed to provide more robust data on long-term effectiveness, to help determine the place of regenerative medicine in the pain management algorithm.

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Spinal surgery: Final Solution or New Drama Beginning

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ABSTRACT

Spinal surgery is one of the pillar in the treatment of spinal disorders, together with drug therapy and physical therapy. Over the past several decades, spinal surgery has gained incredible advancement in surgical approaches, surgical technique and quality of implants. Hence, the indications for spinal surgery have broadened over time. Current there is no spinal disorder which can not be addressed surgically, from clear discal pathology to complex spinal deformity, infection and tumor surgery. It is to expect that this trend will continue in the future, based on minimal invasive strategy, utilization of new imaging methods and robot. As in other surgical fields, the use of artificial intelligence is unavoidable scenario in future. However, spinal surgery is accompanied with certain degree of complications. This review emphasizes current spinal surgery philosophy and evidence based drawbacks.

Key words: *Spinal surgery, minimal invasive, approaches, complications*

INTRODUCTION

Spinal fusion

Spinal fusion has become one of the most commonly performed spinal procedures.Since first spinal fusion performed by Dr. Russell A. Hibbs in 1911, the indications for spinal fusion have broadened over time with basic idea to stabilize instabile segment. This instability can be caused by injuries, deformities, tumors, infections, deformities and degenerative conditions of the spine. In modern times, pedicle screws,

inter-body devices, and osteoinductive and osteoconductive bone grafts all work to assist in forming a solid fusion mass (1).The incidence of lumbar spine fusions increased from 9 (CI 5–17) per 100,000 person-years in

1997 to 30 (CI 21-43) per 100,000 person-years in 2018 (2). The need for patient-specific treatment plans has pushed scientists to create new instrumentation, novel bone grafts, and translational medical research for spinal fusion. The future of spinal fusion is based on stem cell utilisation, nanotechnology, improvement of osteoconduction and osteobiologics. The goal is the same as at the very beginning of spinal fusion (patients with Pott's disease in the late 1800s) : to design instrumentation that provides more reliable fixation and bone grafts with greater potential to promote fusion (3,4).

Trauma

Despite safety promotions and protection devices in traffic, spinal injuries remain a huge problem worldwide. The male patients, age 18-30 and over 65 are under highest risk, traffic accidents are still the most frequent cause of spinal injuries (5). Introduction of new classification systems for tramatic spinal injuries (upper cervical spine, lower cervical spine, thoracolumbal spine and sacral fractures), leads to clear indication for surgery which should provide stability of spinal column, decompression of spinal cord in neurological findings and to maintain the alignment of the spine (table 1).

Table 1. General indications for surgery in spinal trauma

Indications for surgical treatment:
Incomplete neurologic deficit
Progressive neurologic deficit
Spinal cord compression
Fractures with dislocation
Kyphosis more then 30 degrees
Associated injuries who require fast mobilization

With the increase in life expectancy, osteoporotic fractures have become an top issue regarding treatment. Osteoporotic vertebral fractures (OVFs) are conventionally treated conservatively with one aim: pain relief. That include: short term bed rest, analgesics, antiosteoporotic drugs, exercise, and braces. Although most OVFs heal well, approximately one third of patients with unstable fractures, chronic back pain, severely collapsed vertebra (leading to neurological deficits and kyphosis), or chronic pseudarthrosis frequently require surgery. Surgical strategy consist of two philosophies: minimal invasive intervention (with main goal to reduce the pain) and definitive surgery (with aim goal to achieve stability, decompression of neural structures and to reduce deformity). Vetebroplasty and kyphoplasty are well known minimal invasive procedures

consist of injection of bone cement (PMMA) under local anesthesia in fractured vertebral body, which leads to immediate pain relief and increase of stability. However, there is still debate and controversy regarding the effectiveness of VA. The main drawback of this procedure is relative high rate of complication (3-13%) and adjacent segment fracture (incidence is up to 40% in vertebroplasty procedures).

Regarding definitive treatment, there are five typical surgical fusion techniques: anterior spinal fusion, posterior spinal fusion, combined anterior and posterior spinal fusion, posterior three-column osteotomy including shortening osteotomy or vertebral column resection, and vertebroplasty with posterior spinal fusion.

Prevention and management of osteoporosis is the key element in reducing the risk of subsequent OVFs, regardless of treatment strategy. Bisphosphonates and teriparatide are mainstay drugs for improving fracture healing in OVF. (6)

Infection

In the era before contemporary implants and meticulous surgical technique, the mainstay treatment of surgical infection was conservative, which had been associated with long term drug administration, log term bed rest, very poor quality of life and very poor outcome. There are two main types of spinal infection: vertebral osteomyelitis and surgical site infection. Vertebral osteomyelitis can be pyogenic caused by diverse bacteria (staphylococci are the main germ) and granulomatous cause by TBC or Brucellosa. Apart from general symptoms (pain, fever), the product of inflammation can be pus or granuloma. The combination of mechanical compression of the spinal cord by those products can result in ischemia with spinal cord infarction, which is the main reason for the rapid neurologic progression. Patients with a spinal epidural abscess may progress to complete paralysis within minutes to hours, even while receiving optimal antibiotic therapy. In addition, patients with vertebral osteomyelitis can develop pathologic fractures, caused by the softening of the bone, presenting with significant deformity. Indications for surgery include the following:

Significant osseous involvement

- Neurologic deficits – Neurologic deterioration can be caused by significant kyphosis, by infection behind the vertebral body under the posterior longitudinal ligament, or by infection in the epidural space
- Septic course with clinical toxicity from an abscess not responding to antibiotics
- Failure of needle biopsy to obtain necessary cultures
- Failure of intravenous (IV) antibiotics alone to eradicate the infection (7)

Significant increase of spinal instrumentation lead to higher rate of surgical site infection worldwide (with incidence 2-4%). The main issue is removal of hardware from patientswith SSIs after spinal procedures. In these patients, topical placement of

antibiotic impregnated beads with slow release of antibiotics has been recommended. One of the solution to avoid this complication is use of minimal invasive approach (8).

Tumors

Spinal tumors can be benign (non-cancerous) or malignant (cancerous). Primary tumors originate in the spine or spinal cord, and metastatic or secondary tumors result from cancer spreading from another site to the spine. Spinal tumors can be divided in two ways:

1. By the region of the spine in which they occur- cervical, thoracis, lumbar and sacrum.
2. By their location within the spine- intradural-extramedullary, intramedullary, extradural. The bony spinal column is the most common site for bone metastasis. Estimates indicate that at least 30% and as high as 70% of patients with cancer will experience spread of cancer to their spine. The most common primary spine tumor (originated in the bony spine) is vertebral hemangiomas. These are benign lesions and rarely cause symptoms such as pain. Common primary cancers that spread to the spine are lung, breast and prostate. Lung cancer is the most common cancer to metastasize to the bone in men, and breast cancer is the most common in women. Other cancers that spread to the spine include multiple myeloma, lymphoma, melanoma and sarcoma as well as cancers of the gastrointestinal tract, kidney and thyroid. Prompt diagnosis and identification of the primary malignancy is crucial for outcome.

Indications for surgery vary depending on the type of tumor. Primary (non-metastatic) spinal tumors may be removed through complete en bloc resection for a possible cure. In patients with metastatic tumors, treatment is primarily palliative , with the goal of restoring or preserving neurological function, stabilizing the spine and alleviating pain. Generally, surgery is only considered as an option for patients with metastases when they are expected to live 3 months or longer. Surgery in adults for a variety of spinal tumor types has been associated with a risk for major complications (reports of up to 14%). The real issue in spine tumor treatment are not primary tumors (the goal is complete removal), but metastatic spinal tumors. The proper treatment of spinal metastases is a medical challenge requiring interdisciplinary collaboration. Treatment must be individually tailored for each patient in consideration of multiple factors including bony stability, the compression of neural structures, tumor radiosensitivity, pain, and the patient's overall prognosis (9).

Deformities

Spinal deformity is a complex and dynamic change that occurs in the sagittal, coronal or planes. There are two types of spinal deformity : coronal plane deformations

(scoliosis) and sagittal plane deformations (kyphosis). They can appear alone or in combination. Successful treatment aims to achieve a satisfactory balance on both planes (Table 2). The primary goal of deformity surgery is to achieve a balanced spinal alignment through rigid fusion, prevent further deformity and alleviate neurological symptoms. A secondary goal of spinal deformity surgery is to improve appearance for cosmetic purpose. The main indication for adult spinal deformity surgery is severe pain associated with the curve progression. Decreased pulmonary function is also indicated for spinal deformity surgery.The success of spinal deformity surgery depends on patients' satisfaction after surgical intervention. Patient satisfaction after spinal deformity surgery was approximately 90%, but the complication rate of spinal deformity surgery is very high (up to 33%) (10).

Table 2: Surgical algorithm for degenerative kyphoscoliosis

	I	II	III	IV	V
lower leg pain	+	+	+	+	+
low back pain	−	+	+	+	+
Instability	−	+	+	+	+
SVA ≥50mm	−	−	+	+	+
scoliosis ≥30°	−	−	+	±	±
kyphosis smooth	−	−	+	+	−
kyphosis sharp	−	−	−	−	+

Level I: decompression

Level II: decompression+fusion

Level III: Ponte+(Rod rotation) or LLIF

Level IV: PSO

Level V: PVCR

(LLIF- Lateral Lumbal Interbody Fusion PSO- Pedicle Subtraction Osteotomy PVCR- posterior vertebral column resection)

The future of spinal deformity surgery will face with 5 groups of complications:

– systemic complications- (pulmonary complications- 7.6%, cardiac complications, deep vein thrombosis (DVT) renal complications, excessive bleeding -11.4%) which may lead to massive blood transfusion.

– neurologic complications-10.8%. The primary neurological deficits could be the results of spinal cord ischemia, screw malposition, or retraction of neural tissues.

– infection - up to 4%, and main risk factors are: diabetes, obesity, previous spine surgery, significant blood loss, and prolonged operation time.

– implant failure- Mechanical implant failure incidence was found between 12% and 47% in postoperative patients. The common complications that lead to implant failure are PJK (proximal junction kyphosis) and rod breakage.

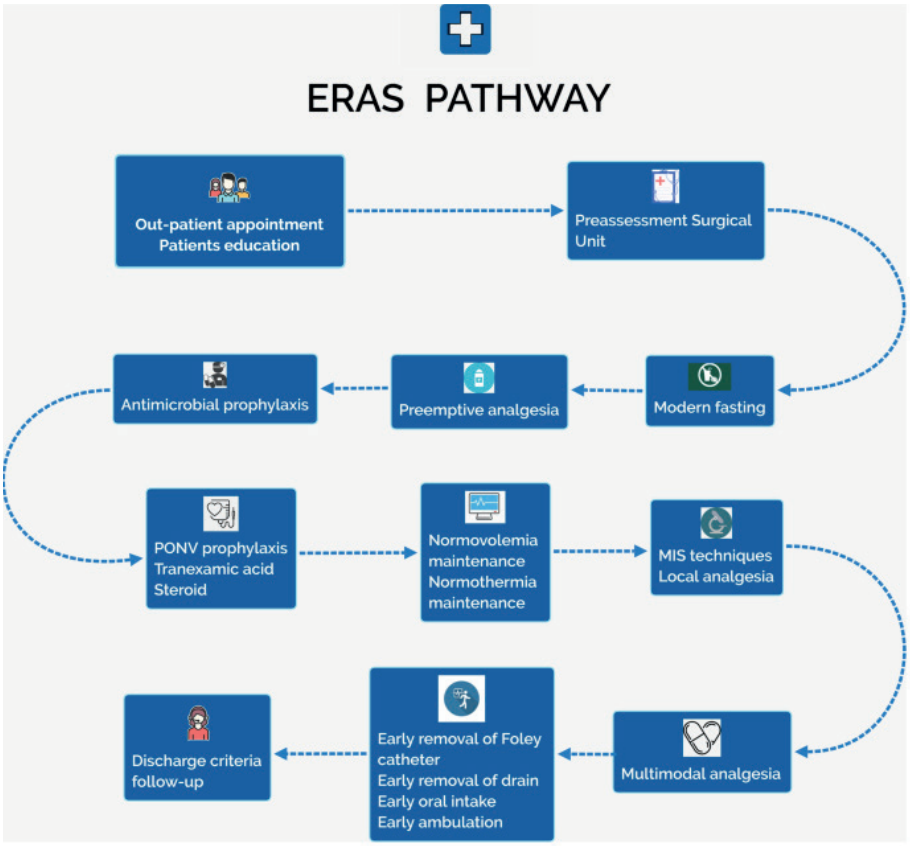
– revision surgery - up to 25%. The need for revision surgery is mostly seen after adjacent segment disease, PJK, and nonunion (11).

Disc surgery

The main indication for disc herniation surgery is fail of conservative treatment, progressive or persisting neurological deficits, as well as for persisting pain which alters the quality of the patient`s life. Results of surgery are strongly dependent on the preoperative duration of symptoms. Paramount is the "timing" of surgery: poorer surgical results associated with increasing preoperative duration of symptoms and if conservative treatment modalities have not been exhausted. There are 2 main surgecal technique (endoscopic/microsurgical) and 5 different approach strategies (endoscopic: interlaminar, transforaminal; microsurgical: interlaminar, translaminar, extraforaminal), whereby the choice is determined by morphology and location of the herniated disc. All techniques are minimally invasive and lead to comparable clinical results. For all techniques, patients are mobilized early. Light sports activities allowed after 2 weeks and return to work after about 4 weeks. Good clinical outcomes in meta-analyses/large case series are between 80-95 %. (12).

Recovery after spinal surgery- what is new?

Enhance recovery after surgery (ERAS) is a new and promising paradigm for spine surgery.(13).Enhanced recovery after surgery (ERAS), known as fast-track or rapid recovery surgery, is an integrated, multimodal and evidence-based approach to improve patient care and outcomes and was first introduced by Henrik Kehlet in 1997 (13). The aim of ERAS is to minimize surgical stress responses, reduce the length of stay (LOS), decrease complications and improve patient experience (Figure 1)



CONCLUSION

Spinal surgery has been one of the most common treatment options in orthopedic and neurochirurgical spinal pathology for years, thanks to improvement in diagnostic, implants design, surgical technique. Thanks to advancement in diagnostic tools and implants, surgical technique, patient expectations and satisfactory outcome, the number of indications for spinal surgery has been increased worldwide. This led to increase number of some complications, which were rare in the era before spinal surgery "boom". According to available studies , we can conclude that spinal surgery is a definitive solutions for good indications (trauma, infection, tumor, deformities) , but complications and long term outcome can be the beginning of new drama.

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Od vodiča do prakse: Tretman kancerskog bola

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APSTRAKT

Kancerski bol ili bol koji je povezan sa postojanjem maligniteta, tz cancer-related pain, različito se doživljava kod onkoloških pacijenata u odnosu na pacijente sa bolom koji nemaju malignitet. 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. Izbor terapije hroničnog kancerskog bola je danas 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 (National Comprehensive Cancer Network) 2019.g. put je ka pravilnom terapijskom izboru. Bol kod pacijenata sa karcinoma deli iste neuro-pato--fiziološke puteve bol bez karcinoma. To je bol mešovitog mehanizma, koji se retko manifestuje kao čisti neuropatski, visceralni ili somatski sindrom bola. Time je izbor terapije, a posebno kombinovanje terapijskih režima daleko složeniji u odnosu na izbor terapije hroničnog nekancerskog bola. Individualini pristup kao princip terapijskog pristupa je pored svih vodiča koji se danas koriste u terapiji hroničnog kancerskog bola možda i najvažniji. Složenost patofizioloških mehanizama hroničnog kancerskog bola i nova saznanja u oblasti imunomodulacije lekovima će sigurno doprineti razvoju novih terapijskih vodiča. Postoji nekoliko potencijalnih novih „targeta" za lečenje kancerskog bola koji su u fazi ispitivanja kao jedinjenja koja mogu posredovati u snažnoj analgeziji sa značajno manjim rizikom od respiratorne depresije, gastrointestinalnih efekata kao najčešćih i drugih neželjenih efekata sveobuhvatne analgetske terapije.

Ključne reči: *analgetici, hroničan kancerski bol, neopiodni analgetici, opioidi*

UVOD

Kancerski bol ili bol koji je povezan sa postojanjem maligniteta, tz cancer-related pain, različito se doživljava kod onkoloških pacijenata u odnosu na pacijente sa bolom koji nemaju malignitet. Pored razvijenih smernica za lečenje kancerskog bola, podaci navode da i dalje postoji veliki broj onkoloških pacijenata kod kojih bol nije adekvatno lečen, kako kod nas, tako i u drugim zemljama sveta.

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. Cilj upravljanja bolom je ublažiti bol do nivoa koji omogućava prihvatljiv kvalitet života (1). Preživljavanje od malignih tumora predstavlja sve veći klinički izazov za lekare koji učestvuju u onkološkom lečenju tako i onih specijalista koji se bave terapijom kancerskog bola. Populacija preživelih od malignih tumora se poslednjih godina uvećava i mnogi od ovih pacijenata doživljavaju bol kao posledicu svoje bolesti i/ili njenog lečenja. Iz perspektive definicije kancer preživeli „cancer survivors" i prisustva bola, definicija preživelih sa kancerskim bolom obuhvata različite periode prema stadijumu bolesti od postavljanja dijagnoze (kada je samo prisustvo tumora uzrok bola), preko stadijuma lečenja (koji takođe mogu rezultirati bolom), do stanja mirovanja ili izlečenja od bolesti (gde se često susreću uporni i na terapiju refraktorni oblici hroničnog kancerskog bola, najčešće neuropatskog porekla) (2). Danas u svetu postoje definisani mnogobrojni vodići za terapiju hroničnog kancerskog bola. Prepreke u adekvatnom lečenju hroničnog kancerskog bola odnose se na nejednaku primenu vodiča 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 (3). Preporuka broj 4 (stepen preporuke IA) koju je izdala NCCN (National Comprehensive Cancer Network) 2020. godine u svojim vodičima za tretman hroničnog kancerskog bola, iako uopštena, osnova je svih ostalih preporuka, a ona glasi: Pacijenti treba da dobiju prilagođen multimodalni tretman koji smanjuje bol i njegov uticaj na svakodnevni život, a koji može uključivati kombinaciju lekova, nefarmakoloških tretmana, onkoloških intervencija, fizičke rehabilitacije i psihosocijalne ili duhovne podrške (3). Optimizacija ishoda lečenja bola najbolje se dobija primenom principa koje se naziva „5 As", a koji je takođe predložen od strane NCCN 2020. godine. podrazumeva: Analgezija: optimizovati analgeziju (ublažavanje bola); Aktivnost: optimizovati aktivnosti svakodnevnog života (psihosocijalno funkcionisanje), Neželjeni efekti (Adverse effects): minimizirati neželjene događaje, Aberantno uzimanje lekova: izbegavati aberantno uzimanje lekova (ishodi povezani sa zavisnošću), Uticaj (Affect): naglasak na odnos između bola i raspoloženja (4).

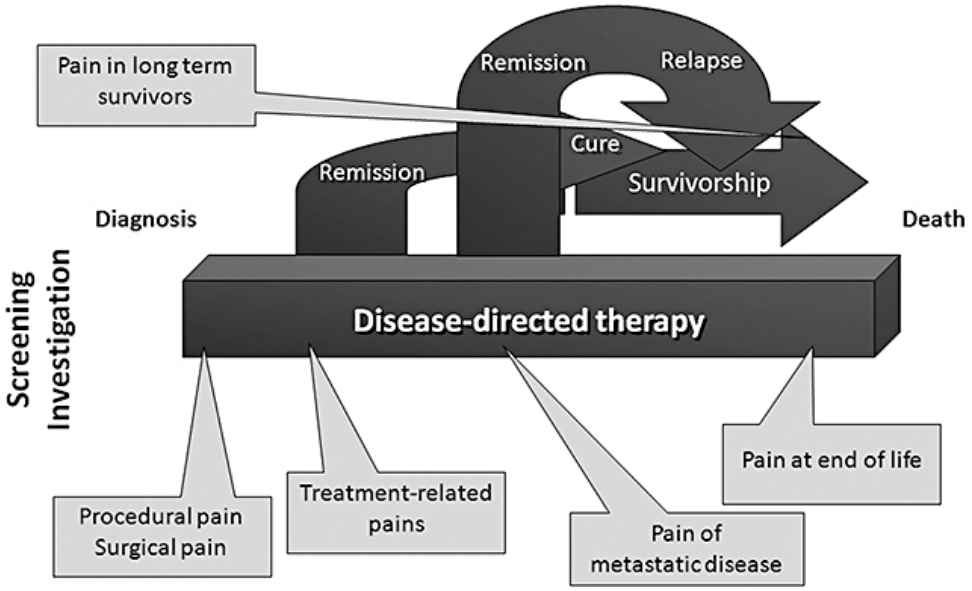
Patofiziološki mehanizmi hroničnog kancerskog bola

Inicijalna i tekuća procena bola treba da bude sastavni deo nege onkološkog bolesnika i ukazuje na to kada je dodatna sveobuhvatna procena potrebna. Redovno samoprijavljivanje uz pomoć validiranih alata za procenu bola je prvi korak za efikasan i individualizovan tretman. Najčešće korišćeni „alati" za procenu intenziteta bola su standardizovane skale (5) i predstavljaju vizuelnu analognu skalu (VAS), skalu verbalne ocene (VRS) i numeričku skalu ocenjivanja (NRS). Multidimenzionalni aspekt bola se ogleda i u mogućnosti nekoliko načina za klasifikaciju bola. Prema patofiziološkom mehanizmu nastanka, bol se klasifikuje kao nociceptivni i neuropatski bol. Nociceptivni bol nastaje kao odgovor na draži sa kože, iz mišića ili kosti (somatski bol) ili unutrašnjih organa (visceralni bol). Neuropatski bol nastaje kao odgovor na oštećenje perifernog i/ili centralnog nervnog sistema. Bol kao subjektivni fenomen, postoji tek kad ga prepozna centralni nervni sistem,tako da proces koji se dešava na periferiji, sam po sebi, ne znači bol.

Proces doživljaja bola uključuje četiri faze:
Transdukcija – nociceptori prepoznaju bolnu draž na periferiji (pretvaranje energije koja je izazvala draž u električnu energiju samog receptora koja će dalje biti preneta);
Transmisija – „poruka" se prenosi od receptora na periferiji do centralnog nervnog sistema;
Modulacija – poruka se modifikuje kroz uticaj ekscitatornih i inhibitatornih mehnizama;
Percepcija – mozak prepoznaje nadražaj kao bolnu senzaciju.

Receptor je specijalizovani deo ćelije koji prepoznaje draž i odgovara na nju, i obično se nalazi na površini ćelijske membrane, mada ne uvek. Kada receptor prepozna draž ona se pomoću akcionog potencijala prenosi perifernim nervima i ascedentnim putevima duž kičmene moždine do centralnog nervnog sistema. Međutim, pod uticajem aktivnosti drugih nervnih puteva, ascedentnih ili descedentnih, na prenos bolnih nadražaja, ova informacija može biti modifikovana (modulacija). Ceo proces se završava percepcijom– prepoznavanjem bola od strane viših centara u mozgu (6). Bol kod pacijenata sa karcinoma deli iste neuro-pato-fiziološke puteve kao i bol bez karcinoma. To je bol mešovitog mehanizma, koji se retko manifestuje kao čisti neuropatski, visceralni ili somatski sindrom bola. Umesto toga, može uključiti inflamatorne, neuropatske, ishemijske i kompresivne mehanizme na više mesta, što kod ovih pacijenata otežava delotvornu terapiju bola (7). Dodatno, 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 (8). 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. Uzroci hroničnog kancerskog bola od momenta postavljanja dijagnoze maligne bolesti pa do kraja života predsatvlenji su na Slici 1 (9).



Slika 1. Model toka maligne bolesti i kancerski bol (9)

Lečenje hroničnog kancerskog bola – princip stepenica SZO

Osnovni princip lečenja bola prema savremenim NCCN preporukama za lečenje kancerskog bola kao i ESMO (Evropsko Udruženje za Medicinsku Onkologiju) preporukama podrazumeva da:

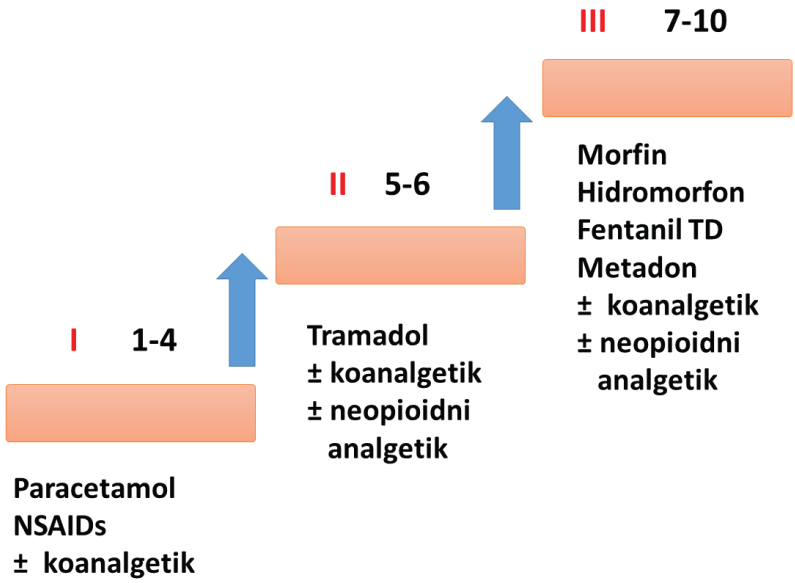
- Pacijent treba da bude informisan o bolu i terapiji bola i treba da bude ohrabren da aktivno učestvuje u njegovom rešavanju.
- Početak bola treba da se prevenira lekovima primenjenim „po satu“, uzimajuću u obzir poluživot, bioraspoloživost i trajanje dejstva različitih lekova.
- Analgetici za hroničan bol treba da se propisuju redovno a ne po potrebi.
- Oralna primena analgetika treba da bude prvi izbor.

Korištenje preporuka SZO prema stepenicamam koje definišu lečenje bola prema njegovoj jačini podrazumeva: 1. stepenica: za blagi bol (1–4/10 NRS) neopioidi su analgetici izbora. Njima se mogu dodati koanalgetici ako je potrebno. 2. stepenica: (umereno jak bol: 5–6/10 NRS): ukoliko lek prve stepenice ne može da ublaži bol, ili pacijent

procenjuje bol kao umereno jak, onda se primenjuju slabi opioidi, u kombinaciji sa neopioidima i koanalgeticima, kada je to potrebno. 3. stepenica: jak bol ili bol koji je prethodno loše kontrolisan drugim lekovima, zahteva primanu jakih opioida. Jaki opioidi se takođe mogu kombinovati sa neopioidima i mogu im se dodavati koanalgetici.

Lekovi za terapiju kancerskog bola

1. Neopoidni analgetici
2. Opoidni analgetici
3. Koanalgetici (adjuvansi) (ne daju se rutinski već se uvode u zavisnosti od specifičnih potreba pacijenata)
4. Lekovi za terapiju neželjenih dejstava analgetika (4,10)



Slika 2. Princip stepenica SZO u lečenju hroničnog kancerskog bola (4,10)

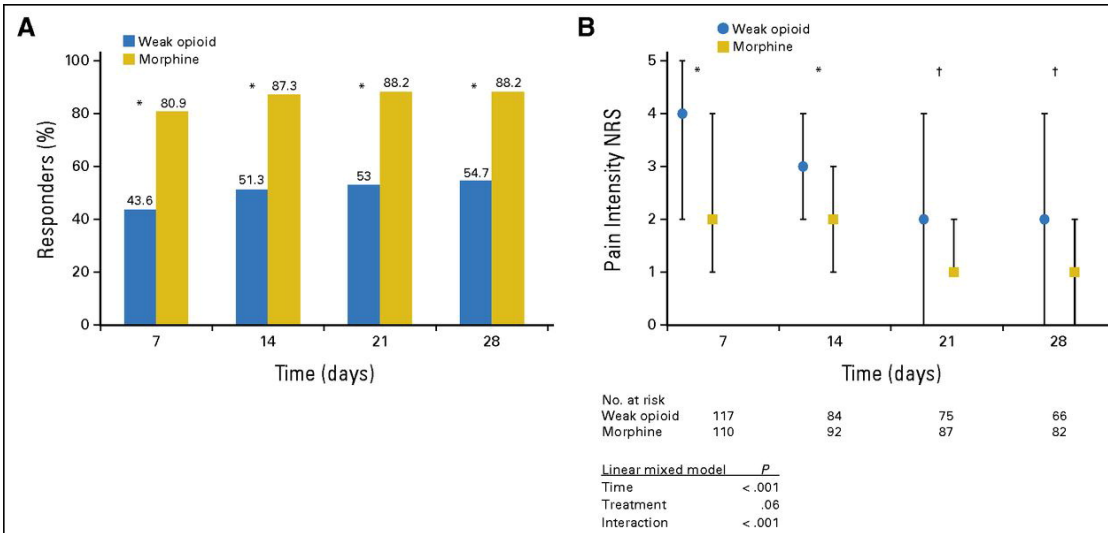
Neopioidni analgetici – nesteroidni anti-inflamatorni lekovi (NSAIL) u terapiji hroničnog kancerskog bolapain

Nesteroidni anti-inflamatorni lekovi (NSAIL) su velika grupa lekova različitog hemijskog sastava koji svi deluju na isti način: analgetički, antipiretički i antiinflamatorno. Osnovni mehanizam dejstva se odvija putem inhibicije enzima ciklo-oksigenaze (obe varijante i Cox 1 i Cox 2) koji je važan za sintezu prostaglandina (dominantni medijatori zapaljenja, ali su uključeni i u mehanizme nastanka bola i povišene temperature). Iako ih na tržištu ima u različitim formulacijama, njihov analgetički efekat je nepredvidiv, a primena ograničena zbog: (a) efekta platoa: svaki od ovih lekova ima svoju maksimalnu dnevnu doza koja se sme primenjivati, tako da se povećanjem doze iznad

savetovane ne postiže bolji analgetički efekat, ali su neželjena dejstva jače ispoljena; (b) neželjenih dejstava: gastrointestinalna toksičnost, inhibicija agregacije trombocita, retencija vode i soli, nefrotoksičnost i moguća preosetljivost na lekove. Upala je ključna komponenta metastatskog procesa i čak smatra se da ciljanje ovog elementa ima kritičnu ulogu u prevenciji metastaza (11). Protivuupalni efekti NSAIL-a su dobro poznati, sa studijama koje potvrđuju smanjenje cirkulišućih inflamatornih medijatora povezanih sa primenom tradicionalnih NSAIL-a i COKS-2 inhibitora perioperativno (12). Štaviše, postoji zabrinutost u vezi sa imunosupresivnim svojstvima opioida, čime potencijalno mogu uticati na recidiv karcinoma. Svojstva NSAID-a koji štede opioide mogu se koristiti da bi se minimizirali ovi imunosupresivni efekti. Uprkos ovoj zabrinutosti, ipak velika prospektivna kohortna studija koja je uključivala 34 188 pacijenata nije pronašla klinički relevantne dokaze o povezanosti između opioida i recidiva karcinoma dojke (13). Nedavni sistematski pregled koji je razmatrao perioperativnu upotrebu NSAIL za dugotrajno preživljavanje nakon operacije nakih vrsta karcinoma, zaključio je da su studije (pretežno retrospektivne i opservacijske) dale oprečne rezultate, ali određeni broj tekućih RCT-a (Randomised Clinical Trials) imaju za cilj da pruže preko potrebnu jasnoću o ovoj temi (14).

Male doze morfina u odnosu na primenu slabih opioida u terapiji srednje jakog kancerskog bola

Opioidi za lečenje blagog i umerenog bola "slabi" opioidi nazvani su slabim opioidima jer imaju gornju granicu efikasnosti. Primenjuju se za bolove jačine od 4-6 na numeričkoj skali za bol. Najčešće se kombinuju sa neopioidnim analgeticima, paracetamolom ili lekovima iz grupe NSAIL. Međutim u ranoj retrospektivnoj studiji Ventafride i kolega, efikasnost koraka (stepenika) II SZO imala je vremensko ograničenje od 30 do 40 dana i, za većinu pacijenata, prelazak na korak III je napravljen uglavnom zbog neadekvatne analgezije, a ne neželjenih dejstva slabih opioida. U trenutnoj svakodnevnoj kliničkoj praksi, korak II je često zaobiđen u korist jakih opioida, iako strategija nije potkrepljena snažnim naučnim dokazima, jer su prikazane samo dve randomizovane kontrolisane studije koje su uključile 92 pacijenata od kojih 54 terminalno obolelih , i jedna prospektivna studija sa 34 terminalno obolela pacijenta. Studija Elene Bandieri je pružila prvi formalni dokaz da, iako su opioidi iz koraka II efikasni kada se koriste u ograničenim vremenskim intervalima, niske doze morfijuma (korak III) mogu biti korisne i mogu zameniti slabe opioide kod pacijenata sa umerenim hroničnim kancerskim bolom od kojih je više od polovine primalo aktivnu antitumorsku terapiju (Slika 4), zbog veće efikasnosti i a skoro identičnim profilom toksičnosti (15).



Slika 3. Prednost M (morfina) u odnosu na VO (weak opioids-slabi opijati) evidentna na prvoj kontroli u 1. nedelji posmatranja (15)

Objašnjenje slike 3. *Pacijenti koji reaguju i intenzitet bola (numerička skala ocenjivanja [NRS]) u različitim vremenima praćenja po grupama lečenja. (A) Procenat pacijenata sa odgovorom (koji su postigli smanjenje bola za ≥ 20% u odnosu na početnu liniju) pri svakom praćenju. P vrednost je za poređenje između grupa koje se izvodi pomoću χ2 testa. (B) Intenzitet bola procenjen korišćenjem NRS-a pri svakom praćenju. Podaci su prikazani kao medijana i interkvartilni opseg. Linearni mešoviti režim za ponovljena merenja je urađen na osnovu rezultata intenziteta bola. *P < .001, †P = .02 prema Mann-Vhitney U testu.*

Morfin kao „zlatni standard“ u lečenju jakog hroničnog kancerskog bola, nove modulacije opioidnih analgetika

Morfin je opioid izbora SZO za lečenje umereno jakog/jakog bola. On se još uvek smatra „zlatnim standardom” sa kojim se porede svi drugi opioidi. Za optimalno lečenje bola potrebne su dve formulacije: kratkodelujući morfin (IR, eng. immediate release, sa brzim otpuštanjem aktivne supstance) i dugodelujući morfin (SR, eng. slow release, sa sporim otpuštanjem aktivne supstance). Kod nekih pacijenata morfin dovodi do teških neželjenih efekata i to je razlog zbog koga neki pacijenti ne žele ili ne smeju da ga uzimaju. U takvim slučajevima primenjuju se drugi alternativni opioidi. 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 (16). 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 (17–19). 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. Nove formulacije spomentuh opioida korisne su u lečenju kancerskog neuropatskog bola (za koji je poznato da se samo kod 40–60% pacijenata postiže delimično ublažavanje bola), a koji se leči kombinacijom opioidne terapije, antikonvulziva - gabapentin, pregabalin, duloksetin i tricikličnih antidepresiva (75mg/dnevno) i oni se danas uz kortikosteroide preporučuju kao jedini lekovi u prvoj liniji za neuropatski bol (ESMO preporuke 2018.).

ZAKLJUČAK

Hronični kancerski bol ostaje preovlađujući i jak za mnoge pacijente, posebno kod pacijenata 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.

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Konflikt interesa: Autori odbacuju mogućnost postojanja konflikta interesa

14

Pain in outdoor athletes: a study by SSAI committee for medicine in extreme environments

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ABSTRACT

Here we report the main results of the ongoing "Pain in Outdoor Athletes" study conducted by members and collaborators of the SSAI Committee for Medicine in Extreme Environments. The study aims to explore the relationship between psychological characteristics and acute musculoskeletal pain in outdoor athletes, and so far, 157 athletes participating in skyrunning, hiking, and climbing in Serbia have been included. The study found that higher pain scores were associated with higher physical effort, as well as with pain catastrophizing, anxiety, and depression. Depression and anxiety may explain 15% of the variability in acute musculoskeletal pain. The ongoing nature of the research highlights the complexity of investigating the relationship between psychological characteristics and acute musculoskeletal pain in outdoor athletes, emphasizing the need for further exploration in this field.

Introduction

The Committee for Medicine in Extreme Environments is a part of the Serbian Association of Anesthesiology and Intensive Care, which was established in June 14th 2021. The main idea behind the committee's formation is that the human body's physiological response to extreme environments, including high altitude, underwater environments, and physical exertion, is similar to that of critically ill patients and those under anesthesia. As a result, research conducted in extreme environments could provide valuable insights into understanding the physiology of patients in critical care and undergoing anesthesia.

The "Pain in Outdoor Athletes" study is a collaborative effort by teachers from two universities, medical doctors from two fields of medicine, and medical students

who are members of the Commetee for Medicine in Extreme Environments of the Serbian Association of Anesthesiologists and Intensive Care. The study, which is still ongoing, aims to investigate the relationship between psychological characteristics and acute musculoskeletal pain in outdoor athletes.

The interdependence of personality traits, anxiety, depression, and chronic pain is well-established. Studies have shown that anxiety and depression can affect the development and maintenance of chronic pain (1, 2), while other research has highlighted the role of personality traits in pain sensitivity and perception (3,4). However, the influence of these conditions, as well as personality traits, on acute pain, particularly musculoskeletal pain, remains relatively unexplored.

The choice of athletes as a model for acute pain is based on the fact that, unless an injury is the cause, muscle pain is caused by physical exertion and does not typically require treatment. In contrast, acute postoperative pain, which is commonly treated by anesthetists, is caused by injury, albeit iatrogenic, and its perception is influenced by various factors such as overall care perception and concerns related to the underlying condition requiring surgery. Therefore, athletes represent a simpler model for acute pain compared to surgical patients. From an ethical perspective, conducting experiments on relatively healthy individuals who knowingly and repeatedly expose themselves to pain is more favorable than on sick individuals seeking medical attention. Additionally, the concept of using athletes as a model for acute pain has been explored in previous studies (5).

Our study aims to investigate the relationship between psychological characteristics and acute musculoskeletal pain in outdoor athletes. The ongoing nature of the research highlights the complexity of investigating the relationship between psychological characteristics and acute musculoskeletal pain in outdoor athletes, and the need for further exploration in this field.

Methods

The study received approval from the institutional Ethical Committee and all participants provided informed consent. A total of 157 subjects engaging in skyrunning, hiking and climbing were recruited for the study. The sample size was determined for convenience and included all willing Serbian athletes from the selected disciplines.

Demographic and physical activity data

In terms of demographics and physical activity data, participants were asked to report their age, gender, height, and weight. For skyrunners and hikers, the total elevation gain, length of the track, and time needed to complete the track were recorded. The factual intensity of the physical activity was calculated as elevation gain in meters

per hour and kilometers per hour. Additionally, participants were asked to evaluate the perceived subjective intensity of the physical activity using an 11-point Likert scale.

Pain Assessment

Participants were instructed to assess their maximum and average pain intensity during the event or activity, as well as during training, using a Numeric Rating Scale (NRS). The perceived unpleasantness of the pain during the activity was evaluated on an 11-point Likert scale. Additionally, participants were asked to identify the primary site of pain using a modified version of the questionnaire developed by (6). To control for the potential influence of the concurrent use of analgesics, participants were asked to report whether they had used any analgesics or caffeine within 24 hours before or during the event.

Psychological assessment

The psychological assessment of participants in the study consisted of five self-report questionnaires. The HEXACO 100 Personality Inventory was used to assess six personality dimensions, including Honesty/Humility, Emotionality, Extraversion, Agreeableness, Conscientiousness, and Openness to Experience (7). The Pain Catastrophizing Scale (PCS) was used to measure pain catastrophizing, with three subscales assessing magnification, rumination, and helplessness (8). The Anxiety Sensitivity Index-3 (ASI-3) was also employed, consisting of three subscales assessing physical, cognitive, and social concerns related to anxiety sensitivity (9). In addition, the Generalized Anxiety Disorder-7 (GAD-7) scale was utilized to screen for and assess the severity of anxiety, with a score of 5 or more indicating anxiety (10). Depression severity was assessed using the Patient Health Questionnaire-9 (PHQ-9), with a score of 5 or more indicating depression (11).

Statistical analysis

The statistical analyses were conducted using IBM SPSS Statistics software version 22.0 (IBM, Armonk, NY, USA). The data were reported as either the median and interquartile range or frequencies, depending on the type of data. The significance of difference between subject groups was assessed using Kruskal-Wallis test. To measure the strength and direction of the association between variables, the Kendall tau-b correlation coefficient was calculated. Hierarchical regression modeling was used to assess potential predictors of acute pain. The level of statistical significance was set at 0.05.

Results

The psychological assessment of climbers was not completed by the manuscript submission deadline, so their data were not included in the analysis presented here. Table 1 shows the available data for demographics, physical activity, pain, and psychological assessment. Skyrunners had higher objective and subjective measures of activity intensity and reported higher maximum and average pain during the event, as well as higher pain unpleasantness compared to hikers. Hikers had significantly higher scores on emotionality, social concerns, and both anxiety scales. However, there was no significant difference between the two groups in terms of depression.

Table1. Demographics, physical activity, pain and psychological assessment.

	Skyrunners (n = 51)	Hikers (n = 54)
Age (years)	39.00 [34.00 – 45.50]	39.00 [33.00 44.00]
Gender (male/female)	30/21	22/32
Body Mass Index (kg/m2)	23.87 [22.74 – 25.60]	25.58 [23.34 – 28.09]
Average altitude gain (m/h)	329.00 [297.00 – 393.00]	157.00 [109.00 – 170.00]**
Average speed (km/h)	4.88 [4.51 – 5.87]	2.00 [1.91 – 2.30]**
Subjective activity intensity	8.00 [6.00 – 9.00]	4.00 [2.25 – 5.75]**
Maximum pain during event	6.00 [3.00 – 7.50]	3.00 [1.00 – 5.00]**
Average pain during event	3.00 [1.00 – 5.00]	2.00 [0.25 – 3.00]**
Unpleasantness of pain during event	3.00 [2.00 – 6.00]	1.00[0 – 3.00]**
Honesty/Humility	3.88 [3.50 – 4.19]	3.78 [3.25 – 4.13]
Emotionality	2.75 [2.38 – 3.19]	3.06 [2.69 – 3.39]**
Extraversion	3.56 [3.31 – 4.00]	3.44 [3.04 – 3.94]
Agreeableness	3.88 [3.50 – 4.13]	3.74 [3.25 – 4.00]
Conscientiousness	3.88 [3.50 – 4.13]	3.74 [3.25 – 4.00]
Openness to Experience	4.19 [3.81 – 4.49]	4.19 [3.88 – 4.38]
Magnification	3.00 [2.00 – 4.00]	2.50 [1.00 – 5.00]
Rumination	4.00 [2.00 – 7.00]	4.50 [1.00 – 7.25]
Helplessness	4.00 [2.00 – 6.00]	2.00 [0.75 – 6.00]
PCS score	10.00 [6.00 - 17.00]	8.00 [4.00 – 18.00]
Physical Concerns	2.00 [0 – 4.00]	2.50 [0 – 6.00]
Cognitive Concerns	1.00 [0 – 2.00]	1.00 [0 – 4.00]
Social Concerns	2.00 [1.00 – 4.00]	5.00 [3.00 – 7.00]**
ASI-3 score	6.00 [3.00 – 9.00]	10.00 [6.00 – 15.00]**
GAD-7 score	1.00 [0 – 3.00]	3.00 [0.75 – 6.00]**
PHQ-9	3.00 [1.00 – 6.00]	3.50 [1.75 – 6.00]

Data are expressed as median and interquartile range. Kruskal-Wallis test. *$p < 0.05$, ** $p < 0.01$. PCS – Pain Catastrophizing Scale, ASI-3 – Anxiety Severity Index-3, GAD-7 – Generalized Anxiety Disorder assessment-7, PHQ-9 – Patients Health Questionnaire-9.

There was a positive association between higher physical effort and higher maximum and average pain scores. Additionally, the pain scores were positively correlated with the magnification and rumination subscores of the PCS, the cognitive concerns subscale of the ASI-3, and the PHQ-9 scores (Table 2).

Table 2. Correlation between maximum and average pain during event and psychological characteristics.

	Maximum pain during event	Average pain during event
Subjective activity intensity	0.396**	0.411**
Average altitude gain (m/h)	0.297**	0.200**
Average speed (km/h)	0.308**	0.198**
Magnification	0.166*	0.163*
Rumination	0.136	0.159*
Helplessness	0.121	0.144
PCS score	0.142	0.166*
Physical Concerns	0.031	0.100
Cognitive Concerns	0.163*	0.245**
Social Concerns	-0.088	-0.007
ASI-3 score	0.010	0.121
GAD-7 score	0.114	0.182
PHQ-9	0.178*	0.190*

Kendall tau b correlation analysis. *p < 0.05, ** p < 0.01. PCS – Pain Catastrophizing Scale, ASI-3 – Anxiety Severity Index-3, GAD-7 – Generalized Anxiety Disorder assessment-7, PHQ-9 – Patients Health Questionnaire-9.

Based on the results of our correlation analysis, we aimed to assess the influence of depression and anxiety on acute musculoskeletal pain. Our findings, as presented in Table 3, suggest that the PHQ-9 score and the cognitive concerns subscale of the ASI-3 may explain 15 % of the variability in average pain experienced during the event, after controlling for physical effort and caffeine intake.

Table 3. Predictors of average pain during the event

	Average pain during the event		
Predictors	Standardized Beta	Adjusted R^2	Change R^2
Control variables		0.050	0.071*
Average speed (km/h)	0.110		
Caffeine during event	0.225		
Dependent variables		0.185	0.150**
PHQ-9	0.225*		
Cognitive concerns	0.229*		

Hierarchical regression linear model *p < 0.05, ** p < 0.01. PHQ-9 – Patients Health Questionnaire-9.

Conclusion

Our study aims at investigating the relationship between psychological characteristics and acute musculoskeletal pain in outdoor athletes. So far, we included 157 athletes engaging in skyrunning, hiking, and climbing in Serbia. Our results show that higher pain scores were associated with higher physical effort, as well as with pain catastrophizing, anxiety, and depression. Depression and anxiety may explain 15% of the variability in acute musculoskeletal pain. The ongoing nature of the research highlights the complexity of investigating the relationship between psychological characteristics and acute musculoskeletal pain in outdoor athletes and the need for further exploration in this field.

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Palliative radiation therapy in the treatment of cancer bone metastases pain

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ABSTRACT

Painful bone metastases are the most common indication for palliative radiotherapy. They are most commonly originating from breast, lung or prostate cancer and can be osteolytic, osteoblastic or mixed. Most cancer patients are treated with radiotherapy as one of the therapeutic modalities and 80% of them have a symptomatic benefit from radiation. Radiotherapy reduces tumor size, reduces symptoms, and additionally has an anti-inflammatory, antisecretory, antiedematous and analgesic effects. The use of radiotherapy should be safe and effective, with controlled number of side effects. Radiotherapy of bone metastases is carried out with aim to reduce pain, stabilize the osteolytic bone or to reduce the risk of pathological fractures and paraplegia. For analgetic purpose, palliative radiotherapy treatments are used with different fractional regimes. Fractional radiotherapy regimens are significantly more effective than single shoot technique in stabilization of patients and prevention of pathological fractures. Furthermore, one of the options is surgical decompression and stabilization followed by postoperative radiotherapy, that has been used in patients with spinal cord compression at one level and patients with instability of spinal cord that have expected longer survival time. Moreover, combination of transcutaneous radiotherapy of bone metastases and bisphosphonate application work effectively and synergistically in pain control.

Key words: *cancer pain, palliative radiotherapy, bone metastasis*

INTRODUCTION

Bone metastases are the most common cause of pain in patients suffering from cancer. Pain occurs as a result of compression of nerve endings, periosteal stretching

of nerves or growth within nerves and in the surrounding tissue. Cancer pain of bone metastasis varies in its character and can be intermittent or constant, can be associated with physical activity, and also it could became worsen during the day (1, 2).

Bone metastases occur in 30% to 70% of cancer patients. Studies have shown that 75% of patients with bone metastases have associated pain. Mostly bone metastasis originated from cancer of breast, prostate and lungs and they make about 50-80% of all bone metastasis. Moreover, common tumors with higher incidence of bone metastases are kidney and thyroid cancers. Hematologic malignancies such as lymphoma and multiple myeloma can lead to bone destruction.

By localization, the most common metastases have been seen in axial skeleton, mostly in vertebrae, but also in pelvic bones, femur and bones of the skull (3). Upper extremities are less affected with the incidence of 10% to 15% of all bone metastases.

Common treatments for bone metastasis include medications, radiation therapy and surgery. Medications used in people with bone metastasis include bone-building medications, intravenous radiation, chemotherapy, hormone therapy, targeted therapy, steroids and pain medications. Surgical procedures can help stabilize a bone that is at risk of fracture or repair a fractured bone.

Radiotherapy is one of the local modalities treatments of patients with malignant tumors that have pain. Radiation therapy may be an option if bone metastasis is causing pain that isn't controlled with pain medications or if the pain is confined to a small number of areas. Moreover, radiotherapy in patients with bone metastases may not affect disease outcome in terms of survival but may significantly improve the patient's quality of life during the survival time. Effective administration of palliative radiotherapy is based on three goals: (a) to achieve meaningful relief of symptoms; (b) to use treatment that reconciles patient inconvenience in the context of a limited survival time with the need for palliation that is as complete and durable as possible; and (c) to administer therapy with negligible or mild toxic effects. (4)

DIAGNOSIS OF BONE METASTASES

There are several diagnostic methods by which we visualize bone metastases such as radiography, skeletal scintigraphy, computed tomography, magnetic resonance imaging or PET scanner. Bone metastases in the form of lytic lesions, sclerotic lesions or pathological fractures can be visualized by radiography of the skeletal system, which is one of the oldest diagnostic methods. Sclerotic or blast lesions can also be detected by skeletal scintigraphy and computed tomography. They can detect both lytic and blast bone changes. However, the magnetic resonance imaging of bones represents gold standard in the detection of bone metastases and contributes to a better evaluation of metastases. The PET scanner is also one of the diagnostic methods that can detect bone

metastases, but it is less available. Invasive methods, such as biopsy of bone metastases are rarely applied in detection of bone metastases and in most cases it is not possible to determine the origin of the tumor (1, 5).

The role of radiotherapy

Numerous studies have confirmed that radiotherapy is an efficient and an adequate way of treating bone metastases (6, 7). Up 80% to 90% of radiated patients indicates a decrease in pain, and 50% of treated patients states complete pain loss after radiotherapy (8).

Palliative therapy involves the implementation of local or regional therapy, systemic therapy and supportive therapies. Local therapy is based on radiotherapy and surgical treatment of metastases. Systemic therapy includes chemotherapy, hormone therapy and bisphosphonates. Supportive therapy includes analgesics and psychosocial care.

Indications for the treatment of bone metastases with radiotherapy are:

1) Treatment of pain syndrome
2) Prevention of threatening fracture
3) Prevention of neurological compressions
   (a) the root of the nerve
   (b) indirect equivalent
   (c) the spinal cord

Compression of the spinal cord and threatening fractures are an urgent condition that requires an emergency implication of radiotherapy treatment.

The main objectives of bone radiotherapy metastases are a decrease in pain, a decrease in use analgesics, improving neurological outbursts and patient mobility, preventing complications of pathological fractures and compression of the spinal cord (6, 8).

Transcutaneous radiotherapy regimens and pathophysiological process of radiotherapy

Transcutaneous radiotherapy is a treatment with ionizing gradiation where is a distance between the source of radiation and the target (tumor of the body) 5cm to 2m. Typically, it is conducted on a linear accelerator (LINAC) by supervoltage electromagnetic radiation, mostly X rays and photons, less often electrons. For individual localizations, treatment with orthovoltage therapy can also be used (X-rays of higher energies up to 450KeV).

Transcutaneous megavoltage radiation therapy is standard therapy in palliative treatment of bone metastases. Numerous studies have examined different regimens of radiotherapy fractionation. In practice multiple fractional modes have been used, such as 30 Gy in 10 sessions, 20 Gy in 8 sessions, 20 Gy in 5 sessions, 16Gy in 4 sessions and 8 Gy in 1 session, also known as single shoot. There are a lot of different factors which determine which of the regimens will be applied, such as performance status of the

patient, the expected time survival, the presence of oligometastatic disease or status of multiple metastases. Some studies have shown that longer fractional regimens such as 30 Gy in 10 sessions provide longer time control of pain (6).

A group of radiation oncologists (RTOG) reported prospective randomized study RTOG 74-02 with different fractional regimes for radiotherapy of bone metastases. In this trial, patients were stratified into a group with solitary bone metastasis and a group with multiple bone metastases. Patients with solitary metastasis are divided into subgroups in relation to the primary tumor and the site of metastasis, and were irradiated with a dose of 40.5 Gy in 15fractions or 10 Gy in 5 fractions. Patients with multiple bone metastases are divided in the same way, and were irradiated with fractional regimes: 30 Gy in10 fractions, 15 Gy in 5 fractions, 20 Gy in 5 fractions and 25 Gyin 5 fractions. The results show that in patients with oligometastatic disease – up to 3 metastases, there was no differences in response to radiotherapy, i.e. effects of radiotherapy was the same in use of different fractionation regimes. In patients with multiple bone metastases, there was also no difference in the effects of radiotherapy between different fractionation regimens. Of all treated patients, 83% had a partial response, showing reduce in pain after radiotherapy, while53% of treated patients shown complete loss of pain. Reporting of pain after several months, occurred in 54% previously treated patients (9). Furthermore, results showed that low-dose shorter fractional regimens were equally effective as well as high-dose fractional regimes.

Blitzer and the authors reanalyzed the data RTOG 74-02 studies using multivariate regression analysis and found that extended fractionation regimens, 40.50 Gy in 15 fractions and 30 Gy in 10fractions, are more effective in controlling pain compared to shorter framing regimes. Logistic regression analysis showed that the number of fractions is related with complete control of the pain. Complete disappearance of pain had 55% of patients that were treated with 40.5 Gy in 15 fractions compared to37% of patients who received 20 Gy in 5 fractions (10).

The pathophysiological process of reducing pain after radiotherapy works in several ways. Radiation reduces tumor mass by leading to cell death with apoptosis. Radiation also destroys inflammatory cells by apoptosis, which reduces the release of mediators of cytokines that lead to the appearance of pain. Early reduction of pain primarily occurs based on direct damage to the osteoclast, reducing the release of cytokines and damaging the nerve endings by radiation. Direct devitalization of tumor cells is not most likely main mechanism by which the patient relieves pain after radiotherapy. It has been shown that patients note reduction of pain after 24 hours of completed radiation, indicating that the reduction of tumor mass is not a mechanism by which the patient relieves pain. However, it has been shown that even small doses of radiation can lead to a decrease in tumor mass (11).

The analgesic effect of radiotherapy has been usually occurred one to three weeks after radiation therapy. In some there is an increase in pain so-called "flare phenomenon"

that is prevented by the introduction of corticosteroids (dexamethasone) during radiation therapy. Analgesic therapy that has been used should be corrected during radiotherapy to avoid overdose or subdose (12). For these purposes, standardized tests are most often used to assess pain.

In 22% of patients treated with single-shot technique for bone metastases pain, there is a need for reirradiation, compared to 7%of patients with a need for retreatment after fractional radiotherapy (13). One of the most recent meta-analysis, involving 5,000 patients, shows that the rate of pathological fractures after one fraction and after fractional radiation is the same (3%v 2.8%) (14). When it comes to recurrent pain, in 63% of patients retreatment with radiation therapy had the same effect in pain control, as well as in the first radiation treatment (15).

In conclusion, we can say that fractional radiotherapy is significantly more effective than single shoot technique when it comes to stabilization of the patient and prevention of pathological fractures, but the possibility of performing fixation, general condition and associated the disease significantly affects the choice of the regimen (15).

Planning of radiotherapy of painful bone metastases is carried out on a conventional simulator (2D radiation technique) or CT simulator (3D technique radiation). After planning radiotherapy, the patient is radiated on a linear accelerator using high energy X-rays photons.

Evaluation of response of bone metastases to palliative radiotherapy

Classical biochemical and radiological scintigraphy methods are often not correlated with clinical benefit and performance status improvement.

The evaluation criteria include:

- Pain reliever score
- Quality of life
- Clinical examination
- Radiological-scintigraphy score
- Biochemical analyzes
- Histology (biopsy)

Methods for evaluating pain and quality of life

- LASA pain scale
- Categorical pain scale
- Analgesic score
- Rotterdam check list
- EORTC score 30 questionnaire

American Association of Radiation Oncologists (ASTRO) and the European Association of Radiation Oncologists (ESTRO) have established a consensus group that

has the goal to develop a standardized method of assessing the response to palliative radiotherapy of bone targets that will be applied in future studies (Table 1).

Table 1. Palliative radiotherapy: Fractionation regimens and response to radiotherapy

Mde of fractionation	Prognosis and indications	Length of therapy	Response to therapy
1x8Gy	Expected survival <3 months; painful uncomplicated bone metastases	1 day	60-90%
5x3-4Gy	expected survival 3-6 months; bone metastases affecting soft tissues; ulcerated or painful metastases in soft tissues	1 weeko	60-90%
10x3Gy	expected survival < 1 year; bone metastases with recalcification spinal cord or nerve compression pathological fracture	2 weeks	60-90%
13-15x3Gy	expected survival > 1 year; solitary bone metastases	3 weeks	60-90%

Prevention of pathological fractures

Metastases in the bones (especially the femur, vertebra) require the implementation of radiation therapy to prevent pathological fractures (1, 6). Bone metastases with more than 50% bone cortex destruction have been sent to an orthopedic surgery, to consider surgical or other forms of stabilization. In radiotherapy planning, it is necessary to assess the risk of pathological fracture in relation to the location of metastases, as well as percentage of bone mass destruction, primary histology of cancer and level of pain. If there has been done surgical stabilization, postoperative radiation therapy and radiation field should cover the entire length of the implanted stabilizer (18).

Radiotherapy of spinal cord compression

Radiotherapy of spinal cord compression is an emergency state in radiation oncology. Spinal cord compression occurs at 5% of patients who have malignant disease. At beginning, the pain usually increases over 7 weeks, showing the signs of neurological deficit. Magnetic resonance of the spine is the most appropriate diagnostic method to detect the compression of spinal cord. The most common place where spinal cord compression occurs is the thoracic spine. The most important prognostic indicator of

patient recovery is the ability of patient to walk; patients who walk during the treatment have an average survival of 12 months, while those who do not walk survive on average one month (18, 19, and 20). Furthermore, in prognostic factors has been included the timing of diagnosis of spinal cord compression, showing that given diagnosis earlier has been associated with better prognosis. After detection of spinal compression, in patients with pain is necessary include high doses of corticosteroids to reduce edema (12-16mg dexamethasone). Patients who do not have pain and that move normally do not require the use of corticosteroids. For radiation of spinal cord compression, prolonged radiation regime has been used, most often 30 Gy in 10 fractions. Clinical trials have shown that after palliative radiation71% of patients experience a decrease in pain (54% CR,17% PR), while 76% of patients become movable again, and44% of patients report improved sphincter function (18).

Neurological and orthopedic consultation before radiotherapy is performed in a certain group of patients (21). In patients with medulla spinalis compression, 10-15% of patients are referred to surgical treatment and postoperative radiation therapy, based on the neurological deficit and the expected survival. Patients whom surgical treatment have been performed have a Karnofsky index over70%, expected survival time more than 3 months, paraplegia lasting less than 48 hours and compression of the spinal cord at one level (1).

Patients who walk normally at the beginning of radiotherapy have 80% chance of staying mobile. In patients with paraparesis, 40% maintain normal mobility, while in paraplegic patients only 7% have become mobile. Fast paralysis progression in patients is a less favorable prognostic factor compared to those with slow development of neurological symptoms. Slow developments of neurological symptoms, compression and neurological deficit have been originated from venous congestion, which is reversible. Contrary to that, in patients with rapidly occurred paralysis, artery compression is associated with consequent ischemia of the spinal cord, or even with a spinal cord infarction (22).

Radiotherapy of nerve root compression or cauda equina syndrome

Cauda equina syndrome in patients with bone metastases manifests itself in the form of pain in lower back, unilateral or ischiatic pain, then bladder or bowel dysfunction, sensory disorders in the sedentary part or weakness of the lower extremities. Most often primary bone or bone tumors metastases in the lumbar spine led to the development of cauda equina syndrome (spinal cord ends at the level of the first lumbar vertebra). The same as when it comes to compression of the medulla spinalis, urgent treatment is required in the form of corticosteroids (dexamethasone) and conducting palliative radiation therapy at the level of fractured bone structures. When it comes to compression of the cauda equina or nerve roots, longer fractional regimens are applied, such as 30Gy in 10fractions. Shorter fractional regimens, like 20Gy in 5 or16 Gy in 4 sessions are performed in patients with expected shorter survival, poor general

condition or with difficult mobility. As in the case of compression of the spinal cord, and in compression of the nerves or cauda equina the most important parameter in the response to radiation therapy and better survival is the early diagnosis of compression and early treatment (23).

Palliative radiation therapy of multiple bone metastases

Palliative radiation therapy of multiple bone metastases can be carried out by half body irradiation (HBI). Conducting transcutaneous radiation therapy in large (wide) fields may be better than applying multiple local fields but requires centers with experience in large field dosimetry and treatment of acute therapeutic toxicity. Radiation of one half of the body is most often carried out in one session: 6-7Gy on the upper half of the body, and 7-8Gy on the lower half of the body. If it is carried out in two fractions, the time between them should be 2-4 weeks. It has been necessary a medical treatment for acute toxicity that half body radiation can lead to. Pain reliever effect is achieved at 55-100%patients, and complete pain loss in 5-50% of patients (24). Start of response to radiation therapy occurs between first and fourteenth day after radiation therapy, while about 50% of patients report a reduction/loss of pain in the first 48 hours after radiation. In the more than 50% of patients with a positive response in control or loss of pain, pain control lasts until the end of the disease. Half body radiation has been applied in patients with multiple bone metastases, especially in patients with prostate cancer. In addition to pain control, HBI extends the time to the new painful bone metastases. Finally, application of HBI reduces the number of patients requiring retreatment in one year (25, 26).

Systemic radiation of bone metastases

Numerous studies have shown that radionuclides have been absorbed in the places of bone demages. They can be effective as monotherapy or as an adjuvanted to conventional radiation therapy in bone metastases. Most often, systemic radiation is applied in patients with bone metastases originated from breast cancer or prostate cancer. If the patient has adequate bone marrow reserves and is without spinal cord compression, in certain specialized centers systemic radiation can be applied with strontium or quadrammet. It has been shown relief of the pain in 3 to 6 weeks after systemic radiation. Unwanted effects that occur after the application of the systemic radiation are leucopenia and anemia that occur in 10 to 30% of treated patients. The systemic radiation can be combined with transcutaneous radiation therapy and can be repeated several times (1, 6).

Bisphosphonates in the treatment of painful bone metastasis

Bisphosphonates are analogues of pyrophosphate which act by blocking the function of osteoclasts and thus reduce bone resorption in painful bone metastasis. Multiple bone metastases often lead to hypercalcemia due to bone breakdown, and bisphosphonates are a key therapy for the resulting hypercalcemia. Moreover, the use of bisphosphonates leads to a decrease in pain in patients with painful bone metastases

and prevents the occurrence of pathological fractures and spinal cord compression caused by bone metastases. Numerous studies have shown that the bisphosphonate application in patients with painful bone metastases originating from breast cancer led to better pain control, but also in patients with primary bone tumors. After the first administration of bisphosphonates, a transient increase in pain may occur, so it is necessary to increase the existing analgesic therapy (1, 2, and 27). Demonstrated efficacy of bisphosphonate in the prevention of bone complications (spinal cord compression, compression of nerves or the formation of pathological fractures) led to the use of bisphosphonates in an adjuvant approach. One of the most effective bisphosphonates is zoledronic acid. Impaired renal function can be contraindication for zoledronic acid application. Studies have shown their effectiveness in pain control and the treatment of bone metastases in patients with lung cancer, prostate cancer, multiple myeloma and breast cancer. Denosumab is monoclonal antibody for NFKβ activator receptor (nuclear factor kapa b-RANKL). Denosumab is the latest therapy in the treatment of bone metastases. Blocking RANKL factor leads to deactivation and a decrease in the viability of osteoclasts and thus leads to a decrease in resorption and increased density of bones that prevent the formation of pathological fractures.

As mentioned before, radiation therapy of bones metastasis has the same mechanism of action as bisphosphonates. Bisphosphonates cause a decrease in the activity and viability of osteoclasts. Radiation therapy reduces the activity of osteoclasts, which reduces the production of osteoclast activating factors (OAF's) and acts synergistic with bisphosphonates. Previous studies have not confirmed that certain radiation fractionation regimens and certain bisphosphonates have higher efficiency than others (28).It is recommended to use bisphosphonates and palliative radiation therapy of bone metastases at the same time, because it effectively controls pain and helps reossification of damaged bones.

CONCLUSION

Transcutaneous radiation therapy of bone metastases is one of the most important therapeutic modalities in treatment of painful bone metastases. Different regimens of fractionation such as 8 Gy in one fraction, 16 Gy in 4 fractions, 20 Gy in 5 or 8 fractions and 30 Gy in 10 fractions provide excellent pain control and minimal side effects. Conducting retreatment of radiation therapy for painful bone metastases can be a safe and effective therapy in patients with expected shorter survival time. Surgical decompression and stabilization of the spine jointed with postoperative radiation therapy is administered to patients with spinal cord compression in one vertebral level, with expected longer survival time and in patients with instability of the spinal column.

Bisphosphonates together with transcutaneous radiation therapy of bone metastases act effectively and synergistically in pain control.

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16 Interventional treatment of cervical pain syndromes

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Abstract

The article attempts to summarise the x-ray anatomy and technical aspects of basic interventional pain management in the cervical spine.

Key words: *cervical spine, x-ray anatomy, medial branch block*

Introduction

In this article we will discuss cervical x-ray anatomy and the basics of x-ray guided pain interventions in the neck. The main techniques used in the cervical spine are the medial branch block (MBB), radiofrequency ablation (RF), translaminar epidural and transforaminal epidural. Occipital nerve block and suprascapular nerve block are the two important techniques that may not directly involve the spine, but are indispensable in the management of cervical pain syndromes.

MBB is the most commonly used procedure. It is the first technique to be considered - for neck pain, upper limb radicular pain and cervicogenic headache. In the latter case we often combine MBB with an occipital nerve block. In the majority of cases MBB is effective enough, and the more definitive RF ablation, or epidural injection in radicular pain is only needed in a minority of cases. We carry out MBB with plain 0.5% L-bupivacaine and no steroids. The view that local anaesthetic blocks 'do not last' is incorrect, and it is especially incorrect in relation to the cervical spine. Some patients need repeat blocks, and some need RF ablation, and it goes without saying that no procedure has a 100% success rate.

Postoperative dizziness is a common side effect. We avoid bilateral blocks, with some exceptions that are beyond the scope of this article. Dizziness can still be significant after a unilateral procedure, sometimes to a degree of fainting. A useful trick is to administer glycopyrrolate if the patient is bradycardic.

We perform all cervical procedures in the standard anaesthetic environment - ventilatory equipment, oxygen, monitoring and IV cannula. In our experience conscious sedation is helpful. We use a combination of midazolam and alfentanil. In older patients we skip midazolam and reduce the dose of alfentanil.

It is our practice to use interventional procedures in combination with cervical spinal exercises, life-style advice, and, importantly, weaning the patient off pain medication. The crucial element of the treatment is to use exercises in the immediate postoperative period, in the recovery area, while the painful elements are anaesthetised. In some cases, postoperative exercises allow to restore neck and arm movement to a degree that would be impossible with any form of physical rehabilitation. Pain is linked to function. Functional improvement tends to reduce pain.

The key structure of the x-ray anatomy is the articular pillar (or column) in the lateral view. Articular pillar is the x-ray landmark of the medial branch, and it is used for both MBB and RF ablation (Fig. 1). It is not enough to simply screen the cervical spine in the lateral projection. It is necessary to obtain the true lateral view where articular pillars and facet joints from the opposite

sides are fully superimposed and there are no double shadows. Levels may need to be adjusted individually.

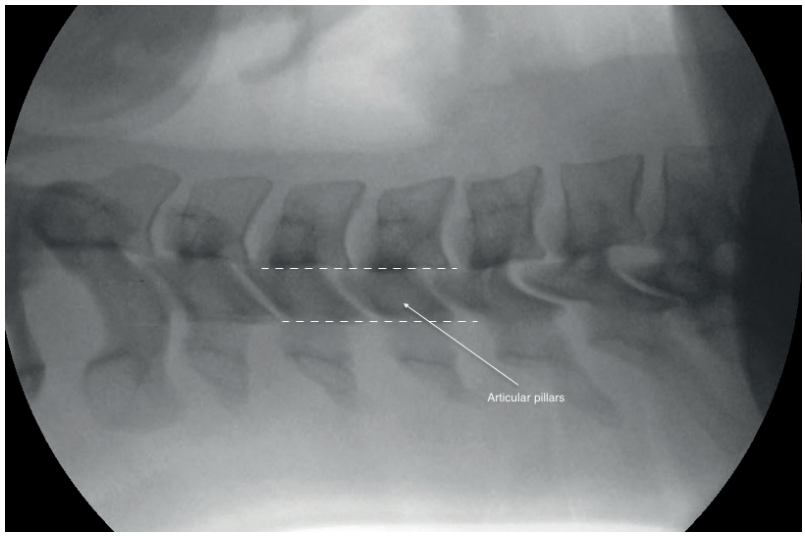

Figure 1. True lateral view with correctly visualised articular pillars

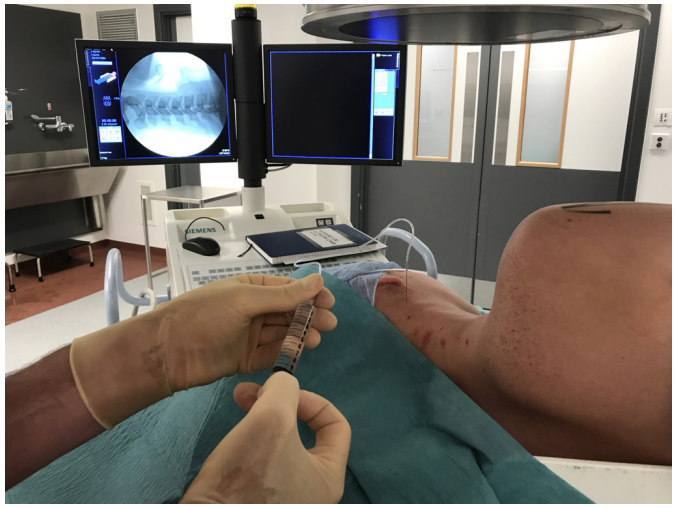

Figure 2. Positioning (in the picture the screen was moved from its usual position in front of the operator).

The true lateral view is a skill that needs a fair amount of training, and it starts from positioning the patient. On the operating table, we prefer the patient in the lateral position with the head supported by a stack of sheets, the image intensifier above the patient's neck (Fig. 2). It is easy to add or remove a sheet - to adjust the hight of the head level with the thoracic spine. Note the longitudinal alinement of the C-arm and the table, i.e. the C-arm is at the top of the table, not the side - to keep the operator access unobstructed. The operator stands behind the patient with the screen opposite, straight ahead of the operator.

We like to aline the x-ray view with the patient - the horizontal orientation of the spine, with the cranium in the direction of the patient's head, spinous processes facing down (Fig. 2). There is no need for a long spinal needle. A fine 60 mm 23-24G needle is long enough and safer because it is short. There are needles with a built-in extension (Fig. 2). The needle in the picture is on the C2/3 joint space for the C3 medial branch, and the entry point is just below the ear. At full depth the needle is hardly half-length deep in a slim patient. About 0.5ml of local anaesthetic per level is probably enough although with experience we increased the volume to about 1ml per level.

Somewhat contrary to the accepted practice, we block all cervical levels from C2 down, regardless of the pain distribution. We advise against blocking a smaller number of levels selectively, as we do not believe in the clinician's ability to pinpoint the responsible level by examination alone, but also because dogmatic attribution of certain symptoms to certain levels can be counterproductive. It is different with RF where one should narrow the levels down using diagnostic MBBs.

To count vertebrae in the lateral view, we tend to start from C2 because of its unique elongated shape resulting from the odontoid peg. There is no facet joint between C1 and C2, hence open access into the vertebral canal (Fig. 3).

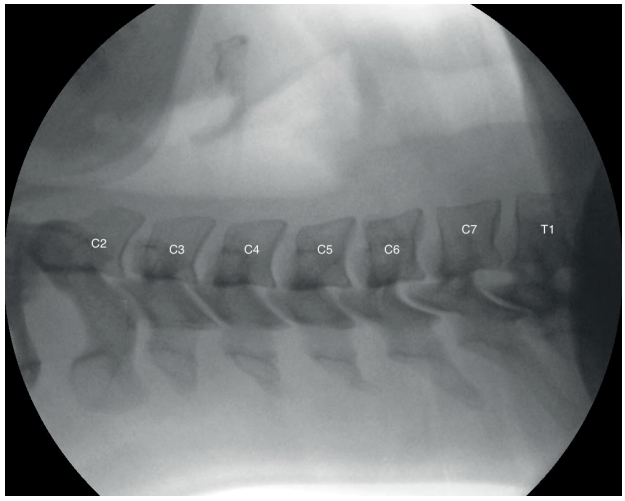

Figure 3. Vertebral count. At C1/2 there is no articular pillar and the access to spinal canal is wide open.

The operator must be aware of the spinal canal and vertebral artery (Fig. 4). The vertebral artery, that passes through the transverse foramina, is anterior and medial to the articular pillar, and is outside its boundaries in the true lateral view. The spinal canal is shielded by the articular pillars, except for C1/2 level, but the posterior aspect of the canal is easily accessible through the interlaminar spaces and should be avoided (Fig. 5). Note the significant distance between the posterior margin of the articular pillar and the spinous process, representing the laminae, that are inside the boundaries of the canal in the lateral view.

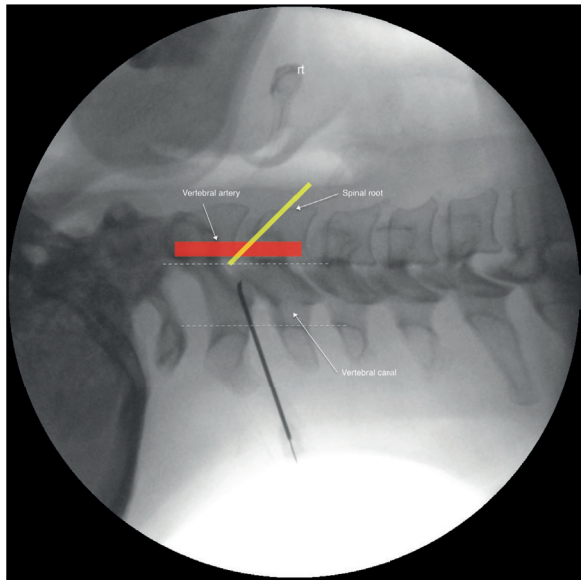

Figure 4. Vertebral artery and spinal canal in the lateral view. The curved RF needle is half-way to its final position along the C2/3 joint.

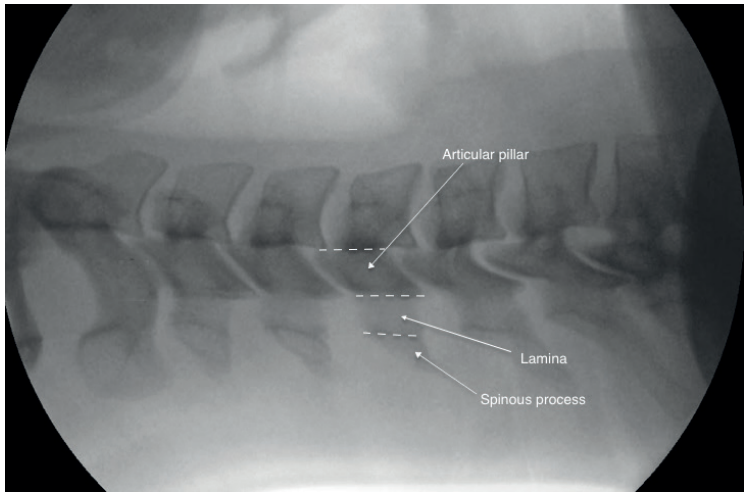

Figure 5. (also see Figure 4). Interlaminar spaces are within the boundaries of spinal canal in the lateral view.

The x-ray target for the MBB is the intersection of the diagonals in the articular pillar's parallelogram (Fig. 6). The C3 has a superficial medial branch (the 3d occipital nerve) that overlies the C2/3 joint, and a deep medial branch that is blocked at the diagonal intersection of the C3 articular pillar. The superficial branch is targeted in the vicinity of the joint on both sides (Fig. 7). It is likely that the local anaesthetic spreads across the pillar substantially beyond the point of the needle as can be demonstrated by injecting contrast medium.

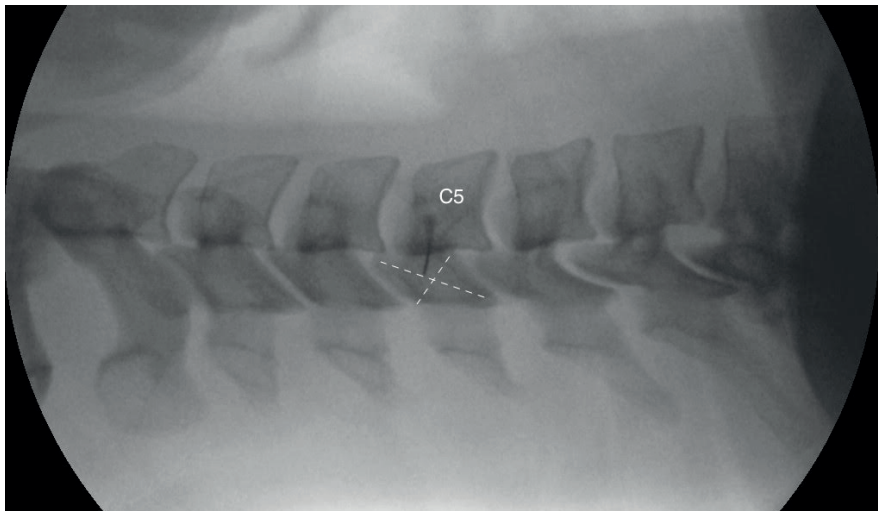

Figure 6. Diagonal intersection - the target for MBB.

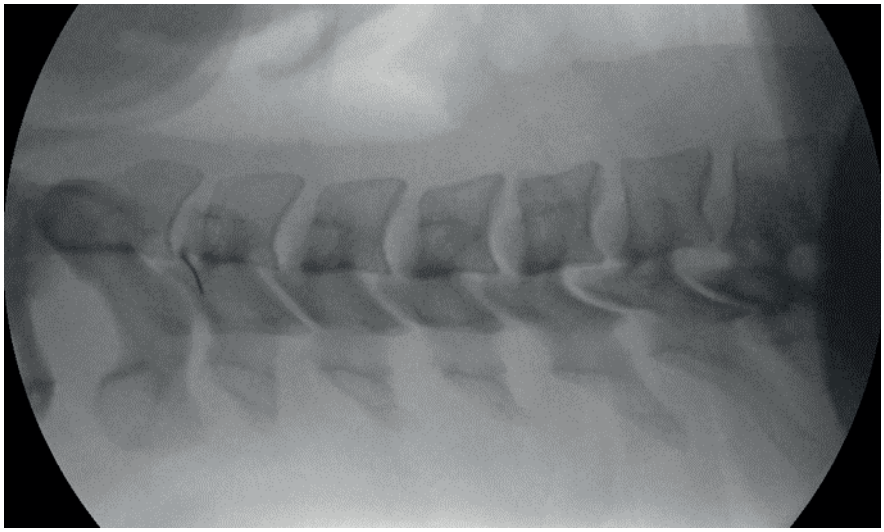

Figure 7. C2/3 joint margins - target for C3 MBB, superficial branch.

The C7 medial branch runs more cranially, over the superior articular process rather than the middle of the articular pillar (Fig. 8)

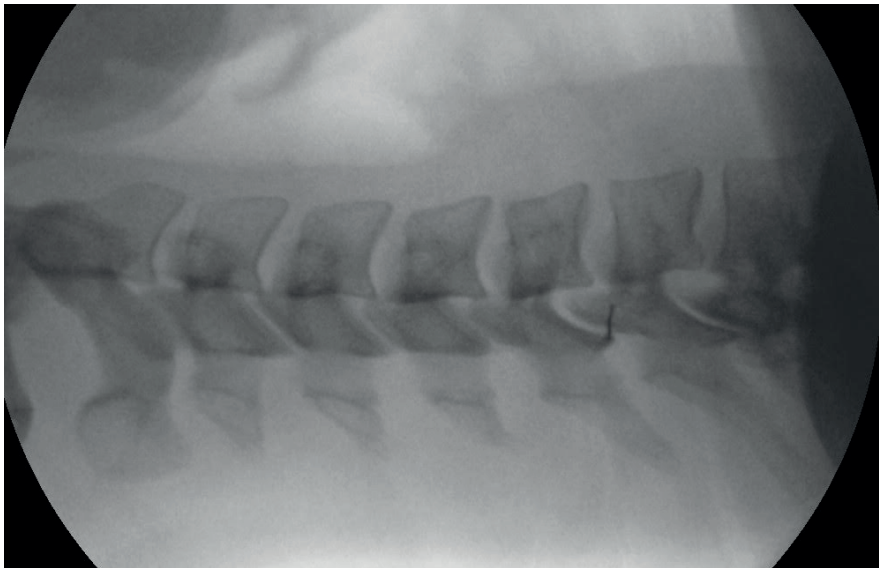

Figure 8. C7 MBB.

Conclusion

This article is mainly about the x-ray anatomy of the lateral view - the basis of pain interventions at the cervical level. It provides the necessary foundation for MBB and RF.

The practical aspects of RF procedures as well as translaminar and transforaminal epidural, complications and consent are outside of its scope. It is important to emphasise two practical lessons of interventional work in the cervical spine. First, interventions must not come in isolation. They need to be combined with an adequate exercise regime and daily living/occupational adjustment. Second, in cervical pain syndromes, be it neck pain, shoulder/arm pain or headache, a sustained resolution of the presenting complaint is achievable, and it helps greatly if both the doctor and the patient have a clear goal of a good long-term outcome.

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17 Beyond Opioids: Ultrasound-guided Peripheral Nerve Blocks for Pain Management

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Ultrasound-guided peripheral nerve block

Ultrasound-guided regional anesthesia (UGRA) can be used to avoid risks associated with general anesthesia, enhance operating theatre efficiency, and reduce hospital length of stay (1-3). Evidence also supports a role in improving outcomes after surgery and in mitigating the need for systemic analgesia with potentially dangerous side effects, such as opioids (4,5).

Ultrasonography (US) is one of the most frequently used imaging modalities for evaluating each individual's soft-tissue musculoskeletal system components and nerves. Ultrasound imaging is a quick, cost–effective, noninvasive, and uncomplicated imaging technique that clearly shows the peripheral nerve anatomy and its surroundings (6).

Significant progress has been made in managing regional anesthesia with the advent of ultrasound guidance (7). It has gained popularity as a complement or alternative to nerve stimulation techniques. Ultrasound-guided nerve blocks (USGNB) involve identifying the target nerve, observing the adjacent anatomy (including blood vessels, lymph nodes, and other vital structures), the needle tip, and real-time monitoring of the local anesthetic distribution (8). Identifying and tracing peripheral nerves to other sites where local anesthetics can be administered without risking neurovascular injury is possible. Direct visualization of the target nerve and the deposition of local anesthetic have increased the efficiency of block operations while reducing placement problems and patient discomfort (9). However, patient access to UGRA may be impeded by needing a specialist with the necessary expertise and abilities. The capture and interpretation of ideal ultrasound pictures, including identifying critical sono-anatomical features, are fundamental abilities.

Nerve Block Safety and Technique

As with any medical procedure, it is essential to consider the steps necessary to safely and effectively perform a nerve block, avoid potential complications, and know how to maximize patient safety in the event of an adverse outcome (10).

Setup Before Blocking

Before performing a USGNB, the clinician must identify the source of pain and evaluate potential contraindications: such as coagulopathy, anesthesia allergies, or a history of neurologic deficiency (11). Consent should be obtained after discussing the risks and benefits of the procedure, and a comprehensive neurologic exam (including the presence of pulses) should be documented in the patient's medical record before administering the nerve block. Discuss the block with the orthopedic consultant if a fracture is present, or an orthopedic intervention may be required to ensure that it does not affect their management. Place the patient on a cardiac monitor to assess systemic toxicity, and be prepared to administer lipid emulsion if necessary. The provider must identify the block's extremity and location and confirm the administered dose with two-person verification. Lastly, remember to take and record a time-out!

Adverse Effects of Nerve Block

Clinicians administering UGNBs must be aware of local anesthetic systemic toxicity (LAST) signs and symptoms and have a 20% lipid emulsion available to treat this uncommon but potentially fatal complication.

Although nerve blocks are safe when administered with a sterile technique and following the safety procedures outlined above, potential risks must be considered against the analgesic benefit. If an excessive quantity of nerve block is injected directly into the circulation, there is a danger of infection, hematoma, nerve injury, and local anesthetic toxicity. Patients may suffer from LAST due to direct infusion of anesthetics into the vasculature, although this is uncommon. Patients with organ dysfunction are at higher risk. Confusion, anxiety, a sense of impending doom, headache, drowsiness, dizziness or lightheadedness, and tremors are all side effects of local anesthetic toxicity, as are hemodynamic collapse, widened PR, QRS prolongation, and the possibility of ventricular tachycardia, ventricular fibrillation, hypotension, and asystole (12). Seizures are treated with benzodiazepines, and 1-1.5 ml/kg of intravenous fat emulsion (intralipid, 20% solution) is administered over 1 minute (which can be repeated every three minutes to a total of 3 ml/kg, with the patient already on an infusion if necessary 0.25 ml/kg/min) until the circulation is restored.

Post-Block Evaluation

Repeat the neurologic exam and write a patient procedure note detailing the amount and type of anesthesia used, the location of the nerve block, the time of administration, and any potential complications associated with the nerve block (1-5).

Conclusion

In the context of both safety and effectiveness considerations, nerve blocks are an excellent adjunct to pain presentations. Peripheral nerve blocks are an easy-to-learn, non-opioid analgesic technique for optimal perioperative and postoperative pain management. With a multimodal analgesic approach incorporating a nerve block, the adverse effects of opioids, such as postoperative nausea and vomiting (PONV), sedation, respiratory depression, and inpatient delirium, can be minimized. A step-by-step approach to pre-block assessment, anesthetic administration, and post-block reassessment enables clinicians and providers to reduce pain and limit adverse effects associated with the local anesthetic injection.

The Most recent research and a Look to the Future

We are all witnessing the increasing use of artificial intelligence in medicine. According to the most recent study, using artificial intelligence to interpret ultrasound images in regional anesthesia has excellent potential.

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18 Opioids in palliative care, pharmacological attitude

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Opioids are the most commonly used drugs for the treatment of moderate to severe pain in malignant patients, according to the principle of "analgesic ladders" of the World Health Organization (WHO)[1,2]Recent evidences suggest that patients with moderate pain due to malignant disease respond better to low doses of strong opioid (e.g. morphine, oxycodone) instead of higher doses of mild opioids (e.g. codeine)[2,3]. Morphine is the gold standard in the treatment of moderate to severe malignant pain, and the first therapeutic choice according to the most clinical guidelines4. Morphine exhibits the same effectiveness, but is not superior, compared to other strong opioids (oxycodone, buprenorphine, hydromorphone, methadone, fentanyl)4.

Opioids, depending on the specificity of binding to receptors (mi, kappa, delta), cause numerous effects according to the function of organ systems and the distribution of receptors (e.g. in the brain, spinal cord and in the periphery). The primary clinical application of opioids is to reduce pain, but numerous other effects have also been noted. At the level of the central nervous system, opioids, in addition to the analgesic effect, exert a motivational effect, euphoria, alertness, affect autonomic, hormonal and motor processes. Peripherally, they affect the visceromotor systems (eg, gastrointestinal motility and smooth muscle tone)[3].

There are differences in the therapeutic effect of opioids in different individuals. For example,. 30% of patients with malignant pain do not have an adequate therapeutic response to the administered morphine, the so-called "morphine non-responders"[4]. The causes of inadequate therapeutic response to the prescribed opioid are different, e.g., pharmacokinetic, genetic polymorphism, polymorbidity, polytherapy, etc. [4].

Genetic variations occur at different levels of opioid metabolism (e.g. transporters in the process of opioid absorption, P-glycoproteins; genetic polymorphism of

isoenzymes of the microsomal oxidative system of the liver, such as CYP2D6 in codeine metabolism; CYP -2B6 and -2D6 in methadone metabolism; or glucuronyltransferase, UGT2B7, during the metabolism of morphine) [4]. Pharmacogenetic differences result in an unpredictable clinical response (reduced or enhanced effects of opioids, including side effects).4 Routine, genetic testing would allow the selection of the right opioid and the appropriate dose for each patient individually4. Present comorbidity and reduced organ function (e.g., liver, kidney) can significantly change the pharmacokinetics of the administered opioid, with the ultimate outcome of an inadequate therapeutic response.

Renal insufficiency Caution is required when using opioids with active metabolites in people with impaired kidney function (increased analgesic effect due to accumulation of metabolites). The accumulation of morphine-6-glucuronide in people with weakened kidney function contributes to increased analgesia, while the accumulation of morphine-3-glucuronide can have toxic effects (antianalgesic and excitatory effects) [4]. In patients with a mild to moderate decrease in glomerular filtration (eGFR 30-89 ml /min) all opioids can be prescribed, with a dose reduction or an extension of the dosing interval (transdermal fentanyl, hydromorphone, morphine, oxycodone, tilidine and tramadol)5. Tapentadol and buprenorphine transdermally can be prescribed without dose correction[5]. In the case of advanced renal insufficiency (CKD 4: eGFR < 30 ml/ min), opioids are used more cautiously[5]. The use of tapentadol is not recommended (due to lack of data), and buprenorphine, fentanyl or hydromorphone are recommended, as well as in hemodialysis patients5. The starting dose should be therapeutically effective, but lower than usual starting doses, individually adapted to each patient, with active monitoring of the effects of therapy (analgesic effect vs. side effects) [5].

Hepatic insufficiency. Opioids can be prescribed, but carefully with a lower starting dose, with a very careful increase in the dose (risk of hepatic encephalopathy) [5]. Special attentions should be paid to the prevention of constipation[5]. Short bowel syndrome. Patients with short bowel syndrome may be at risk for reduced absorption of orally administered modified-release drugs5. Liquids, capsules, uncoated tablets, or transdermal application are recommended5. In patients with a colostomy, opioid absorption occurs smoothly (stomach, proximal small intestine), without specific recommendations for the form and dose of opioids5. In patients with small intestine stomas (jejunostomy, ileostomy), the pharmacokinetics of drugs depends on the remaining length of the small intestine, so better absorption of soluble drug formulations is expected[5].

ADVERSE EFFECTS

The most common side effects in malignant patients treated with opioids for pain are sedation, nausea, vomiting, constipation, dry mouth, drowsiness, confusion, bad dreams4.Less common are itching, sweating, opioid-induced hyperalgesia, myoclonus,

delirium (acute confusional state), hallucinations, and respiratory depression, but they require serious attention[3,4, 6,8] .

Most patients are advised to use laxatives prophylactically, especially if they have previously had problems with bowel movements (decreased number of bowel movements, straining, gas production, hard stool consistency and abdominal discomfort) 5.The use of antiemetics may be necessary at the start of therapy, in the first 2 - 4 weeks (period of tolerance development) if nausea and vomiting occur[5]. If psychiatric side effects occur (drowsiness, delirium, hallucinations, persistent anxiety or depression, suicidal thoughts), myoclonic movements, itching, urinary retention, or sleep-disordered breathing the opioid dose should be reduced as much as possible or opioid rotation performed[5].

In the case of an increase in pain intensity, the cause should be determined, e.g. disease progression, tolerance, opioid-induced hyperalgesia5. If continuous tolerance develops with a repeated need to increase the dose, without adequate analgesia (even after 2 opioid rotations), instead of further opioid rotation, a gradual reduction or withdrawal of opioids is advised5. If the intensity of pain increases despite an increase in the dose of opioids, and worsening of the disease and tolerance are excluded, opioid-induced hyperalgesia can be suspected5. It is characteristic that nociception increases over time, pain spreads to other fields, there is hyperalgesia to external stimuli (Colvin et al. 2019) [5]. The possibility of reducing opioids should be evaluated, as much as possible5.

DRUG - DRUG INTERACTIONS

Adverse effects of opioids are most often caused by the opioid itself or, more seriously, by a combination of opioids and other drugs[6,9]. Polymorbidity and polytherapy increase the risk for drug-drug interactions[6,8]. Drug-drug interactions can be pharmacokinetic (one drug affects the pharmacokinetic characteristics of the other drug - absorption, distribution, metabolism and excretion) and pharmacodynamic (the effects of two drugs are potentiated or antagonized)6,10. Pharmacokinetic interactions in a malignant patient are inhibition or induction of opioid metabolism (CYP450 enzymes), reduced renal excretion of opioids, inhibition of other drugs metabolism by opioid6. The effects of opioids that are metabolized by the cytochrome P450 isoenzyme CYP3A4 (fentanyl, methadone, oxycodone, buprenorphine) can be enhanced by the simultaneous use of CYP3A4 inhibitors (voriconazole, fluconazole, clarithromycin, cimetidine and sertraline, etc.). Increased effect of opioids can also occur due to sudden discontinuation of therapy with inducers of CYP3A4 (carbamazepine)6. Pharmacodynamic interactions enhance analgesic efficiency and toxicity, or reduce opioid effect (antagonism), through opioid and non-opioid mechanisms (e.g. termination of opioid effect by administration of opioid receptor antagonists; modification of cholinergic, adrenergic, dopaminergic and serotonergic actions in the CNS)6. The simultaneous use of opioids with other

sedative drugs significantly increases the frequency of adverse events, due to the depressant effect on the central nervous system (Dowell et al., 2016)6. E.g. the combination of opioids with benzodiazepines[5,6] or gabapentinoids increases the risk and potentiates depressant effects on the CNS (reduced respiratory function, McAnally et al., 2020, with the risk of fatal overdose)5. Other CNS symptoms include delirium (hyperactive or hypoactive) with or without hallucinations, serotonergic syndrome, myoclonus, hyperalgesia, extrapyramidal symptoms, catatonia, and neuroleptic malignant syndrome[5].

The risk for the occurrence of serotonergic syndrome is increased with the simultaneous use of opioids (eg fentanyl, methadone, oxycodone, tapentadol and tramadol), with serotonergic drugs (eg newer SSRI and SNRI antidepressants, tricyclic antidepressants, MAO-inhibitors, NaSSA (mirtazapine), John's wort, L-tryptophan, lithium, triptans) (Baldo, 2018)5. Symptoms, mild to fatal, include altered mental status, autonomic dysfunction and neuromuscular excitation5. The diagnosis can be made in patients on serotonergic drug therapy with the existence of one more symptom , such as: spontaneous clonus, provoked clonus with agitation and diaphoresis, ocular clonus with agitation and diaphoresis, tremor and hyperreflexia, hypertonia, body temperature over 38 C with ocular and provoked clonus (Simon & Keenaghan, 2019)[5].

Simultaneous administration of opioids with anticholinergic drugs (antihistamines, antitussives, tricyclic antidepressants, antipsychotics, anticonvulsants, carbamazepine, antiemetics, local ophthalmoplegics, Kiesel et al., 2018)[5] can cause, especially in elderly patients, symptoms of anticholinergic syndrome, such as constipation, urinary retention, tachycardia, hypertension, mydriasis, dry skin and mucous membranes, decreased alertness, aggressiveness, agitation, hallucinations, coma, dizziness and dysarthria[5].

Patients with cardiovascular disease or on therapy with drugs that affect the QT interval before starting therapy with opioids, methadone, oxycodone (> 100 mg/d) and tramadol, should have an ECG performed. If the QT interval is prolonged, prescribing these opioids should be avoided5. Methadone, even in low doses, poses a high risk, with the potential for dose-dependent prolongation of the QT interval and the development of vascular tachycardia (Krantz et al., 2003)5. Tramadol and oxycodone are drugs of moderate risk, and can develop long QT interval and ventricular tachycardia at high doses5. Morphine and buprenorphine are drugs of low risk and do not cause prolongation of the QT interval, at usual doses (Behzadi et al., 2018).[5] Therapeutic and supratherapeutic doses of tapentadol do not affect the QT interval in healthy individuals (Oh et al ., 2010) [5].

CONCLUSION

Pain is a common symptom in cancer survivors and in those living with progressive, advanced disease7. Unfortunately, for a large part of patients, pain remains poorly controlled[7]. Barriers to successful pain therapy include poor pain testing, inadequate

access to strong opioids, complications during opioid therapy (adverse effects, drug-drug interactions) [7,8]. Professionals should know possible risks for the failure of opioid therapy and methods of prevention (choice of an adequate opioid, dose, dosing regimen, in accordance with the individual characteristics of the patient, comorbidity and polytherapy, with frequent re-evaluations of pain and the effects of therapy).

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Treatment of acute postoperative pain, the new face of multimodal analgesia

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ABSTRACT

Management of pain remains undertreated in the pediatric population. Multimodal analgesia (MMA) integrates the use of several analgesic medications, each of which targets a different pain-related receptor, and thereby exhibits its pain reducing effect by way of a different mechanism of action. MMA approach to pain management includes pharmacologic and non-pharmacologic options. Effective postoperative analgesia in infants and young children continues to evolve with innovative methods of therapy using newer drugs or older drugs introduced via novel routes.

Key words: *child, postoperative pain, analgesia*

INTRODUCTION

The concept of balanced or multimodal analgesia (MMA) was first introduced decades ago, and the concept rejects the notion that monotherapy (the use of a single drug alone), is an adequate approach to acute pain management and instead claims that the combination of several analgesics offers superior pain control. MMA integrates the use of several analgesic medications, each of which targets a different pain-related receptor, and thereby exhibits its pain reducing effect by way of a different mechanism of action. When two or more analgesic medications are combined for pain relief, it allows for lower doses of each drug to be administered and thus minimizes the risk of adverse drug effects (1). MMA is recommended for postoperative pain in many clinical situations and is the key focus of a joint clinical practice guideline from the American Pain

Society, American Society of Regional Anesthesia and Pain Medicine (ASRA), and the American Society of Anesthesiologists (2). The application of multimodal pain management to current perioperative clinical practice, however, has been slow and inadequate (1). The practice of pediatric pain management has made great progress in the last decade with the development and validation of pain assessment tools specific to pediatric patients (3). Nevertheless, there are marked differences in financial and personal resources in different institutions and countries and also considerable variations in the availability of analgesic drugs and techniques across Europe (4). Also, there is a lack of adequate research in this field, and more specifically on identifying which pediatric patient is at higher risk of poor postoperative pain management (5).

ASSESSMENT OF PAIN

Management of pain remains undertreated in the pediatric population. Additionally, it has been identified that pain may not be adequately or regularly assessed in pediatric patients admitted to hospital. Appropriate, frequent, and clearly documented assessment of pain is vital to satisfactory pain management. Self-report is preferred where possible because pain is a subjective experience. When self-reporting may not be accurately relied upon in young or non-communicative children, additional assessment approaches such as behavior-based measures can aid in, or serve as an alterative to self-reporting. Reviewing physiologic parameters and reports from caregivers can round out the pain assessment. Numerous pain assessment tools exist for the pediatric population. Currently, there is no evidence to recommend any one single tool as superior. Pain assessment tools should not be the only method of quantifying pain. The pain score should be contextualized with assessment of patient satisfaction, family feedback, feedback from the patient's nurse, and physiological parameters. Pain assessment should be performed every 2-4h (6).

ELEMENTS OF MULTIMODAL ANALGESIA

It is important to define the minimum standards of pediatric postoperative pain relief that children can expect after surgical procedures even in settings with limited resources. It is also incorrect to believe that all surgical patients require opioids (7). Surgical pain may be nociceptive, neuropathic, mixed, psychogenic, or idiopathic, depending on the surgery (8). A good MMA protocol is a checklist rather than a recipe; it will standardize the categories of analgesics while still allowing for some flexibility in the individual components based on patient comorbidities, allergies, medications, and previous surgical experiences. It should be taken into account that approximately 80% in the

United States and over 50% in Europe of drugs given to children are prescribed 'off-label', because they have not received approval for their use in younger age groups (9).

Non-opioid analgesics are the cornerstone on which to build a successful perioperative MMA regimen. In addition to the absence of opioid side effects, many of these agents are highly effective in reducing postoperative pain and allowing for faster mobilization and meeting milestones. Non-steroidal anti-inflammatory drugs (NSAIDs) represent class of medication that is highly effective for perioperative pain management and should be considered for MMA protocols.

Patient-controlled analgesia (PCA) with intravenous opioids is a commonly used modality for acute pain management in the pediatric population. PCA use is generally accepted as safe in the pediatric population. It can be offered to any child who is able to grasp the concept of pressing a button to help relieve pain. Typically, for institutions with an age requirement for PCA use, PCA can be used for children 6 years and older. Although opioid consumption has been found to be higher with PCA compared with non-patient controlled regimens, generally severe adverse effects have not been found to be higher with PCA (6).

Regional anesthesia continues to be an important component of peri-operative care and analgesia for pediatric patients. Use and feasibility of different peripheral nerve blocks for perioperative analgesia continues to expand, with data from the Pediatric Regional Anesthesia Network (PRAN) providing safety information (10).

The multimodal approach to pain management also includes non-pharmacologic options. These include both physical and psychological strategies. Patients may benefit from massage, heat compresses, ice packs, repositioning, or some physical activity (such as walking or sitting up in a chair for a short period of time). Some patients may find cognitive behavioral strategies, such as using imagery or relaxation, to be helpful. In pediatric patients, hypnosis has been shown to be effective for reducing pain.

PERSISTENT POST-SURGICAL PAIN

In pediatric practice, potential adverse effects of anesthesia on the developing brain are an important area for ongoing research, and there is also evidence that early life pain and surgery can produce long-term changes in sensory processing and future pain response. At all ages, effective analgesic management needs to extend beyond the immediate perioperative period, to also consider pain at home following discharge (as discussed above) and the potential for more persistent postsurgical pain (PPSP) (11). Parental responses and attitudes also need to be considered. Higher catastrophizing by parents (i.e. thoughts and beliefs that an event or situation is worse than it is) was associated with increased child pain at 2 weeks (12) and persistent pain at 12 months (13).

CONCLUSION

The evidence regarding the efficacy of analgesics and techniques available to guide postoperative pain treatment in pediatric patients are still limited. Effective postoperative analgesia in infants and young children continues to evolve with innovative methods of therapy using newer drugs or older drugs introduced via novel routes. Age appropriate pain assessment tools continue to be critically evaluated, validated and improved as one of the most critical components of pain management. A multimodal approach to preventing and treating pain is usually used to minimize the side effects of individual drugs or techniques.

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How to read statistics? How to present your data (tables vs. graphs)?

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Introduction

During our daily clinical and research work, we encounter numerous problems. However, one of the more common problems is the statistical analysis of data, the methodologically correct setting of the research and the correct presentation and interpretation of data (1). Universal aspects of science include collecting, analyzing, and reporting data. In each of these aspects, errors can and do occur (2). Here, as a rule, it is necessary to consult experts who deal with the field of biostatistics and methodology on a daily basis. In human clinical research, study results, which are statistically significant are often interpreted as being clinically important. While statistical significance indicates the reliability of the study results, clinical significance reflects its impact on clinical practice (1). The aim of this paper is to show the basic assumptions on which the correct interpretation of the presented results is based.

Variables

Variable is each phenomenon whose characteristics change in quantity or quality (3), and it can be presented in the form of descriptive values or amounts (4). The independent variable is manipulated by the investigator and its effects on the dependent variable are measured.

Qualitative (categorical) variables are those that express a qualitative attribute (3, 5). The values of a qualitative variable do not imply a numerical ordering. Quantitative (numerical) variables are those variables that are measured in terms of numbers. Thes variables can expresed as integer (discrete variables) and as number in decimals (continuous variables) (4).

Whenever possible we should work with continuous variables because they give us the possibility to use a wide range of statistical tools. If it is not possible to use a continuous variable that is obtained by measuring some phenomenon, then we can use variables that are obtained by counting, that is, they are expressed in whole numbers. On the other hand, when working with descriptive variables, if possible, these variables should be scaled and some logical division based on the intensity of the phenomenon should be obtained. If it is not possible, then we use descriptive parameters to display some variable with a certain number of categories. The choice of statistical method depends on the type of data presentation. A common problem is the poor choice of statistical tools depending on the type and characteristics of the variables, which can lead to wrong conclusions.

Randomization and bias

In clinical trials, patients are assigned to groups that receive different treatments. The process of assigning patients to these groups by chance is called randomization. In the simplest trial design, one group receives the new treatment (investigational group), and the other group receives standard therapy (control group). The end of the clinical trial, researchers compare the groups to see which treatment is more effective or has fewer side effects. A computer is usually used to assign patients to groups.

Randomization, in which people are assigned to groups by chance alone, helps prevent bias. Bias occurs when a trial's results are affected by human choices or other factors not related to the treatment being tested.

Randomization is the process of by which each subject has the same chance of being assigned to either intervention or control. Neither the subject nor the investigator should know the treatment assignment before the subject's decision to enter the study. This removes investigator bias. Bias may be defined as systematic error. Therefore, bias reduction is an extremely important issue in the trial design and implementation phase. Randomization tends to produce groups that are comparable, and it guarantees the validity of statistical tests. In generaly, the benefits of randomization are that it eliminates the selection bias, balances the groups with respect to many known and unknown confounding or prognostic variables, and forms the basis for statistical tests, a basis for an assumption of free statistical test of the equality of treatments (6).

Randomization requires generating randomization schedules. Generation of a randomization schedule usually includes obtaining the random numbers and assigning random numbers to each subject. Random numbers can be generated by computers or can come from random number tables. Today, the best metod of randomization is to use the computer programming to do the randomization (6, 7).

Statistical significance vs. clinically important

One of the common problems faced by authors of medical articles is in the interpretation of the word "significance" (1). The term "statistical significance" is often misinterpreted as a "clinically important" result. The confusion stems from the fact that many people equate "significance" with its literal meaning of "importance". Measures of statistical significance quantify the probability of a study's results being due to chance. Clinical significance, on the other hand, refers to the magnitude of the actual treatment effect (i.e., the difference between the intervention and control groups, also known as the "treatment effect size"), which will determine whether the results of the trial are likely to impact current medical practice. The "P" value, frequently used to measure statistical significance, is the probability that the study results are due to chance rather than to a real treatment effect. The conventional cut off for the "p" value to be considered statistically significant is of 0.05. What a $p < 0.05$ implies is that the possibility of the results in a study being due to chance is <5%.

In clinical practice, the "clinical significance" of a result is dependent on its implications on existing practice-treatment effect size being one of the most important factors that drives treatment decisions (8).

Statistical significance is heavily dependent on the study's sample size; with large sample sizes, even small treatment effects (which are clinically inconsequential) can appear statistically significant. For example, in one study compared overall survival in 569 patients with advanced pancreatic cancer who were randomised to receive erlotinib plus gemcitabine versus gemcitabine alone (9). Median survival was found to be "significantly" prolonged in the erlotinib/gemcitabine arm (6.24 months vs. 5.91 months, $p = 0.038$). The $p = 0.038$ means that there is only a 3.8% chance that this observed difference between the groups occurred by chance (which is less than the traditional cut-off of 5%) and therefore, statistically significant. In this example, the clinical relevance of this "positive" study is the "treatment effect" or difference in median survival between 6.24 and 5.91 months – a mere 10 days, which most oncologists would agree is a clinically irrelevant "improvement" in outcomes.

Authors should bear in mind that interpretation of study results should take into account the clinical significance by looking at the actual treatment effect (with confidence intervals) and should not just be based on "P" values and statistical significance (10).

Sample size and power study

Clinical research studies need to be carefully planned to achieve the aim of the study. The study must have an adequate sample size, relative to the aims and the possible variabilities of the study (11). A power calculation needs to be before a study is initiated

to determine the appropriate sample size. Sample must be 'big enough' such that the effect of expected magnitude of scientific significance, to be also statistically significant. Same time, it is important that the study sample should not be 'too big' where an effect of little scientific importance is nevertheless statistically detectable. Sample size also is important for economic reasons: An under-sized study can be a waste of resources since it may not produce useful results while an over-sized study uses more resources than necessary. In an experiment involving human or animal subjects, sample size is a critical ethical issue. Since an ill-designed experiment exposes the subjects to potentially harmful treatments without advancing knowledge (12-17). Thus, a fundamental step in the design of clinical research is the computation of power and sample size. Power is the probability of correctly rejecting the null hypothesis that sample estimates does not statistically differ between study groups in the underlying population. Large values of power are desirable, at least 80%, is desirable given the available resources and ethical considerations. Power proportionately increases as the sample size for study increases (18, 19).

The calculation of an appropriate sample size relies on choice of certain factors and in some instances on crude estimates. There are 4 factors that should be considered in calculation of appropriate sample size: alpha level, power, effect and alternative hypothesis (one- or two-tailed) (20-22). The each of these factors influences the sample size independently, but it is important to combine all these factors in order to arrive at an appropriate sample size. Also, study design has a major impact on the sample size.

Sample size calculated is the total number of subjects who are required for the final study analysis. There are few practical issues, which need to be considered while calculating the number of subjects required: 1) all eligible subjects may not be willing to take part the study; 2) missing data for any reasons. It may, therefore, necessary to consider these issues before calculating the number of subjects to be recruited in a study in order to achieve the final desired sample size. Additional 10-20% subjects are required to allow adjustment of other factors such as withdrawals, missing data, lost to follow-up, etc (23).

Graphical and tabular methods presented of data

Data can be presented in one of the three ways: as text; in tabular form; or in graphical form (24, 25). Nominal (and ordinal) data can be summarized in a table that lists individual categories and their respective frequency counts, i.e., a frequency distribution. One can also use a relative frequency distribution, which lists the categories and the proportion with which each occurs. Frequency distributions and relative frequency distributions can also be summarized as bar charts and pie charts, respectively. Interval data are typically summarized in a histogram. Steps for constructing a histogram is as follows: Partition the data range into classes or bins; Count the number of observations that fall in each class; and Summarize the resulting frequency distribution as a table or as a bar chart.

Tabular Methods are used to summarize the data in table form. It is a systematic organization of information in grid row and columnar structure. The most frequently used tabular format for data summarization is Frequency table and Cross-tabulation.

On the other hand, graphical methods are a visual way of presenting data using charts and graphs. The visuals make the data intuitive and self-understandable. The most frequently used visual representation of data are Bar Plot, Histogram, Pareto Chart, Box Plot, Pie Chart, Line Plot, and Scatter Plot.

Bar Plot: Only one categorical variable or one categorical variable and one continous measure. A bar plot is a chart that presents categorical data with rectangular bars with heights or lengths proportional to the values that they represent. Visually represents frequency distribution.

Stacked Bar Plot: Two categorical variables. A stacked bar chart, also known as a stacked bar graph, is a graph that is used to break down a category by another category and compare parts of a whole. Visually represents cross-tabulation data.

Histogram: Only one continuous variable. A histogram is an approximate representation of the distribution of numerical data. It is created by converting a continuous variable into categorical by binning/bucketing it.

Distribution Plot (Density Plot): Only one continuous variable. A density plot is a representation of the distribution of a numeric variable. It uses a kernel density estimate to show the probability density function of the variable. It is a smoothed version of the histogram. Visually shows Skewness in data.

Box Plot (Box and Whisker Plot): Only one continuous variable or one continuous and one categorical variable. The box plot is a standardized way of displaying the distribution of data based on the five-number summary: minimum, first quartile, median, third quartile, and maximum. The Minimum and Maximum in box-plot are Lower Control Limit (LCL) and Upper Control Limit (UCL). Any data point beyond the LCL or UCL is typically considered as an outlier. Quickly helps find outliers in data.

Line Plot: One of the dimension has to be Time and the second dimension a Continuous Variable. A line plot is a type of chart that displays information as a series of data points called 'markers' connected by straight line segments. Visually shows trends in Time Series Data.

Scatter Plot: Two continuous variables. A graph in which the values of two variables are plotted along two axes. The pattern of the resulting points on the plot visually depicts the existence of Correlation between the two variables. Quickly helps find Correlation.

Pie Chart: One categorical variable associated with a continuous measure. A pie chart is a circular statistical graphic, which is divided into slices to illustrate numerical proportions. Quickly helps compare parts of a whole.

Statistics are used every day

Note that statistics are used every day. For example, have you chosen a option of therapy that your doctor said would extend your life expectancy by 5 years if successful, but had a 10% risk of serious side effects? This is one everyday situation where a good understanding of statistics can serve as a guide to making better decision. The very significant fenomen in statistics is average- the usual, or what might be considered ordinary. In this situation, for easier survival of statistics, find some software that will help you manipulate a given set of values.

What is an Interquartile Range?

The interquartile range is a measure of where the "middle fifty" is in a data set. Where a range is a measure of where the beginning and end are in a set, an interquartile range is a measure of where the bulk of the values lie (26). That's why it's preferred over many other measures of spread when reporting things with nonparametric distribution.

Conclusion

Statistical data processing should be pre-planned, purposeful, and realistic, since inadequate data processing can lead researchers to the wrong way of concluding. Therefore, the proper selection of variables, randomization, calculate power study and sample size and adequatly graphical and tabular methods presented of data are the one of the many key steps of each study.

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Perioperative opioid versus non – opioid analgesia: risks and benefits

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ABSTRACT

Opioids are widely used in the treatment of perioperative pain but there have been great advances in alternative non-opioid options for pain management during and after surgery. Pharmacokinetic and pharmacodynamic properties of opioids vary with age, especially in neonates and very young children, so their doses and dosing intervals have to be adjusted. Assessment of pain is challenging in infants and small children, and it is hard to distinguish pain from discomfort and appropriate pain assessment is necessary to guide analgesia during perioperative period. Inadequately treated pain has long term deleterious consequences so it is necessary to find a good balance between analgesia and potential side effects. Perioperative pain control utilizing analgesia without opioids is becoming more popular because of all side effects of opioids and growing evidence suggesting that nonopioids are very useful. Multimodal analgesia and multidisciplinary approaches to treat pain, decreases opioid consumption and increases patients outcomes.

Key words: *Children, perioperative analgesia, opioids, non- opioids.*

INTRODUCTION

The treatment of perioperative pain in children is very important topic but there are few evidence-based reports available to guide their use in this sensitive population. Opioids as antinociceptive agents are widely used in perioperative period as essential part of balanced anaesthesia and their pharmacokinetic and pharmacodynamic properties vary with age. Greatest variations in pharmacokinetic parameters are in neonates

and very young children. Neonates have larger volume of distribution and decreased protein binding which results in a greater free fraction of the morphine in the blood. Blood brain barrier is more permeable, hepatic enzymes and glomerular filtration are immature, the clearance of morphine is decreased. The primary metabolite of morphine (morphine-6-glucoronide) has greater analgesic and respiratory depressant effect than morphine, so doses should be 50-70% lower and dosing intervals age-adjusted and much longer in this age group. Opioid administration in infants younger than 3 months should be monitored in intensive care unit, and after this age they are not in increased risk of respiratory depression compared to older children and adults at the same blood concentration of opioid. Older children, from 2 – 11 years of age have a higher clearance and larger volume of distribution of morphine than older children and adults (1).

Fentanyl, sufentanil, alfentanil also have lower clearance in neonates, while remifentanil clearance is greatest in neonates and decreases with age (2). The dose od opioids should be similar to older children after 6 months of age.

Patient-controlled analgesia (PCA) has become the standard after major surgery in children. There were no randomized controlled studies that compared PCA with intermittent administration of opioids in children. PCA is not applicable in small children, and trials showed no benefit of PCA over nurse – administrated IV opioids and parent - controlled analgesia, but with appropriate training and monitoring (3).

Continuous opioid infusion with PCA fail to show better pain control in children with increased level of sedation and according to randomized controllled trials pediatric patients have lower risk of serious adverse effects associated with this way of administration of opioids compared to adults, possible because of continuous respiratory monitoring (4).

Tramadol is often used in postoperative pain control but with restricted use in children after tonsillectomy, children who have obstructive sleep apnea (OSA), lung disease and obesity. Tramadol is a prodrug metabolized by enzyme CYP3A4 and CYP2D6, and in case of the ultra rapid metabolizm, it can cause apnea as well as seizures (5).

Codeine should be avoided in children because 1% od North Europeans and 29% of Ethiopians experience ultra rapid metabolism of codein to morphine, while 10% of people lack the ability to metabolize codeine to morphine, so they have little analgesic benefit from this drug (6).

Although widely used and nesessary, side effects of opioid therapy are very common. Respiratory depression, urinary retention, constipation, pruritus, nausea and vomiting are most often side effects responsible for delayed patients' recovery after surgery. It is also known that opioids can cause postoperative delirium and high doses of intraoperative opioids are associated with hyperalgesia and increased postoperative opioid requirements due to opioid tolerance (7). Opioid induced hyperalgesia (opioid paradox) is a neuroadaptation process which enables chronic pain development (8). Any opioid is capable of potentially inducing hyperalgesia, particularly short-acting

opioids. Moreover, opioids cause immunomodulation that may have a negative impact on infectious or cancerous pathologies (9) and possible neurotoxicity (10). Finally, perioperative opioid administration predisposes to opioid dependence. There is also growing incidence of opioid overdose in pediatric patients, particularly teenagers (11).

Concern about all these effects emerged new strategies to move from the mainstay of perioperative pain control with mainly opioids toward the use of multimodal analgesia. Utilizing two or more drugs with different mechanisms of action produce synergistic interaction, which able dose reduction of opioids, minimizing the side effects (12).

Most frequently used antinociceptive agents apart from opioids include NMDA (N-methyl D-aspartate) antagonists (e.g., ketamine), alpha 2 -agonists (dexmedetomidine, clonidine), NSAIDs (nonsteroidal anti-inflammatory drugs), gabapentin, tricyclic antidepressants, lidocaine, neuraxial anaesthesia, regional nerve blocks. They decrease the need of opioids for adequate intraoperative antinociception and post operative analgesia, and the choice of non-opioid adjuvants depends on surgery performed and the patient itself.

The use of ketorolac as an adjunct to PCA for perioperative pain control in children is highly recommended, as well as other NSAID. Studies showed that single dose of ketorolac intraoperatively reduces morphine requirements in the first 12 hours (13).

Acetaminophen as an adjunct to opioids, also has opioid sparing effect and the incidence of vomiting and sedation in these patients is lower. There is evidence that acetaminophen is less effective for neonates then older children, particularly for procedural pain (14).

The opioid-free anaesthesia (OFA) technique is based on combining different drugs that act on different receptors, have analgesic effect and minimize sensitization of the central nervous system caused by opioids, including locoregional analgesia. It means no administration of intraoperative systemic, neuraxial or intracavitary opioids. There is evidence that OFA compared with opioid-based anaesthesia, provides good results regarding pain scores postoperatively and less nausea and vomiting (15).

Systematic review and meta-analysis by Grape, et al. showed that dexmedetomidine opioid-free anaesthesia was superior to remifentanil opioid-based anaesthesia with better postoperative pain control and lower requirement of i.v. morphine equivalents (16). Hontoir et al, reported lower postoperative pain scores in their trial with patients using clonidin (17). Nonetheless, many trials reported a statistically longer stay in post-anaesthesia care unit in the opioid-free group. This is related to the fact that dexmedetomidine has a long half-life (2-2.5 h), thus associated with slow recovery (18). Another limitation is its delay of action (6 minutes), clonidine even longer delay (20 minutes) and halflife of 15 hours. Both drugs are associated with risks of hypotension and bradycardia.

Other limitations of opioid free analgesia are side effects of non - opioid analgetics. Nonsteroidal anti-inflammatory drugs (NSAIDs) can be harmful to the gastrointestinal

system. Acetaminophen can be hepatotoxic and has been associated with agranulocytosis, and local anesthetics at high doses can result in neurological and cardiac complications. Dexmedetomidine should be given over at least given over 10 min to avoid hypertensive episodes, bradycardia, and even asystole. Clonidine in low dose has an increased risk of clinically relevant hypotension. Many drugs used in this technique such as ketamine and gabapentin also have substantial addictive potential and may also lead to long-term difficulties (19).

Neuraxial anesthesia and peripheral nerve blocks require a certain skill set, and patients that receive neuraxial anesthesia need to be monitored closely postoperatively.

CONCLUSION

Whether it is possible to deliver safe and stable anesthesia without intraoperative opioids to many patients undergoing various surgical procedures, OFA still raises questions.

Current trend is ndividualized anaesthesia with individual monitoring and titration of medication for the patient (20). Monitoring of nociception is essential for titration of pain medication but accurate monitoring is not jet available although would be ideal to guide perioperative pain management on patients.

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Jedinstvenost S-ketamina - od mehanizma dejstva do kliničkog efekta
The uniqueness of S-ketamine - from the mode of action to its clinical effect

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SUMMARY

The chemical specificity of ketamine produces the different receptor type interreactions and consequently its clinical indicationes. By the FDA (Food and Drug Administration) and EMA (European Medicines Agency), ketamine is approved for the treatment of pharmacoresistant depression, but not as monotherapy, but in combination with antidepressants. Ketamine is a phenyl-cyclidine derivative that achieves its mechanism of action primarily by non-competitive blockade of NMDA-receptors (n-methyl-d-aspartate) distributed in the brain (reticular formation of the brain stem) and interneurons of the posterior horn of the gray matter of the spinal cord. Ketamine indirectly activates the GABA system, agonizes mi- and kappa-opioid receptors, inhibits L-type voltage-dependent calcium channels (smooth muscle relaxation), blocks K-type calcium channels (BK channels), primarily suppresses spinal microglia, influencing the therapy of neuropathic pain. Ketamine acts as an allosteric molecule that changes the conformation of the NMDA receptor and blocks the receptor ion channel. In order for ketamine to reach its phenylcyclidine binding site, the channel needs to be open and the receptor active. Metabolism of ketamine takes place in the liver via the cytochrome system to the active less potent metabolite, nor-ketamine. Metabolites of ketamine show a significant antidepressant effect. Kidney elimination pathway of ketamine metabolites is crutial. Ketamine isoforms show different affinity for the NMDA receptor. S-ketamine has 3-4 times higher affinity for the NMDA receptor compare to the r-form and 2 times higher affinity for the same receptor compare to the racemate. The higher receptor affinity of s-ketamine results in a faster onset and shorter elimination halftime, considering that

it is necessary to apply a lower dose of s-ketamine to produce the same clinical effect compared to the r-isomer and the racemate. Consequently, the dose-dependent side effects are less prevalent after the administration of s-ketamine.

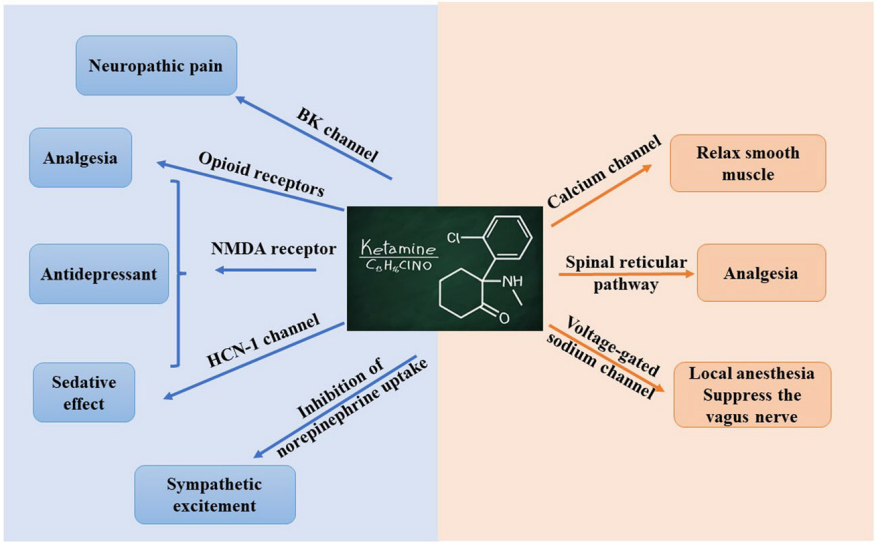
Key words: *s-ketamine, alosteric modulation, NMDA*

UVOD

Nakon što je 1962. godine sintetisan, kroz 2 godine je zabeležena i prva preklinička primena ketamina kao bezbednog anestetika na laboratorijskim životinjama, da bi kroz nešto manje od 10 godina zabeležena i prva zloupotreba ketamina u humanoj populaciji (Ketalara) pošto su uočena njegova psihomimetska svojstva (1). U novijoj istoriji, zapažen je i pozitivan učinak u lečenju hroničnog bola sa izraženom neuropatskom komponentom, pozitivan učinak u kontroli akutnog postoperativnog bola i prevenciji nastanka hroničnog postoperativnog bola kod rizičnih populacija pacijenata kao i pozitivan efekat u suzbijanju suicidalnih ideja (2). Hemijska specifičnost ketamina uslovila je receptornu raznolikost i posledično kliničku primenu. Od strane FDA (Food and Drug Administration) i EMA (European Medicines Agency), ketamin je odobren za lečenje farmakorezistentne depresije, ali ne kao monoterapija,već u kombinaciji sa antidepresivima (3).

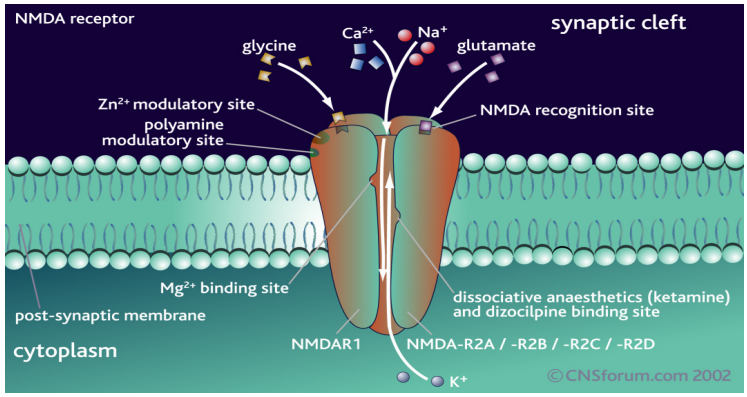
Struktura i metabolizam ketamina, strukturne razlike između S- i D- forme

Ketamin je fenil-ciklidinski derivat i niz godina je prisutan u obliku racemske smeše koja sadrži S- i D- enantiomere u istom odnosu, ali isto tako ketamin postoji i kao izolovana, S-forma. Ketamin svoj mehanizam dejstva ostvaruje primarno, nekompetitivnom blokadom NMDA-receptora (n-metil-d-aspartat) rasprostranjenih u mozgu (retikularnoj formaciji moždanog stabla) i interneuronima zadnjih rogova sive mase kičmene moždine čime indirektno aktivira i GABA sistem, agonizuje mi- i kapa-opioidne receptore, inhibira L-tip voltažno zavisnih kalcijumovih kanala (relaksacija glatke muskulature), blokira K-tip kalcijumovih kanala (BK kanala) čime primarno suprimira spinalnu mikrogliju utičući na terapiju neuropatskog bola. Takođe, blokira i HCN kanale (hyperpolarization activated-cyclic nucleotide) i transport monoamina čime utiče na simptome depresije. Noviji mehanizam dejstva podrazumeva i aktivaciju AMPA (a-amino-3-hydroxy-5- methyl-4-isoxazole propionicacid) receptora od strane metabolita ketamina (hidroksi-norketamin) što se manifestuje brzim antidepresivnim efektom. Mehanizam dejstva ketamina i njegovi efekti prikazani su na slici 1(4,5,6).



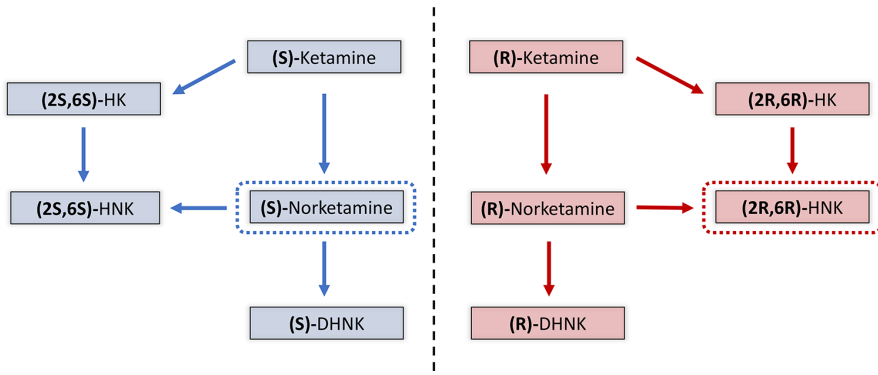
Slika 1: Mehanizam dejstva ketamina i njegovi klinički efekti (4)

Osnovni mehanizam dejstva ketamina u terapiji bola potiče od njegove interakcije sa NMDA-glutamatnim receptorom, ponašajući se kao alosterički molekul koji menja konformaciju receptora i blokira jonski kanal. Ketamin se vezuje za fenil-cikldinsko mesto sa unutrašnje strane jonskog kanala glutamatnog receptora. Kako bi ketamin mogao da stigne do svog vezujućeg mesta, potrebno je da kanal bude otvoren, a receptor aktivan. Kada je receptor neaktivan, jon magnezijuma je vezan za NMDA receptor i blokira kalcijumovu struju. Aktivna forma receptora, odnosno otvoren kanal podrazumeva vezivanje glutamata i glicina za receptor, disocijaciju magnezijuma sa svog vezujućeg mesta (koje je takođe, sa unutrašnje strane jonskog kanala), što za posldicu ima influks velike količine jona kalcijuma i aktivaciju sekundarnih mesendžera: NO, prostaglandini, ... NO direktno inhibira GABA aktivnost (smanjuje presinaptičku inhibiciju) i podstiče presinapsno oslobađanje glutamata. Prostaglandini direktno učestvuju u prenosu nociceptivnog signala. Otvoren jonski kanal receptora je posledica influksa brze natrijumove i kalcijumove struje, što je uslov za vezivanje ketamina. Međutim, postojanje efluksne spore kalijumove struje održava kanal dovoljno dugo otvorenim i omogućuje vezivanje ketamina, istovremeno povećavajući vrednost membranskog potencijala, započinjući hiperpolarizaciju i zatvaranje jonskog kanala (Slika 2). Ketamin sporo disosuje sa svog vezivnog mesta na receptoru. U momentu zatvaranja jonskog kanala, kada glutamat disosuje sa svog vezivnog mesta, 86% ukupno vezanog ketamina ostaje zarobljeno u zatvorenom kanalu i nastavlja da blokira receptor, čineći ga neosteljivim na nove količine glutamata (7-10).



Slika 2: *Prikaz vezujućeg mesta ketamina na NMDA receptoru*

Metabolizam ketamina se dešava u jetri putem sistema citohroma (CYP3A4, CYP2B6, CYP2A6), do aktivne forme nor-ketamina, potom do dihidro-norketamina, odnosno do hidroksi-norketamina koji se ekskretuju putem urina (Slika 3), sa višestruko manje potentnosti u odnosu na ketamin. Dokazana je značajna efikasnost u kontroli depresivnih epizoda od strane metabolita ketamina. Ketamin podleže metabolizmu prvog prolaza kroz jetru te su određeni putevi primene manje zastupljeni zbog manje bioraspoloživosti leka (oralna primena-45% biološke raspoloživosti). Nakon preuzimanja leka, poluživot distribucije je 15 minuta, uz veliki Vd od 3 l/kg i poluvreme eliminacije od 2-3 sata uglavnom preko bubrega (11).



Slika 3: Prikaz metabolizma enantiomera ketamina (HK- hidroksi-ketamin, HNK-hidroksi-norketamin , DHNK- di-hidroksi-norketamin), (4)

U humanoj populaciji, S-ketamin ima 3-4 puta veći afinitet za NMDA receptor u poređenju sa dekstrogirom formom, što za posledicu ima višestruko izraženiji klinički efekat kada se primene u jednakim dozama. Kliničke studije koje su poredile efekte obe forme ketamina došle su do zaključka da razlika u afinitetu za NMDA-receptor dozvoljava primenu s-ketamina u dvostruko manjoj dozi što za posledicu ima i manje izražene ili

odsutne ekscitatorne fenomene i kardiovaskularnu stimulaciju. S obzirom na potrebnu manju pojedinačnu dozu, metabolizam s-ketamina je brži, a posledično i oporavak (12).

ODNOS FARMAKOLOŠKE SPECIFIČNOSTI I KLINIČKOG EFEKTA

S obzirom da je ketamin rastvorljiv u vodi i u mastima, postoje različiti putevi primene: intravenskim, intramuskularnim, oralnim, transmukozalnim i off-lable- epiduralnim. Oralna formulacija daje 45% biološke raspoloživosti supstance te je i najbezbednija. U novije vreme, zabeležen je i inhalacioni put primene esketamina i ketamina s obzirom da je veličina mikropartikula manja od 5μm. Ovaj put primene dozvoljava bržu apsorpciju, veću biološku raspoloživost i brži efekat leka u poređenju na neinvazivnim, oralnim putem primene. Iako je s-izomer potentniji od r-izomera 3-4 puta, kada se primene u ekvipotentnim dozama, oba leka imaju slične kliničke efekte. U poređenju sa racemskom smešom, s-izomer je 2 puta potentniji, odnosno ima dvostruko veći afinitet za NMDA receptore, te je nastajanje i povlačenje kliničkog efekta dvostruko brže usled primenjene dvostruko manje doze, što umanjuje rizik od neželjenih disocijativnih, kardiovaskularnih i cerebrovaskularnih događaja koji su dozno zavisni usled manjeg stepena simpatičke stimulacije (disocijtivno stanje, povećanje intrakranijalnog pritiska, hipertenzija i tahikardija), (13). Farmakološke studije su dokazale da je klirens s-izomera dvostruko brži u poređenju sa racemskom smešom ili u poređenju sa s-izomerom u racemskoj smeši, što dokazuje da prisustvo r-izomera menja farmakološki profil s-izomera i usporava njegovu eliminaciju (14).

ZAKLJUČAK

Zahvaljujući specifičnom receptornom afinitetu i neselektivnosti putem kojih ostvaruje različite kliničke efekte dozno zavisne, osim primene u Jedinicama intenzivne nege i operacionim salama, ketamin i njegov izomer s-ketamin otvaraju značajan spektar indikacija u medicini bola i urgentnim stanjima, u postupcima procedurale sedacije, a od strane evropskog i američkog udruženja odobreni za terapiju farmakorezistentne depresije. Zbog prisustva r-ketamina u racemskoj smeši, s-ketamin kao izomer predstavlja povoljniju terapijsku opciju u poređenju sa racematom.

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From Guidelines to Practice: Pain Treatment in Rheumatology

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ABSTRACT

Despite the clinical importance of pain in patients with rheumatic diseases, rheumatologists have not delegated a proportionate amount of effort to its investigation and treatment. Some of the assumptions that have hindered progress in pain management for rheumatologists include a preference for immunologic research over pain research, a reluctance to provide opioid therapy, and inadequate compensation. The characterisation of categories of pain by mechanism (e.g., inflammation, joint degeneration, abnormalities of central pain processing) can help guide treatment. However, such categorisation can overlook the overlap of these processes and their interaction to create mixed pain states. Further complicating the assessment of pain, outcome measures in rheumatic disease often assess the degree of pain indirectly while concentrating on the quantification of inflammation. Non-inflammatory pain often persists despite treatment, highlighting the need for alternative analgesic therapies. Recommended therapies include nonsteroidal anti-inflammatory drugs, acetaminophen, and stimulators of the pain inhibitory pathway. Each of these non-opioid therapies has incomplete efficacy and potential toxicities that can limit their utility. Pain management is becoming an area of increasing research and clinical effort in the field of rheumatology. In the future, rheumatologists will need to expend greater time and effort in the study of pain management to remain pertinent to the needs of their rheumatic disease patients.

Key words: rheumatic diseases, pain,nonsteroidal anti-inflammatory drugs

INTRODUCTION

Pain associated with rheumatic diseases and musculoskeletal disorders are of significant public health importance. Many rheumatic and musculoskeletal pain conditions are chronic in nature and require a comprehensive approach to ensure long-term effective pain management (1).

The prevalence of rheumatic diseases is high and in some cases, such as osteoarthritis, likely to increase in prevalence with an aging population (2). Osteoarthritis (OA) is the most common joint disorder, which is thought to be a result of aging and wear and tear on a joint. OA is thought to affect more than 80% of people over age 50 and also occurs in younger people following injury or repetitive stress (3). Rheumatoid arthritis (RA) is a chronic autoimmune disorder that leads to inflammation of the joints, surrounding tissues, and may affect other organs. The prevalence of RA estimated to be 1%-2% of adults (ranging from .3% in people under age 35 to 10% in people over age 65) (4). Fibromyalgia syndrome (FMS) is a condition characterized by widespread pain and tenderness in joints, muscles, tendons, and other soft tissues. FMS condition affects about 2% of adults and is estimated to affect up to 6% of school-age children (5). Low back pain is the most highly prevalent musculoskeletal pain condition, with a life-time prevalence of 70–85% (6,7).

Most rheumatologists do not consider themselves to be pain specialists, despite diagnosing and treating musculoskeletal pain on a daily basis. Rather, most rheumatologists consider themselves to be subspecialists who treat acute and chronic musculoskeletal pain associated with rheumatic disorders

THE PAIN MANAGEMENT IN RHEUMATOLOGY

The major focus of the the American College of Rheumatology (ACR) and The European League Against Rheumatism (EULAR) recommendations continues to be pharmacological therapyfor certain rheumatological diseases, The concept of 'disease modification' comprises a combination of relief of signs and symptoms; improvement or normalisation of physical function, quality of life and social and work capacity; and most characteristically the inhibition of occurrence or progression of structural damage to cartilage and bone.

In rheumatological diseases, we have acute and chronic pain. Inflammation is the cause of pain in rheumatic conditions, but after the inflammation subsides, the lingering pain can be caused by other mechanisms. Therapy is adjusted according to the type of disease and an individual approach is used for each patient. The first line in the treatment of pain in rheumatological diseases are non-steroidal antirheumatic drugs (NSAIDs) (8).

The pain Visual Analog Scale (VAS) is a unidimensional measure of pain intensity,wich has been widely used in adult populations with rheumatic diseases. The scale is most commonly anchored by ”no pain” (score 0) and “pain as bad as it could be” or “ worst imaginable pain” (score 100/ 100mm scale).The pain VAS is self-completed by the respondent. The following cut points on the pain VAS have been recommended: no pain 0-4mm, mild pain 5-44mm, moderate pain 45-74mm and severe pain 75-100mm (9).

The strongest pain in rheumatology follows acute arthritis in gout. Recommended first-line options for acute flare are colchicine at a loading dose of 1 mg followed 1 hour later by 0.5 mg on day 1 and/or an NSAID (plus a proton pump inhibitor if appropriate), oral corticosteroids (30–35 mg/day for 3–5 days) or articular aspiration and injection of corticosteroids. Acute flares of gout should be treated as early as possible. Fully informed patients should be educated to self-medicate at the first warning symptoms. The choice of drug(s) should be based on the presence of contraindications, the patient's previous experience with treatments, time of initiation after flare onset and the number and type of joint(s) involved. Prophylaxis against flares should be fully explained and discussed with the patient. Prophylaxis is recommended during the first 6 months . Recommended prophylactic treatment is colchicine, 0.5–1 mg/day or prophylaxis with NSAIDs at a low dosage with the main urate-lowering therapy (10).

Chronic pain (that is pain lasting three months or longer) is highly prevalent in patients with rheumatic diseases and can cause various physical and psychological impairments. Overall, chronic pain is a difficult entity for both patients and providers. Early diagnosis, improved understanding of its mechanisms, and initiation of early, targeted approaches to pain control may help to improve outcomes in this population (11). Moreover, early and multimodal therapies, to help suppress inflammation, provide necessary analgesia, and optimize functional outcomes (12).

NSAIDs are used to treat pain and for their anti-inflammation properties. Both traditional NSAIDs and the second generation cyclooxygenase- 2 (COX-2) inhibitors offer superior efficacy compared with acetaminophen, but also carry significant risk for serious gastrointestinal (GI), cardiovascular (CV), and renal adverse events (13). A systematic review of 17 prospective observational studies found that 11% of preventable drug-related hospital admissions could be attributed to NSAIDs (14). Studies have documented that the risk of adverse events associated with NSAIDs are both dose-dependent and duration dependent.

There are marked differences in the risk of adverse gastrointestinal (GI) and cardiovascular (CV) events among different NSAIDs. In 2017, publication of two randomized controlled trials and an individual patient-data meta-analysis provided robust data on the relative GI and CV tolerability profiles of currently available NSAIDs (13). The PRECISION study showed similar CV-event rates with celecoxib vs naproxen and ibuprofen (14). In the CONCERN study of high-GI-risk patients, celecoxib was associated with fewer adverse GI-tract events than naproxen. These data add to the body of

knowledge about the relative tolerability of different NSAIDs and were used to propose an updated treatment algorithm (15). The decision about whether to use an NSAID and which one should be based on a patient's risk of developing adverse GI and CV events. Lower- and upper-GI-tract events need to be considered.

The literature data suggests that among widely used NSAIDs, naproxen and low-dose ibuprofen are least likely to increase cardiovascular risk. Diclofenac in doses available without prescription elevates risk. The data for etoricoxib were sparse, but in pairwise comparisons this drug had a significantly higher RR than naproxen or ibuprofen. Indomethacin is an older, rather toxic drug, and the evidence on cardiovascular risk casts doubt on its continued clinical use (16).

Hepatic adverse events associated with the use of nonaspirin drugs and NSAIDs are uncommon, but the widespread use of these drugs may impact public health. In the case/noncase analysis bromfenac, nimesulide, sulindac, and diclofenac had higher proportions of reports of hepatic disorders compared with naproxen,in the US Food and Drug Administration Freedom of Information (FDA/FOI) database and the World Health Organization Uppsala Monitoring Centre (WHO/UMC) database (17).

Because inhibition of COX-1 by nonsteroidal anti-inflammatory drugs (NSAIDs) is linked to gastrointestinal (GI) damage, agents with a better COX-2/COX-1 inhibition ratio may have less GI toxicity. The Clinical studies and databases show that there are differences in GI toxicity according to specific NSAIDs. Aceklofenak, nimesulid and naproxen had the lowest incidence of upper gastrointestinal bleeding (18).

Tramadol is a weak opioid agonist and has been considered a potential alternative to NSAIDs and traditional opioids because of its assumed relatively lower risk of serious cardiovascular and gastrointestinal adverse effects than NSAIDs, as well as a lower risk of addiction and respiratory depression compared with other opioids. In rheumatology, indications for the use of tramadol are osteoporotic fractures, fibromyalgia, osteoarthritis and all other diseases where NSAIDs are not effective enough or are contraindicated (19). Tramadol and acetaminophen are a rational combination product in that their mechanisms of action do not overlap and that in preclinical studies this combination acts synergistically. Also, this combination would be expected to provide more rapid pain relief than tramadol alone, and more persistent pain relief than acetaminophen alone (20).

CONCLUSION

Pain management is becoming an area of increasing research and clinical effort in the field of rheumatology. In the future, rheumatologists will need to expend greater time and effort in the study of pain management to remain pertinent to the needs of their rheumatic disease patients.

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24 Herpes Zoster and postherpetic neuralgia

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Varicella zoster virus- VZV is one of the eight herpes viruses that are pathogenic only for humans.1 It causes a primary infection called varicella most commonly in children that is highly contagious2. It is most commonly transmitted by the airborne route from person to person or by direct contact with the lesion3. During the primary infection, the virus disseminates through the blood stream to the skin, oral mucosa, and lymph nodes, causing the generalized rash of varicella4.

After a primary infection or vaccination, the VZV remains dormant in the sensory dorsal root ganglion cells. Resolution of the primary infection causes an induction of the varicella zoster virus-specific memory T cells. The memory T cell immunity declines over time. The decline below a theoretical "zoster threshold" correlates with an increased risk of herpes zoster infection2,5. The memory immunity to VZV may be enhanced by exogenous boosting (by exposure to varicella) or endogenous boosting (subclinical reactivation from latency)2. The average period of immunity against varicella following an infection is 20 years6.

Age, stress, immunocompromised status, and immunosuppressive drugs are known factors for virus reactivation7. It is recommended to determine the HIV status of those who develop herpes zoster.8 Once the virus is reactivated, it travels along the affected sensory nerve, causes neuronal damage, reaches the respective dermatomes, and forms the vesicular rash of herpes zoster8. Herpes zoster infection is usually characterized by a unilateral, painfulvesicular rash which is limited to a single dermatome9.

Studies have shown that more than 95% of adults are infected with VZV and therefore are at a risk of developing herpes zoster2. After an infection with herpes zoster, the chance of injury to the peripheral and central nervous system is high leading to post-herpetic neuralgia. The two main factors that play a role in the development

of post-herpetic neuralgia are sensitization and deafferentiation.10 The frequency of involvement is thoracic > lumbar and cervical > sacral. An increased spread of the VZV beyond the isolated ganglion nerve dermatome unit is seen among patients who have a deficiency in T lymphocyte and macrophage-mediated immune defense. Involvement of lungs, central nervous system (CNS), mucous membranes, liver, cardiovascular system (CVS), bladder, skeletal system, blood vessels, and gastrointestinal system can be seen among patients with disseminated diseases. Involvement of the lungs, liver, and CNS can be fatall1.

Herpes zoster does not occur following exposure to varicella zoster virus12. However, herpes zoster affected individuals can transmit varicella VZV to seronegative contacts. These contacts develop varicella, not herpes zoster. Individuals exposed to herpes zoster are at a lower risk (16%) of developing varicella infection, when compared to those exposed to varicella zoster virus (61 – 100%)12.Transmission of VZV from cases of herpes zoster occurs most commonly through direct contact with lesions than from airborne route.13 VZV vaccination among children has shown to cause a long-term reduction of risk among vaccinated individuals in developing herpes zoster13. However, a study by Brisson et al. showed that a mass childhood immunization against varicella zoster virus caused an increase in the incidence of herpes zoster during the first 30 – 50 years of life.7

The pathogenesis behind the reactivation of VZV is unknown. But, any factor affecting the cell-mediated immunity may play a role in the reactivation of VZV. The overall annual incidence of herpes zoster in the UK is estimated to be 1.85-3.9 cases per 1000 population,2 increasing with age from fewer than two cases per 1000 among people under 50 to 11 cases per 1000 among people aged 80 or older. In the US, incidence ranges from 1.2 to 3.4 cases per 1000 person years, increasing with age to 3.9 to 11.8 cases per 1000 person years among people aged 65 or older.3 4.14

Complications of herpes zoster are more common among elderly individuals and immunosuppressed patients. Herpes zoster and its complications can impact the patient's quality of life. In most patients, sleep and social activities are affected. Post-herpetic neuralgia is the most common complication of herpes zoster. The other complications noted following post-herpetic neuralgia, include secondary bacterial infections, ophthalmic complications, cranial and peripheral nerve palsies, and segmental zoster paresis.

Severe post-herpetic neuralgia can lead to sleep disturbance, depression, weight loss, chronic fatigue, and inability to perform daily activities. The pain may extend beyond the involved dermatome15. The severity of post-herpetic neuralgia is usually dependent on the presence of pain prior to rash formation, rash severity, inflammation, older age, and immunocompromised status.

Secondary bacterial infection such as cellulitis, septicemia, zoster gangrenosum, and necrotizing fasciitis caused by Staphylococcus aureus and Streptococcus pyogenes are the most common complications seen after post-herpetic neuralgia. Elderly and

immunocompromised patients are more prone to bacterial infections16. Cellulitis can lead to necrosis and scarring. Necrotizing fasciitis is a serious condition which can be complicated by a streptococcal toxic shock-like syndrome17.

A rare, but serious complication of herpes zoster ophthalmicus is granulomatous arteritis. The condition is characterized by headache and hemiplegia on the contralateral side of the lesion secondary to stroke10. Other complications associated with herpes zoster ophthalmicus include blepharitis, conjunctivitis, epithelial keratitis, stromal keratitis, neurotrophic keratopathy, uveitis, episcleritis, scleritis, acute retinal necrosis (ARN, and progressive outer retinal necrosis syndrome (PORN)18,19. Acute retinal necrosis and progressive outer retinal necrosis syndrome are two herpes zoster ophthalmicus complications that lead to retinal detachment. Compared to acute retinal necrosis, PORN syndrome is more severe with a poor prognosis and is more commonly seen in patients with advanced AIDS or in patients with other disease conditions causing immunosuppression19 According to a report by Tran et al., the recurrence rate of herpes zoster ophthalmicus complications at 1, 3, 5, and 6 years were 8%, 17%, 25%, and 31%, respectively.19 This proves that ocular complications can sometimes recur after a long period of up to 10 years following a zoster episode.

Herpes zoster myelitis is a rare neurologic complication with acute onset affecting most commonly patients with immunocompromised status. It occurs shortly after the onset of rash with development of sensory, motor, and autonomic dysfunction19 Herpes zoster is treated with oral guanosine analogues . These medications target VZV by relying on viral kinases for phosphorylation, which promotes incorporation into viral DNA, thus disrupting replication20. Acyclovir is less expensive but has lower bioavailability and must be taken five times per day. Valacyclovir, a pro-drug of acyclovir, is taken three times per day, as is famciclovir. Acyclovir is the only antiviral medication approved for the treatment of herpes zoster in children. Patients with severe disease, especially those with immunocompromise, should be treated with intravenous acyclovir. Although treatment of herpes zoster ideally should be started within 72 hours of the appearance of the rash, treatment is still warranted outside the 72-hour window if new skin lesions are developing or if ophthalmic or neurologic complications are present21.

Postherpetic neuralgia, the most common complication of herpes zoster, is defined as pain in a dermatomal distribution that is sustained for at least 90 days after the rash. It occurs in approximately 20% of patients with herpes zoster, and 80% of cases occur in patients 50 years or older. Pain is described as burning or electric shock–like and may be associated with allodynia or hyperalgesia. Postherpetic neuralgia is caused by nerve damage secondary to an inflammatory response induced by viral replication within a nerve22. Risk factors include older age, severe prodrome or rash, severe acute zoster pain, ophthalmic involvement, immunosuppression, and chronic conditions such as diabetes mellitus and lupus. Pain from postherpetic neuralgia is often debilitating and affects physical functioning, psychological well-being, and quality of life.

Pain-management strategies should focus on symptom control. Although some patients have complete resolution of symptoms at several years, others continue medications indefinitely.23

Earlier, tricyclic antidepressants were used as the first-line in the treatment of post-herpetic neuralgia. However, later due to its increased side effects, including anticholinergic action, gabapentin was preferred over tricyclic antidepressants24. Carbamazepine, a first generation anticonvulsant, is effective in managing chronic neuropathic pain, but several cases of carbamazepine-induced Stevens – Johnson syndrome and toxic epidermal necrolysis have been reported, and hence, it is not recommended. Gabapentin has shown good effect on sleep and quality of life for the patient24. A once daily dose of gastroretentive gabapentin (G-GR) of 600 mg reported rapid pain reduction on day 2 with a decreased incidence of adverse effects25. Pregabalin is often recommended as the first line in the treatment of post-herpetic neuralgia, but at an increased cost26. However, a study by Pérez et al. showed no significant cost differences between gabapentin and pregabalin27. Gabapentin acts by binding to the α2δ-1 subunit of voltage-gated calcium ion channel by reducing their action on dorsal root ganglion (DRG) by inhibiting membrane trafficking (cytoplasm to plasma membrane) and anterograde trafficking (axoplasmic transport). Gabapentin also shows acute analgesic effects by lowering the release of neurotransmitters such as substance P23. Gabapentin and pregabalin should be used with caution in patients with renal insufficiency28.

Topical capsaicin 8% patch is beneficial in managing trigeminal post-herpetic neuralgia. Pain reduction mechanism with capsaicin is unknown but it is thought to be due to the reduction in substancePin the skin29. The major adverse effect with topical capsaicin cream is a burning sensation on the applied site. It has to be applied three to five times a day. Topical 5% lidocaine plasters (≤3 patches/day for 12 hours/day) have shown great benefit for patients with post-herpetic neuralgia especially among the elderly individuals due to its decreased side effects compared to other systemic agents30.], Lidocaine-medicated plasters relieve pain by the action of absorbed lidocaine on sodium channels of sensitized afferents in the affected skin, and through the barrier effect which protects the allodynic skin from mechanical stimuli.30

Two vaccines are licensed for the prevention of herpes zoster and post-herpetic neuralgia in older adults: Zostavax, a live attenuated vaccine, and Shingrix, a recombinant subunit vaccine. Shingrix was approved in the US in 2017 and in Europe in January 2018. Zostavax is still recommended in the UK for adults aged 70-79; however, the US Advisory Committee on Immunization Practices (ACIP) updated its guidance in January 2018 and now recommends Shingrix for adults aged 50 or older. The updated US guidance still lists Zostavax as a recommended option for adults aged 60 or older, but explicitly states that Shingrix is preferred. Zostavax is a lyophilised or freeze dried preparation of live, attenuated varicella zoster virus. The vaccine is given as a single subcutaneous dose and can reduce the risk of herpes zoster by 51% for a mean duration

of 3.13 years (range 1 day to 4.9 years) after vaccination, post-herpetic neuralgia by 67%, and the overall burden of illness by 61%.31 This live vaccine is contraindicated in severely immunosuppressed people, pregnant women, and children. Zostavax becomes less effective with increasing age, and efficacy wanes completely approximately 10 years after vaccination. Shingrix is a recombinant subunit vaccine containing the AS01B adjuvant system and glycoprotein E antigen from the varicella zoster virus. Shingrix requires two intramuscular doses 2 to 6 months apart, and has a substantially higher efficacy than Zostavax, reducing risk herpes zoster infection by 97%56 57 (mean duration of follow-up was 3.2 years). Early studies suggest a single dose does not produce a robust immune response,58 so attendance for both doses is important. Unlike Zostavax, the efficacy of Shingrix is high even for patients over 70.31

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Importance of enteral nutrition and microbiota in pain regulation

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ABSTRACT

Pain is a complex protective mechanism. Pain protects our body from various harmful insults, but pain can often be problematic during persistent pathological states. The role of nutrition as a top modifiable lifestyle factor in pain management is attracting growing attention as a therapeutic target in pain regulation. The relationship between nutrition and chronic pain is complex and may involve many underlying mechanisms such as oxidative stress, inflammation, and glucose metabolism. Numerous evidence also supports the importance of gut-brain interaction in pain perception. 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. As such, pain management requires a comprehensive and interdisciplinary approach that includes nutritional strategies. Optimizing one's dietary intake to ensure adequate intake of vitamins and essential amino acids, increasing intake of nutrients that reduce pain, and restricting nutrients that may facilitate pain or reduce the effectiveness of oral analgesics.

Key words: *pain, nutrition, diet, gut microbiota*

INTRODUCTION

Pain is a serious health issue affecting millions of people worldwide, with critical socioeconomic effects. 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. Based on its neurophysiological mechanism, pain can be classified as nociceptive and non-nociceptive.

Recent data show that about 20% of people worldwide suffer from chronic pain (i.e., pain lasting ≥3 months). [2] This condition is often associated with anxiety, restriction in mobility and daily activities and reduction of quality of life. Analgesics are the first line pharmaceutical treatment method, especially opioids. However, there is a growing concern about prescription opioid misuse and abuse, which made a need for research into alternative treatment methods that avoid side effects of traditional treatment. Dietary interventions are one such mode of a treatment, with numerous studies suggesting that diet has noticeable effect on pain. These affects due to influence of diet on oxidative stress and inflammation, which are widely hypothesized mechanism for pain.

INTERACTION BETWEEN PAIN AND NUTRITION

The interaction between nutrition and chronic pain is bidirectional. However, it is not clear how nutrients interact with the pain generating mechanisms and the potential mechanisms that contribute to this relationship. Few potential nutritional factors that influence chronic pain have been identified.

Inflamation and oxidative stress. Inflammation and oxidative stress are thought to be both important key players in the occurrence, enhancement, and maintenance of both nociceptive and neuropathic pain. They are involved in pain-related diseases, such as diabetic neuropathy, low back pain, neurodegenerative diseases, cancer, and various autoimmune disorders, among others. They act synergistically and their presence can be beneficial, yet detrimental to neurons and nerves if they are in overdrive state.

Inflammation occurs when immune cells respond to biochemical and physical influences, including infection, allergens, tissue injury, radiation and diet-induced oxidative stress. Inflammation is marked by the production of various cytokines and chemokines by the peripheral nerves, spinal cord, the dorsal root ganglion (DRG). In addition, cytokines can be delivered to the DRG and dorsal horn of spinal cord by means of retrograde axonal or non-axonal mechanisms, thus further extending its coverage. Inflammation is a part of natural healing process. However, prolonged inflammation can result in chronic hypersensitivity. There is accumulating evidence demonstrating the involvement of various pro-inflammatory cytokines in the initiation, exacerbation, and maintenance of pathological pain.

Increased extracellular glutamate levels following painful stimuli lead to the activation of numerous intracellular pathways, including free radicals formation (oxygen

(ROS) and nitrogen (RNS) reactive species). Oxidative stress occurs when free radical compounds are imbalanced with antioxidant defense systems in the body. When certain macronutrients are consumed in excess and are broken down, oxidative by-products of their metabolism triggers oxidative stress responses and production of more ROS when bound to their receptors. High levels of free radicals cause damage to essential protein, lipid, and nucleic acid components of cells, eventually leading to damage and apoptosis. The direct link between oxidative stress and painful conditions is not yet completely understood. It is hypothesized that oxidative stress contributes to pain by exacerbating pathological responses like inflammation and neuropathy, which both contribute to pain. Nutritional stress has been shown to both increase free radicals and hinder the antioxidant defense system, thereby creating an imbalance in the local environment leading to oxidative stress. Diets like the Western diet, characterized by elevated intake of processed carbohydrates and saturated fats, have been linked to increased postprandial oxidative stress in the short term and chronic elevation of oxidative stress markers in the long term, causing metainflammation and chronic pain conditions. Current clinical evidence suggests that oxidative biomarkers are lowered by antioxidant supplementation for individuals with above-baseline oxidative stress levels, but antioxidant supplementation does not have significant impact on individuals with normal levels of oxidative stress. Clinical research on the impact of dietary antioxidants on inflammation are also inconclusive.

Microbiota-gut-brain axis. Nutrients meet the gut microbiota initially before being absorbed as bioactive products. Therefore, any issue regarding the relationship between diet and pain is closely related to the gut microbiome (GM). 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 role of the gut-microbiome-brain axis (GMBA) in metabolism and inflammation is crucial. 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 and neurotransmitters or neuromodulators release (GABA). Some microbial derived mediators (Toll-like receptors (TLR) agonist) can directly activate or sensitise primary nociceptive neurons in 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 can indirectly increase the excitability of DRG neurons by inducing pro-inflammatory factors release from immune cells to enhance pain.[4] Gut microbiota 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. SCFAs (butyrate, propionate) constitute an energy source for colonocytes and maintain colonic epithelium homeostasis. They are produced by microbial fermentation of dietary fibres 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.[5] However, SCFAs as acetate and propionate are considered antiinflammatory mediators. The intake of dietary fibers is fundamental to reducing the risk for abdominal and musculoarticular pain, presumably owing to SCFAs acting as mediators and immunomodulators.

Disturbed glucose metabolism. Diabetes has been reported as an important risk factor for chronic pain. A well-known antihyperglycemic medicine, metformin, which is commonly used to treat type-2 diabetes has also shown it can significantly alleviate pain in chronic pain populations and thus could be a potential treatment for people experiencing chronic pain.[6] An excessive carbohydrate intake and a decrease in glucose metabolism efficiency can increase reactive oxygen species and evoke an oxidative stress response. Thus, the identification of a disrupted glucose metabolism and targeting glucose regulation constitute significant places in chronic pain management.

NUTRITION AND PAIN PERCEPTION

It has been proposed that nervous and immune system sensitization can mediate the relation between a poor nutrition status and chronic pain. Even though feeding is a major component of life, it is just lately that the influence of nutrition on brain plasticity and function has been investigated, showing that specific nutrients (like curcumin and salmon) are significant modifiers of brain plasticity and may have an influence on the central nervous system's health and disease . Sensitization of the nervous system, brain perception, and psychosocial factors play a crucial role in the persisting pain experience. Glutamate, the most ubiquitous neurotransmitter in our nervous system, mediates pain transmission. Thus, dietary factors which affect glutamatergic neurotransmission are of considerable interest. Free forms of the amino acids glutamate and aspartate (commonly found in flavor enhancing food additives such as monosodium glutamate (MSG) and aspartame) were associated with many pain conditions. Clinical trials restricting the consumption of additives and foods containing free forms of glutamate and aspartate resulted in significant symptom improvement in patients with fibromyalgia and irritable bowel syndrome (IBS)7. A study in Kenya revealed that participants with chronic pain reported improvement in pain symptoms following a low glutamate diet when compared to controls[8] Research also shows that MSG induces headache and masseter muscle pain when administered over 5 days and the International Classification of

Headache Disorders, 3rd Edition, reports that MSG is a headache trigger.[9] Furthermore, rat models revealed that visceral hyperalgesia can be reduced by blocking glutamate receptors .

IMPLEMENTATION OF NUTRITION IN CHRONIC PAIN MANAGEMENT

Pharmacological and non-pharmacological treatments are available for chronic pain, although the limited efficacy and side effects these therapies make their use controversial. Therefore, it becomes urgent to discover new, safe, and effective strategies to prevent this condition.

In recent years, new therapeutic options to treat chronic pain have been investigated; among them are natural products, especially medicinal herbs. Phytochemicals prevent diseases due to their antibacterial, antifungal, anti-inflammatory, diuretic, and anesthetic effects. Additionally, some phytochemicals protect against oxidative stress damage, and thus inhibit different types of pain. In this regard, numerous studies are currently focusing on the characterization and application of natural agents in various diseases for the reduction in and/or elimination of free radicals.

MAGNESIUM (Mg) has attracted much attention recently for its role in alleviating pain, suggesting that Mg in the diet should play a major role in reducing pain.[10] Mg exerts analgaesic effects in several animal pain models, as well as in patients affected by acute postoperative pain and neuropathic chronic pain. Recent studies suggest that Mg has a much more direct involvement in the amelioration of pain. Experiments in rats with induced diabetic neuropathy showed that per os administration of Mg abolished thermal and tactile allodynia, decreased the development of mechanical hypersensitivity, and reduced N-methyl-D-aspartate receptor (NMDA) sensitivity in the spinal cord.[11] In an orofacial type of pain, Mg prevented hypernociception and attenuated pain via the NMDA receptors in the subnucleus caudalis, reducing pain from the trigeminal pathway.[12] Mg-mediated blockade of NMDA receptors can be a promising new therapeutic option for the management of chronic pain conditions, even especially when central pathways are involved. Clinical application up to now regards efficacy of Mg administration in cases of migraine, postoperative chronic knee pain and chronic pain.

SELENIUM (Se) is an essential trace element. The molecules of selenium act as co-factors for different enzymes, such as GPx, thioredoxin reductase (TrxRs), and iodothyronine deiodinases. Although high concentrations of selenium have cytotoxic effects, low-dose selenium can scavenge ROS and reduce pain. Selenium is believed to play a critical role in protecting neurons from hazardous mitochondrial and inflammation-induced ROS production. Regarding pain syndrome, lower Se levels can be found in the

plasma of patients with neuropathic pain and neurological diseases, especially in patients with fibromyalgia. In patients with chronic myofascial pain, a significant decrease in the content of Se in eryth- rocytes and inadequate food intake of this nutrient has been observed. Supplementation of organic Se in the treatment of patients with chronic pancreatitis accompanied by severe pain led to significant pain relief in >50% of patients and a substantial reduction in the pain score.[13] Association between Se status and pain relief was also observed in patients with fibromyalgia and skeletal muscle disorders manifested by muscle pain . Moreover, Zn can inhibit TRPV1 and reduce neuropathic pain resulting from chemotherapy.[14]

VITAMIN B COMPLEX belong to the hydrosoluble group of vitamins,. Among their major representatives to manage pain there are vitamins B1 (thiamine), B6 (pyridoxine) and B12 (cyanocobalamin)1. B vitamins are important for nucleic acid and proteins synthesis, as well as for acetylcholine synthesis which is a major neurotransmitter. The role of subgroups of vitamin B complex as an adjuvant in causing analgesia is quite controversial. It seems that vitamin B as a supplement itself is not able to produce a strong analgesic effect, but it contributes and synergistically enhances the action of anti-inflammatory agents in both humans and animals. Investigations in chemical and thermal models of nociception in mice suggested that the antinociceptive effect of some vitaminB groups may involve inhibition of the synthesis and/or action of inflammatory mediators. However, a more direct analgesic and possible neuroprotective role of vitamin B complex has been also described in recent research studies in animals, implicating either the activation of astrocytes and microglial cells and increase in synthesis of c-aminobutyric acid (GABA) or the modulation of TRPV1 as possible underlying pathophysiological mechanisms. In addition, animal studies suggest that vitamin B12 may provide an opioid sparing effect, allowing for the reduction of opioid dose when used in combination for pain conditions.

VITAMIN D. Recent reports have outlined that a lack of vitamin D in the body is associated with increased pain, which in observed cases required an elevation of opiate doses.[15] When deficient, vitamin D supplementation has a positive effect on muscle pain, an effect that is associated with anti-inflammation owing to a decrease in the release of cytokines and prostaglandins. Also, vitamin D has an indirect inhibitory effect on PGE2. The role of vitamin D in pain relief can not solely be explained by its role in the mineral metabolism in the bone tissue but also appears to involve regulatory effects on nociceptors and sleep, as it has been established that sleep dysregulation is associated with hyperalgesia. Few recent studies showed a significant pain reduction according to a visual analog scale in patients with chronic non-specific widespread pain taking vitamin D.[16,17] Regarding patients with headache studies suggested some benefit of nutritional intervention, although a sound qualitative interpretation is still missing in this

field. It should be noted that studies concerning vitamin D are known to be rather heterogeneous, yielding contradictory results, often owing to differences in pretreatment evaluation and different dosage and frequency of administration.

AMINO ACIDS are molecules necessary for the production and function of almost every tissue in the body, especially involving the musculoskeletal system. As such they might be able to provide pain relief via accelerating tissue-healing mechanisms induced by an anabolic activity. Indeed, a mixture of essential amino acids improves pain of elderly subjects following elective surgery for hip OA within 2weeks after operation.[18] One of the most remarkable compounds in the treatment of chronic pain is tryptophan, a precursor of 5-OH-tryptamine or serotonin. Its use alone or in combination with a selective serotonin reuptake inhibitor (SSRI) can help in controlling the pain or in reducing the use of SSRI antidepressants. Carnitine has a potential neuroprotective role in many neurological disorders enriched by the assumption that carnitine has an effect on pain reduction. According to a recent study in patients with mild to moderate carpal tunnel syndrome, the possible neuroprotective effect of carnitine relies on the improvement of mitochondrial function. Pain reduction is possibly achieved by the dysregulation of glutamate in the dorsal horns, via carnitine-induced activation of metabotropic glutamate receptor 2 (mGluR2).[19] Preliminary data also suggest that metabolic pathways regarding L- carnitine synthesis may play a role in pain severity and interference in women with fibromyalgia; however, further investigation is necessary to confirm this hypothesis . Taurine a derivative of cysteine, is a major supplementation nutrient against pain. Taurine functions as an osmolyte, antioxidant, Ca2+modulator, inhibitory neurotransmitter, and analgesic such that its depletion in diabetes may predispose one to neuronal hyperexcitability and pain. A receptor agonist, enhances the analgesic effect of the selective COX-2 inhibitor celecoxib when used simultaneously to relieve central pain, thus decreasing the nociceptive response at thermo- and mechanonociception. A clinical study of the effectiveness of an analgesic containing tramadol, paracetamol, caffeine, and taurine in acute back pain showed a good response to treatment in 81% of the patients compared with 45% in the group that only received tramadol or paracetamol ($P < 0.001$) . [20]

OMEGA 3 POLYUNSATURATED FATTY ACIDS (O3-PUFA) eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA) are possibly the most important elements of all. O3-PUFA compete with arachidonic acid (□-6) and participate in the synthesis of prostaglandins, leukotrienes, thromboxanes and prostacyclins. DHA and EPA are precursors of resolvines, which can alleviate pain via multiple mechanisms reducing inflammatory factors, the glia and the spinal cord synaptic plasticity. They are strongly induced not only in the periphery during acute inflammation but also in the dorsal root ganglia and spinal cord. The addition of EPA and DHA to enteral nutritional products

results in a reduction of proinflammatory mediators, decreasing the generation of free radicals. Consequently, O3FA are considered immune-modulating agents, reducing the postoperative inflammatory response to surgical aggression, and decreasing the release of proinflammatory mediators. Long-term dietary intake of O3FA is considered particularly effective in modifying the human gut microbiota. The role of PUFAs in gut microbiota homeostasis is crucial, suggesting that a proper intake of O3-PUFA, with an adequate ratio of □-6 to □-3, may be strategic in ensuring the correct gut microbiota homeostasis and its relationship with the anti-inflammatory and antinociceptive role of PUFAs.[21] Intake of O3-PUFAs appears particularly suitable in reducing joint pain in several inflammatory conditions. Dietary supplementation has shown reduction of pain related to rheumatoid arthritis, inflammatory bowel disease, neuropathy and dysmenorrhoea, with the largest effect on dysmenorrhoea according to recent a systematic review and meta-analysis. [22]

GUT MICROBIOME TARGETED INTERVENTIONS. During critical illness, many factors could disturb the normal physiologic gut microbiota. The trauma or disease induced stress, along with medications like antibiotics, catecholamines and histamine H2 receptor blockers, and other supportive treatments such as artificial respiration might be involved . Remarkable alterations in the gut flora are also seen in digestive surgeries due to bowel cleansing . Many surgeries are accompanied with pre- and post- fasting state as a part of treatment or insufficient nutrition support. The direct effects of starvation on gut microbiota in critical conditions are not still well described. The clinical effects of interventions on microbiota have been assessed in different types of major abdominal surgeries. Few data is available on the relationship of acute postoperative pain with gut microbiota and the effect of relevant interventions. However, the effect of gut microbiota as a key regulator of visceral pain has been stated recently. Preventive or therapeutic strategies designed to ameliorate perioperative pain based on the interactions of gut microbiota on pain inducing mechanisms could be a real promise in finding novel therapeutic approaches in pain management; both for acute and chronic pain.

CONCLUSION

The relationship between nutrition and chronic pain is complex and under-represented despite the emerging evidence which indicates that poor nutrition and dietary intake may play a key role in occurrence and management of painful conditions. Moreover, recent advances in research have described the importance of the microbiota-gut-brain axis in development and perception of pain. As such, pain management requires a comprehensive and interdisciplinary approach that includes nutritional assessments and personalized dietary interventions.

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Application of PEG and nasogastric tube in palliative care

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Nutrition therapy of patients under palliative care leads to ethical issues.(1) Four ethical principles: autonomy, beneficence, non-maleficence and justice must be achieved in patient treatment.(2) When to start and when to stop with nutrition management of these patient mostly depends from disease stadium. Also, the cultural values, religious beliefs, ethnic origin and country of patients and families and quality of life need to be considered and respected in decision making. (2,3) Palliative care covers conditions such as cancer, advanced dementia, other advanced neurological disease HIV/AIDS, heart disease, etc.(4) Coma, decreased consciousness, dementia in patients can be very challenging for diagnosis and prognosis. In these cases is very difficult to identify patients who fulfill criteria for long-term nutrition therapy.(2,3) Cancer associated cachexia is an underestimated consequence of many cancers and can occur in up to 80% of cancer patients with advanced disease. (5) The current definition of cancer cachexia report as " a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment" (6). Almost in all cancer patients under palliative care have been diagnosed cancer cachexia. (6)

Artificial nutrition should be used according a realistic goal of individual treatment, the patient's own wishes and based on assessment case-by-case by three and more the doctors. (3) In neurological and in cancer patients, with the tendency to have benefit for survival and quality of life with nutrition administration, long-term home enteral and parenteral nutrition should be considered.(3) Some general recommendation is if estimated life expectancy is less than one month, HEN usually shall not be initiated. (8) However, there are no clear criteria to determine the beginning of the dying phase and nutritional intervention should be followed in an individualized manner. (3)

Three type of artificial nutrition are recognized (oral, parenteral and enteral). EN should be applied to feed the patient via a tube when oral feeding is contraindicated or insufficient. (7) Enteral nutrition (EN) is the most common route of feeding of patients under palliative care. Tube feeding is artificial nutrition because uses specific access routes to the gastrointestinal tract and industrially manufactured food for certain therapeutic medical purposes. Artificial hydration is also very important and can be needed without administration of nutrients.(3) Enteral nutrition includes oral nutritional supplements (ONS), tube feeding via nasogastric, nasoenteral (nasoduodenal or nasojejunal), percutaneous tubes (gastrostomy or jejunostomy) or surgical gastrostomy or Witzel jejunostomy.(7) The first choice for enteral feeding is nasogastric tube, but for long-term nutrition (longer than 6 weeks), percutaneous gastrostomy is the first choice, especially in case of home enteral nutrition.(8) Depending on the clinical circumstances, the requirement for energy, safety, and the amount of precision necessary, bolus or intermittent continuous or continuous feeding through a pump may be given. (8) Bolus feeding appears to be more physiological and ought to be utilized whenever possible. Bolus feeding is used via nasogastric tube (NGT) and percutaneous gastrostomy (PEG). Bolus feeding via NGT and PEG is performed with a 50 ml syringe. The daily energy requirement must be divided into four to six bolus infusions throughout the day. Typically, the bolus volume of 200 to 400 ml of feed is given during a 15 to 60 minute period, based on the patient's nutrient requirements and tolerance. Due to the protein-rich solutions, the viscosity of the fluid, and the narrow tube lumen, PEG as other feeding tubes (gastric or jejunal) are prone to obstructions. To prevent obstruction, NGT and PEG should be flushed with at least 30 mL of drinking quality water before starting and after termination of feeding. (8,9)

According ESPEN guideline for HEN, standard commercial formula for enteral tube nutrition should be used, except „in specific justification for a blended tube feeds". (8) Risks of microbial contamination, product instability and unknown amounts of proteins, fats and carbohydrates in blended homemade formula lead to concern for using this kind of formula.(10) Despite guidelines, blended food is still used in patients at home without clear benefit.

Palliative care patients on enteral nutrition usually require medications. Administration of medications via nasogastric tube and PEG can be challenging. One of issues is the absorption characteristics of the original medication after administration via tube. The next issue is a form of drug which can clog the tube. To prevent blocking of nasogastric tube or percutaneous gastrostomy, tablets should be crushed into a powder and dissolve with water and given via gastrostomy. Administration of enteric-coated medications can be difficult due to propose of enteric coating to avoid the destruction of drug by gastric acid delaying the medication's onset of action. If medication will be crushed, onset of drug starts in stomach instead in intestine. Enteric-coated medications should be given without crushing. Liquid formulations (suspensions, elixirs and

syrups) can be given via PEG safely. (11) Also, interaction between drugs and enteral formulas should be considered. Morphine sulfate solution which is commonly used drug in palliative care, when giving via NGT or PEG in presence of enteral nutrition, requires higher concentration of drug for achievement the desired dosage.(12) Some of medications which often used for pain therapy in palliative care and can be given safely via PEG are: oxycodone, clonidine, codeine, megesterol, prednisolone, lorazepam, hydromorphone, dexamethasone, amitriptyline. (11)

Enteral feeding in patients under palliative care should be provided if improves survival and quality of patient's life. Enteral nutrition in these patients can be challenging, particularly in patients receiving HEN.

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Pain management in chronic pancreatitis

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ABSTRACT

Chronic pancreatitis remains an enigma in the field of gastroenterology and abdominal surgery and adequate therapy should be based on determing its etiology and pathogenesis. The prevalence in the developed world is reported from 0.4% to 5%. Overall, the most common cause is alcohol consumption. The most significant symptom in CP is abdominal pain that affects up to 90% of the patients and represents the main cause of hospitalization. The etiology of pain in CP involves multiple mechanisms, such as sensitization of the peripheral and central nerves, reorganization of the cerebral cortex and alterations in pain control systems. Treatment should be individualized to adapt the patient's pain phenotype, such as pain characteristics and affected pain mechanisms. Treatment strategies include pharmacological agents, nutritional therapy, lifestyle guidance, endoscopic treatment, and surgery depending on symptoms, pancreatic exocrine and endocrine function, and various complications. A step wise strategy is advised, starting with lifestyle changes including alcohol abstinention and a low-fat diet, then progressing to high dose non-coated pancreatic enzyme therapy and oral analgesic therapy. Endoscopy or decompressive surgery should be taken into account for patients with dilated main pancreatic duct who are not responding to medical treatment. Patients who have non-dilated pancreatic ducts, inflammatory masses, and debilitating pain may be candidates for reconstructive surgery. It is yet unclear to determine the role of total pancreatectomy with islet cell auto transplantation, celiac plexus block,and pain-modifiying agents(antioxidants, antidepressants) will play in treating this condition. On the other hand, neuromodulation has been developed as another treatment option, as it may assist patients wean off opiate drugs, given that opiates not only have harmful side effects but also worsen the patient's underlying abdominal pain because of their effect on slowing GI motility.

Key words: *chronic pancreatitis, pain, analgesic treatment, neuromodulation*

INTRODUCTION

Chronic pancreatitis remains an enigma in the field of gastroenterology and abdominal surgery and adequate therapy should be based on determing its etiology and pathogenesis. The current international mechanistic definition defines CP as a pathogenic fibro-inflammatory syndrome of the pancreas in which a persistent pathological response to pancreatic parenchymal injury or stress occurs in individuals with genetic, environmental, and/or other risk factors (1).

Although chronic pancreatitis is a common problem, its exact prevalence is unknown. The prevalence in the developed world is reported from 0.4% to 5%.(2) CP is most prevalent in the middle-aged population (40–62 years) and more frequently reported in men (55%–85%) (3). Additionally, men are more likely to develop chronic pancreatitis from alcohol abuse than women (4).

The most relevant causes of chronic pancreatitis include alcohol abuse, ductal obstruction (malignancy, stones, trauma), genetics (cystic fibrosis, hereditary pancreatitis), chemotherapy, and autoimmune diseases. According to recent studies deficiencies in certain vitamins and antioxidants may be linked to the disease (5). Overall, the most common cause is alcohol consumption (4).

According to the 2019 clinical diagnostic criteria for CP diagnostic elements consist of characteristic imaging findings, histological findings and five evaluation elements (repeated upper abdominal or back pain, abnormal serum/urine pancreatic enzyme levels, abnormal pancreatic exocrine function, continued heavy alcohol consumption or pancreatitis-associated gene mutation, past history of acute pancreatitis). Patients are diagnosed as having early CP if they have three or more of the five evaluation items and findings characteristic of early CP on endoscopic ultrasound (EUS), endoscopic retrograde cholangiopancreatography (ERCP), or magnetic resonance cholangiopancreatography (MRCP) (6).

According to the level of pancreatic endocrine and exocrine dysfunction, CP is classified into latent, compensatory, transitional, and decompensated stages. Abdominal pain is the main symptom during the latent to compensatory stage. Symptoms of exocrine and endocrine pancreatic dysfunction emerge throughout the decompensated phase. Pancreatic exocrine dysfunction is caused by a deficiency in pancreatic enzymes and manifests as digestive and absorptive disorders. Symptoms of pancreatic exocrine dysfunction include steatorrhea, abdominal distension and deficiency in fat-soluble vitamins (A, D, E, and K) and essential fatty acids, which reduce the patient's quality of life. Pancreatic endocrine dysfunction is demonstrated as diabetes mellitus secondary to pancreatic disease (6).

PAIN MECHANISM

The most significant symptom in CP is abdominal pain that affects up to 90% of the patients and represents the main cause of hospitalization. Pancreatic abdominal

pain is described as a constant, severe, dull, epigastric pain that often radiates to the back and typically worsens after high-fat meals (7). The pain tends to fluctuate over time, some patients experience pain-free intervals, while others experience chronic pain with exacerbations (8).

The etiology of pain in CP involves multiple mechanisms, such as sensitization of the peripheral and central nerves, reorganization of the cerebral cortex and alterations in pain control systems. Also, local complications (pancreatic pseudocysts and duodenal and/or bile duct obstruction) and adverse effects to treatment could contribute in pain etiology in many patients (7). It is necessary to underline that the optimal treatment will only come from a better comprehension of the pain mechanisms in CP. There is a variety of potential pain mechanisms that must be considered.

The mechanistic understanding of pain, called the "the plumbing theory", is explaining that pain is generated by increased pressure in the pancreatic duct or in the pancreatic parenchyma (9). According to "the wiring theory" three aspects of the neural basis of pain in CP are described: peripheral nociception, pancreatic neuropathy and central mechanisms of pain. However, these theories are not mutually exclusive, and aspects of both may contribute in the generation and perpetuation of pain (7).

On the other hand, pain due to complications to the disease is also likely to contribute, such as pancreatic pseudocysts, duodenal and bile duct obstruction, peptic ulcer and splenic vein thrombosis. Adverse effects and complications to medical and interventional therapies may also contribute significally to morbidity in many patients and should be considered as an additional source of pain. (7)

PAIN TREATMENT

Treatment should be individualized to adapt the patient's pain phenotype, such as pain characteristics and affected pain mechanisms. Therefore, pain assessment is crucial. The gold standard for pain assessment is patients' pain selfreports. Recently, a comprehensive pain assessment questionnaire, the Comprehensive Pain Assessment Tool (COMPAT), has been developed specifically for CP, but due to its extensive length, a short form of the COMPAT questionnaire, the COMPAT-SF, has been developed (10).

Treatment strategies include pharmacological agents, nutritional therapy, lifestyle guidance, endoscopic treatment, and surgery depending on symptoms, pancreatic exocrine and endocrine function, and various complications.

LIFESTYLE GUIDANCE AND NUTRITIONAL THERAPY

Abstinence from alcohol and smoking, in addition to adequate treatment, should be strongly advised in patients with CP (12). Nutritional therapy should be adapted

according to the disease stage. A fat-restricted diet is advised for patients in the compensatory stage who have abdominal pain. However, in the decompensated stage with pancreatic exocrine insufficiency, a daily fat intake of 40–70 g or 30%–40% of total calories is recommended in combination with pancreatic enzyme replacement therapy to prevent malnutrition (6).

PANCREATIC ENZYME REPLACEMENT THERAPY AND ANTIOXIDANTS

Patients with CP should not use pancreatic enzyme therapy for managing pain, but given the low risk of using these medications, it is reasonable to continue using them if patients feel that their pain is reduced by pancreatic enzyme therapy, particularly non-enteric-coated formulations with biologic plausibility (11).

Antioxidants might also be useful for treating pain. Antioxidant supplementation (β-carotene, vitamin C, vitamin E, selenium, and methionine) has been used to decrease oxidative stress and relieve pain. Recent meta-analyses of randomized controlled trials have demonstrated the positive effects of antioxidants in CP patients (12). A recent study has shown that a combination of pregabalin and antioxidants resulted in benefit in those who had recurrence of pain after surgical and/or endoscopic therapy (13)

ANALGESIC THERAPY

Guidelines for analgesic therapy in CP follow the principles of the "pain relief ladder" provided by the World Health Organization (WHO) (14,15). This method enables a simple stepwise escalation of drugs with increasing analgesic potency (level I-III) until pain relief is obtained, with simultaneous monitoring and handling of side effects.

Simple analgesics are used as basis in pain treatment. Paracetamol is the level I drug of choice due to its limited side effects. Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided due to their side effects, such as gastrointestinal toxicity, especially as patients in CP are already predisposed to peptic ulcers (7).

Many CP patients appear to require the use of opioid analgesics to reduce their pain, but pancreatologists must be familiar with the complexity of opioids. Opioid based treatments are often associated with many severe adverse effects such as constipation or opioid induced hyperalgesia. It must be noted that only about 25% of patients who are receiving long-term opioid therapy benefit from the medication and that they must be kept under strict clinical observation (15). In patients with CP, tramadol is preferred level II drug of choice and has been found to be superior to morphine and to have less gastrointestinal side effects while providing the same amount of analgesia (16). Recent

reports suggest that the analgesic effect of oxycodone may be better than that of morphine because of its kappa agonist activity (17).

Transdermal administration of opioids should be reserved to patients having trouble with tablet ingestion. Recent study that evaluated the use of transdermal fentanyl vs sustained-release morphine tablets concluded that transdermal fentanyl was not ideal for patients with CP because the dosage had to be increased 50% above the manufacturer's recommendation, and patients on transdermal fentanyl required significantly more rescue morphine administration (18).

It is debatable whether to treat pain in CP with opiates. The possibility of addiction, misuse and tolerance, as well as worries about administering a narcotic to patients who may already have a history of substance abuse (such as alcoholism), are all reasons given against the use of opioids (11). Most importantly, opioids directly affect the pancreas where they decrease fluid secretion from ductal cells and increase the tonus of the sphincter of Oddi, which in combination may lead to impaired pancreatic ductal clearance of activated pancreatic enzymes. This promotes intrapancreatic activation of trypsinogen and may initiate a new infammatory attack (19). Together these adverse effects can lead to the translocation of bacteria to the systemic circulation and further potentiate the severity of pancreatitis (20).

Unconventional treatment with medications like ketamine is useful for some individuals in whom the usage of potent opioids did not result in pain relief, but only when administered by pain experts. Somastotatin-analogue inhibits pancreatic secretion and may theoretically ease pain through reduction of pancreatic ductal pressure. Adjuvant analgesics are a heterogeneous group including antidepressants, anticonvulsants and anxiolytics that have been widely used to treat pain in CP, but only pregabalin has been investigated in this patient group and was found to induce a moderate pain relief (11).

Celiac plexus blockade represents the injection of pharmaceuticals into and/or around the region of the celiac ganglia. Most often used components in celiac plexus blockade are local anesthetic i.e. bupivacaine and triamcinolone and a steroid. Endoscopy, interventional radiology or surgical methods can all be used to conduct celiac plexus blockade. It represents a relatively low-risk, opioid-free method to reduce refractory pain in certain patients with CP. Some patients can have a meaningful reduction in their symptoms, although it is not clear which patients will derive the most benefit. If the patient has had clinical benefit from the initial celiac intervention, celiac plexus blockade can be repeated on a "as-needed" basis, usually with 3 months or more between treatments (11).

SPINAL CORD STIMULATION AND DORSAL ROOT GANGLION STIMULATION

Neuromodulation has been developed as another treatment option. Neuromodulation not only alleviates AP but also has a direct impact on the GI system, as it increases

vagal activity, promotes visceral hypersensitivity, enhances mucosal barrier function, and further decreases sympathetic tone to increase gastric emptying and alleviate GI pain. Neuromodulation may assist patients wean off opiate drugs, given that opiates not only have harmful side effects but also worsen the patient's underlying abdominal pain because of their effect on slowing GI motility (21). Treatment-refractory abdominal pain secondary to CP has been relieved with great success by spinal cord stimulation (SCS). In addition, dorsal root ganglion (DRG) stimulation has grown in popularity among healthcare professionals due to its more accurate pain coverage. Despite this, DRG stimulation has been used much less frequently than SCS, and, notably, there hasn't been a case of using DRG stimulation for CP-related AP. SCS and DRG stimulation are both reversible, so every patient first goes through a trial period before implantation, which is not a possibility with abdominal procedures (22).

CONCLUSION

Abdominal pain is the most prominent complication of chronic pancreatitis. The etiology of pain in CP involves multiple mechanisms, hence treatment should be individualized to adapt the patient's pain phenotype, such as pain characteristics and affected pain mechanisms. A step wise strategy is advised, starting with lifestyle changes including alcohol abstinention and a low-fat diet, then progressing to high dose non-coated pancreatic enzyme therapy and oral analgesic therapy. Endoscopy or decompressive surgery should be taken into account for patients with dilated main pancreatic duct who are not responding to medical treatment. Patients who have non-dilated pancreatic ducts, inflammatory masses, and debilitating pain may be candidates for reconstructive surgery. It is yet unclear to determine the role of total pancreatectomy with islet cell auto transplantation, celiac plexus block, and pain-modifiying agents (antioxidants, antidepressants) will play in treating this condition. On the other hand, neuromodulation has been developed as another treatment option, as it may assist patients wean off opiate drugs, given that opiates not only have harmful side effects but also worsen the patient's underlying abdominal pain because of their effect on slowing GI motility.

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Pain is a master that renders us small,
A fire that burns us to vanity,
One that separates us from our own lives,
One that lights us up and makes us alone.
One of the major features of the poem above by the Swiss–German Nobel laureate poet Hermann Hesse (1877–1962)

Inovacije u terapiji bola/Innovations in pain therapy

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ABSTRACT

Chronic pain is the number one cause of disability. It is more common in women than in men. People over 65 years of age experience pain at some point in their lives. All this leads to increased treatment costs. People with chronic pain are three times more likely to develop some form of anxiety and depression. Certainly, we must not forget the abuse of drugs, which primarily refers to the abuse of opioids and the opioid crisis. There are many novelties in pain therapy. They are divided into pharmacological and non-pharmacological. Some of the pharmacological ones are: different types of monoclonal antibodies, oxytocin, botox, oliceridine, while we include non-pharmacological ones: home sensors, virtual reality, implants. While most of the novelties are in the testing phase, we hope that they will soon become available for widespread use. It remains for us to follow them and when they become available to introduce them into daily clinical practice.

UVOD

Podaci vezani za broj osoba koje u našoj zemlji leče hroničan bol su veoma oskudni, odnosno skoro da ih nemamo, te stoga kao imamo podatke za USA. 1 od 5 odrasilh osoba u SAD ima neku vrstu hroničnog bola. Hronični bol je na prvom mestu kao uzrok nesposobnosti.Češći je kod žena nego kod muškaraca.Stariji od 65 godina u nekom trenutku svog života osećaju bol. Sve ovo vodi ka povećanim troškovima lečnja. Osobe sa hroničnim bolom imaju tri put veću šansu da razviju neki vid anksioznosti i depresije. Svakako ne smemo zaboraviti i zloupotrebu lekoova, gde se pre svega misli na zloupotrebu opioida i opioidnu krizu. Novina u terapiji bola je puno. Dele se na

farmakološke i nefarmakološke. Neki od farmakološki su: različite vrste monoklonalnih anti tela, oksitocin, botox, oliceridin I tako daljem, dok u nefarmakološke ubajamo: kućne senzore, VR, implante i tako dalje (1).

Okstocin nazvan hormon ljubvavi, endogeni produkt hipofize. Tradicionalno se koristi u porodiljstvu. Vezuje se za različite receptore u mozgu, a takođe i u kičmenoj moždini, gde stimuliše produkciju endogeno prisutnih opioida i na taj načim smanjuje pojavu bola. Postoje dokazi da se starenjem smanjuje lučenje oksitocina u organimu i da to može biti jedan od uzroka nastanka hroničnog muskuloskeltnog bola. Na tržištu SAD postoje preparati oksitocina koji se korite za terapiju bola. Način upotrebe intranazalno u obliku spraja ili sublingvalno. Doze potrebne za kupiranje bola jesu od 20-80 i.j. i kod većine pacijenta koji su ga koristili pokazuje dobre efekte u kupiranju bola. Neželjeni efekti jesu vrtoglavica, mučnina i disforija (2,3).

Benzyloxy-cyclopentyladenosine (BnOCPA) je novo jedinjenje koje je u fazi ispitivanja. Po mehanizmu dejstva predstavlja slektivnog anatgonistu A1 receptora i na taj način dovodi do samnjenja bola. Potentan je analgetik, ali za razliku od opioida ne dovodi do neželjenih efekata: sedacije, bradikardije, hipotenzije i respiratorne depresije, a takođe ono što je bitno u dosadašnjim istraživanjima je pokazano da nema stvaranja zavisnosti, što ga čini idealnim analgetikom. Svakako potrebna su dalja istraživanja na ovu temu (4).

Frunevetmab-komercijalno ime mu je Solensia. Monoklonsko antitelo odobreno za primenu veterinarskoj medicini. Mehanizam dejstva: inhibira faktor rasta nerava što dovodi do prekida nervnih impulsa duž nervih vlakana, odnosno prenos bola. Ono gde se koristi jeste terapija osteoartritisa kod mačaka. Ostaje da se vidi da li će u nekoj budućnosti krenuti ispitivanja na humanoj populaciji i samim tim mogućnost lečenja iste bolesti kod ljudi (5).

Tanezumab predstavlja još jedno monokolonalno anti telo-IgG2. Slično kao frunevetmab inhibira nervni faktor rasta koji je odgovoran za pojavu inflamacije u zahvaćenom zglobu, ali i indukciju centralne i periferne senzitizacije. Indikacija za primenu je osteoartritis. Studije i dalje traju. Problem je način primene ovoga leka moguće ga je primeniti i i.v. i s.c., ali naučnici još uvek nisu sigurni koji je način bolji. Iako pokazuje dobre rezultate u terapiji bola, kod nekolicine ispitanika je došlo do teškog neželjenog dejstva pojave rapidno-progresivnog osteoartritisa, što je dovelo u pitanje njegovu bezbednost. Tačan uzrog nastanka ovog neželjenog dejstva nije poznat, te su dalja ispitivanja na tu temu potrebna (6).

Zavegepant predstavlja novi lek za terapiju migrene bez aure. Ovaj lek je lak za upotrebu, jer se pakuje u obliku spreja za intranazalnu primenu. S obzirom na način primene ima brz početak dejstva u roku od 15 minuta dolazi do ispoljavanja efekta, a trajanje istog je do 48h. Pogodan je za upotrebu kod svih bolesnika, a pogotovo onih koji nisu u mogućnosti da uzimaju terapiju per os- kod mučnine i povraćanja. Neželjeni efekti jesu disgeuzija, osećaj nelagodnosti u nosu i mogucnost nastanka mučnine.

Studija Liptona i saradnika koja je je pokazala bezbednost i efikasnosnost ovog leka je objavljena u Lancet-u u martu 2023. Lek je dobio odobrenje od FDA i biće u prodaji od jula 2023 (7).

Atogepant još jedan od novih lekova za terapiju migrene. Mehanizam dejstva: inhibira peptide koji su povezani sa kalcitoninom. Multicentrična studija Ašina i saradnika je pokazala da je lek efikasan i bezbedan, kako u terapiji, tako i u prevenciji nastanka bola kod migrene. Prema FDA pokazuje veoma dobre rezultate u kupiranju bola kod najtežih oblika migrena. Doza dovoljna za većinu bolesnika jeste tableta od 60 mg. Međutim ograničavajući faktor jeste cena ovog leka koja za ide i do nekoliko stotina dolara, što ne čini ovaj lek lako dostupnim svim bolenicima (8).

Oleceridin noviji μ opioidni anlgetik koji je odobren od strane FDA za intravensku primenu, pogodan je za terapiji umerenih do jakih bolova. Njegova efikasnost je ispitivana u više različitih studija. Iako ima sličan farmakološki profil kao morfin, poređen je sa njim kod PCA, gde je pokazano da ima brži početak dejstva 1-2 min, dužinu trajanja dejstva nakon doze do 3h. Neželjeni efekti su mu mučnina, povraćanje i opstipacije, a takođe iako je pokazano da dovodi do manje incidence respiratorne depresije, svakako je neophodan oprez prilikom primene jer može dovesti do nje(9).

Nalokson lek koji se koristi u svakodnevnoj kliničkoj praksi, po mehanizmu dejstva opioidni antagonista, koristi se za poništavanje dejstva opioida kod predoziranja. Novina kod njega je način upotrebe, sprej za intranazalnu upotrebu. Predosti jesu laka upotreba, jedostavno doziranje i brz početak dejstva. Nedostatci su kratko vreme dejstva, potreba za ponavljanjem doza. A takođe i pojava apstinencijalnog sindroma može biti jedno od neželjenih dejstava(10).

Primena **botoksa** u terapiji bola nije novitet, ali se u našoj zemlji osim za estetske svrhe on retko ili skoro nikako ne koristi u svrhu terapije hroničnog bola. Modifikovana formula botulinskog toksina se ubrizgava subkutuno i u predeo oko nerava. Kada se ubrizga on pokazuje neparalitičko dejsto. Dužina trajanja dejstva je od 4 do 5 meseci, a pogodan je za upotrebu kod: miofascijalnog sindroma, bola u donjem delu leđa, glavobolje ,artralgije hroničnog pelvičnog bola i neuropatskog bola (11).

Injekcije matičnih ćelija predstavljaju novu metoda koja je u fazi kliničkih ispitivanja. Prvenstveno se koristi za terapiju degenerativnih pormena intervertebralnih diskova–diskus hernije koja je jedan od vodećih uzroka nastanka low back pain-a tzv bola u donjem delu leđa. Smeša ćelija kostene srži-matične ćelije se ubrizgavaju u oštećeni diskus kao i oko njega. Nakon ubrizgavanja dolazi do bujanja mezenhimnih ćelija i regeneracije prethodno oštećenih diskova. Kod većine ispitanika u dosadašnjim studijama, ova metoda se pokazala kao dobra, dovodi do poboljšanja simptoma kod većine pacijenta dolazi do prestanka bola u roku od nekoliko nedelja, i što je još značajnije ostvaruje se dugotrajan efekat do 36 meseci (12).

Hydrogel - Još jedna od metoda za neoperativno lečenje pacijenata koji boluju od različitih oblika diskus hernije. Koristi se eksperimentalna formulacija hidrogela

prvenstveno kod hroničnog degenerativnog oštećenje intervertebralnog diska. Sama tehnika podrazumeva direktno ubrizgavanje gela u oštećene diskove, igla se pod kontrolom rendgena uvodi u intervertebralni prostor i nakon toga se vrši ubrizgavanje hidrogela. Prednost ove minimalno invazivne procedure nad hirurškim tehnikama je u tome što je oporavak pacijenta i vraćanje svakodnevnim obavezama jako brz, već za dan dva su poptpuno funkcionalni. Iako je ova procedura još uvek u fazi kliničkih studija, ona daje obećavajuće rezultate, kod većine ispitanika pokazan je gubitak bola 6 meseci nakon procedure(13).

Virtuelna realnost se u poslednjih nekoliko godina koristi u kliničke svrhe te je tako našla svoje mesto i u terapiji bola. Postoji sve veći broj dokaza za primenu virtuelne realnosti u lečenju bola, međutim sa različitom efikasnošću. Više studija sa različitom upotrebom modaliteta virtuelne realnosti se bavilo ovom temom. U meta analizi Liera i saradnika koja je obuhvatla vise od 122 studje sa preko 9000 pacijenata pokazano je da upotreba tehnika virtuelene realnosti značajno smanjuje bola kod pacijenta koji su joj bili podvrgnuti u odnosu na pacijente koje su bili lečeni drugim konvencionalnim metodama lečenja. Analiza nije pokazala značajne razlike između tipova boli, efekti virtuelne realnosti su bili slični kod akutnog, proceduralnog i hroničnog bola. Međutim, iako je primetno smanjenje bola u ovim studijama ostalo je nejasno na koji način odnsosno kojim mehanizmima virtuelna realnost dovodi do smanjenja bola, te se stoga preporučuju dalja istraživanja na ovu temu(14).

Bioresorptivni kuleri su mali uređaji za ciljanu i reverzibilnu blokadu perifernih nerava. Imaju lokalni efekat hlađenja koji ima pozitivan efekat na smanjnje prenosa impulsa duž nerava. Malih su dimenzija te implantiraju lokalno duž nerava. Proizvode se od biokompatibilnih materijala što znači da se vremenom razgrađuju bez potrebe za ekstrakcijom. U pretkliničkim studijama pokazuju odličan efekat u smanjenju bola. I dalje su u fazi ispitivanja na eksperimentalnim životinjama, očekuje se da će su ukoro krenuti ispitivanje u humanoj populaciji (15).

Sakroilijačni zglob predstavlja spoj između sakruma i ilijačne kosti. On zapravo deluje kao amortizer i pomaže u preraspodeli sila sa kičme na donje ekstremitete. U više sprovedenih studija je pokazano da disfunkcija ovoga zgloba može biti jedan od uzroka bolova u donjem delu leđa. Da bi se ovo sprečilo poslednjih godina hirurzi su počeli raditi na tehnikama spajanja ove dve kosti uz pomoć titanijumskih pločica. Naime postoji dva pristupa bočni koji se češće koristi i posterolateralni. U većini ovih studija pokazan je benefit ove procedure smanjenjem bolova u donjem delu leđa i smanjena upotreba lekova za kupiranje bolova(16).

Kućni senzori su uređaji koji su razvijeni kao nove strategije koje su potrebne za suzbijanje epidemije predoziranja opioidima, kao i u terapiji opiodine zavisnosti. Opoidini zavisnici često imaju poremećen kvalitet sna, i upravu se zbog toga ponovna upotreba narkotika kao i predoziranje istim dešava noću. Senzori funkcionišu tako što prate pokrete pacijenta u toku sna i samim tim detektuju poremećaje sna, a takođe

mogu da prate puls i saturaciju krvi i na taj način pošalju obveštenje o mogućem nastanku respiratorne depresije. Signal šalju u mobilni telefon i tako obaveštavaju članove porodice obolelog ili njihove negovatelje. Sve ovo je značajno za pacijente koji su na hroničnoj opioidnoj terapiji i svakako predstavlja jednu od metoda prevencije nastanka neželjenih dejstva opioida(17).

Action on pain – Akcija za bol je volonterska organizacija osnovana 1998 u Engleskoj za pomoć pacijentima koji imaju različite vrste bola. Organizacija funkcioniše tako što organizuje različite tribine, predavanja, radionice na ovu temu, podelu promo materijala, a sve u cilju promovisanja pozitivnih strana života sa hroničnim bolom. Dostupan je web sajt koji sadrži brojne informacije o ovoj temi kao i najnovija saznanja o terapiji bola. Pacijenti mogu slati pitanja putem e-maila ili pozvati dostupan broj telefona i na taj način saznati sve što ih zanima vezano za problem koji imaju(18).

ZAKLJUČAK

Na kraju postavlja se pitanje gde smo mi u svemu ovome? Terapija bola kod nas je i dalje u većini slučajeva medikamentozna i to nama dostupnim konvencionalnim lekovima. Dok je većina noviteta u fazi ispitivanja, nadamo se da će uskoro postati dostupini za široku upotrebu. Neophodno je praćenje stručne literature kao i stalna kontinuirana edukacija medicinskog kadra na ovu temu. Svakako treba se raspitati od mogućnostima za uključivanje pacijenta u različite studije na ovu temu. Ostaje nam da ih pratimo i kada postanu dostupni da ih uvodimo u svakodnevnu kliničku praksu.

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Lymphedema: a underrecognized complication of cancer treatments

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Lymphedema is a disease caused by the mechanical insufficiency of the lymphatic system. It is characterized by the accumulation of protein-rich fluids in the interstitial spaces usually drained by an intact system: this leads to an increase in the volume of the body segment. Furthermore, chronic stasis determines a subclinical inflammation of the affected tissues, with their progressive fibrosis and with the appearance of skin alterations and complications of various types. Early recognition and treatment help prevent or limit the progression of the disease.

The WHO calculates a worldwide prevalence of about 250 million people affected. In Western countries, cancer therapy is the statistically most significant cause, with an increase in prevalence as a result of the frequent healing or chronicity of the tumor disease, but with a reduction in the incidence for those tumor forms in which the treatments have become less demolishing.

Another cause is vascular malformation, genetically determined and, in 10% of these forms, with hereditary transmission. Finally, in tropical and subtropical countries Filaria disease is an important cause of lymphedema, with about 40 million people affected in the world.

For breast cancer, axillary dissection is followed in about 22% of cases by lymphedema of the ipsilateral upper limb, while sentinel lymph node dissection causes lymphedema in only 3-6% of cases, with usually less important symptoms and signs.

In the treatment of pelvic tumours the incidence can reach 70% in cases complicated by infection.

It is now internationally established what the appropriate therapeutic approach should be: this is usually of the conservative type, but with the possibility, especially in the less responsive forms, of performing a derivative (lymphatic-venous anastomosis) or debulking surgery.

In the oncological field, lymphedema is often considered the inevitable tribute for a regained life expectancy. In too many cases lymphedema progresses without appropriate diagnosis and treatment, with an increasing impact on function, working capacity and quality of life.

The causes of an underestimation of the pathology are various: in the initial forms the symptoms may not be accompanied by objectifiable alterations; due to the superspecialization of medicine, alterations not specifically connected to the surgical or oncological approach can be ignored; the lack of dissemination of knowledge on lymphangiology; the resulting lack of health personnel specifically trained in the diagnosis and treatment of lymphedema.

ABSTRACTS

ORIGINAL WORKS

The influence of intraoperative pain management on the development of postoperative complications in urology population of patients

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Introduction: The IASP definition of pain states that pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (1).Pain neurology is highly diverse, certain genes and regulatory factors are expressed differently in each individual, so the approach to pain management must be individualized and patient-centered (2).As modern medicine developed and grew, so did the approaches to intraoperative pain management. It is important to determine the balance between negative drug side effects and an altered neuroendocrine pain response (3).

Methods: An observational pilot study included both gender patients underwent surgery procedure under anaesthesia at Urology Hospital, Clinical Centre of Serbia in period from 1st December 2022 to 31st January 2023. All study data were collected from medical history records. Sociodemographic, preoperative laboratory tests, comorbidities, surgery category (endoscopic or open), surgery duration, intraoperative analgesia, intraoperative blood volume lost, intraoperative transfusion therapy, postoperative analgesia and perioperative complications data were recorded. The postoperative complications were divided into five categories: cardiovascular, respiratory, haematologic, gastrointestinal, neurocognitive. The postoperative analgesic regimen included the combination of intravenous bolus doses of tramadol and nonopioids (Paracetamol, Metimazole, or both) given in regular intervals of time followed with pain monitoring. The aim of this substudy was to examined the correlation between the incidence of postoperative complications with intraoperative pain management. The statistical analysis was performed using the IBM SPSS Statistic 23 program.

Results: The study included 287 patients both gender (67,6% male and 32,4% female) mean age 60,91 ± 14,75 devided in two groups: endoscopic (74,91%) and open (25,09%). Most of patients were ASA II group (65,9%) with average BMI 26,85±4,35. Postoperative complications occurred in 3.3% of the endoscopic and 13.89% of the open surgery group. The postoperative complications were positively corelated with age in both study groups (endoscopic p 0,008, open p 0,012). In endoscopic group of

patients significant corelation was found between complications and preoperative hemoglobin concentration (p 0,014 rs -0,168), creatinin concentration (p 0,028 rs 0,150), time of surgery (p 0,025 rs 0,125). In open surgery group corelation was found between complications and LMWH administration (p 0,006 rs -0,32) and hemodinamic stability (p 0,048 rs -0,234). The requirement for additional analgesics was shown to be substantially linked with the dose of intraoperative opioid administration (p< 0.01; rs 0.254). We only determined an association between intraoperative opioid medication dosage and the occurrence of complications following open surgery (p 0,045, rs -0,237).

Conclusion: Even though, anesthesiologist must carefully examine the balance between the negative consequences of pain and the unfavorable side effects of opiate use for each particular patient. In recent years there has been a trend toward using regional anesthesia technicue to give opioid-free anesthesia. Further research is needed for substantial conclusion in our study.

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PENG block, strategy for acute hip pain

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Introduction: Pericapsular nerve group (PENG) block is a novel regional anesthesia technique which has been suggested as an alternative to existing blocks to reduce pain following hip fractures and surgery. The studies suggest that the PENG block can significantly reduce 24h opioid consumption after hip surgery, prolong the time to first request of analgesia postoperatively, reduce the risk of motor block and enable better physiotherapy. It is a plane block involving one ultrasound-guided injection of a local anesthetic into the musculofascial plane, between the psoas tendon anteriorly and the pubic ramus posteriorly. The goal is to block articular branches of the femoral nerve, the obturator nerve and, where present, the accessory obturator nerve that provide sensory innervation to the anterior hip capsule. The aim of this study was to examine the efficacy of the PENG block in reducing postoperative pain after total hip arthroplasty.

Materials and methods: Patients presented for intracapsular hip fracture or coxarthrosis underwent total hip arthroplasty. Six patients received analgesia with PENG block (PENG group), and another six patients received analgesia without any nerve block (Control group). PENG block was performed right before the surgery with ultrasound-guided single shot technique, in plane, and patients received 0.3ml/kg of 0.25% Bupivacaine. The block was always performed by the same anesthesiologist. The endpoint was the Numeric pain rating scale (NRS 0 to 10) in the postoperative 24 hours and the need for opioid analgesics.

Results: Postoperatively, maximum pain score in the PENG group was significantly lower than in the Control group 6h after the operation (NRS score 2.0±0.632 in PENG group, NRS score 3.67±0.52 in Control group, $p<0.001$) and 12h after the operation (NRS score 1.5±0.548 in PENG group, NRS score 4.33±0.82 in Control group, $p<0.001$). The PENG group experienced less pain compared with the Control group 24h after the surgery (NRS score 2.33±1.86 in PENG group, NRS score 3.67±0.52 in Control group) but it wasn't statistically significant. All patients received NSAIDs (Non-steroidal anti-inflammatory drugs), two patients in the Control group received Tramadol and one patient in the Control group received Pethidine. There was no need for opioid analgesics postoperatively in the PENG group. During the operation, patients in the PENG group who received general anesthesia showed significant reduction in opioid consumption compared to the Control group (Fentanyl dose in PENG group

was 260mcg±65.19, Fentanyl dose in Control group was 380mcg±27.38, $p<0.05$). Postoperative recovery was uneventful. These are the first results of our research that will be continued.

Conclusion: PENG block, as a part of multimodal analgesia, provided effective pain relief after hip surgery.

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Pre-emptive Acetaminophen can reduce pain intensity after uretheroscopic lithotripsy

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Introduction: Pre-emptive analgesic strategies are strongly recommended by the International Association for the study of pain, especially in low-resource settings1. Pre-emptive analgesia is an antinociceptive treatment that prevents establishment of altered processing of afferent input that amplifies postoperative pain. Pre-emptive effect suggesting antinociceptive effect of agent after its 5,5 half-lives of elimination2. Pre-emptive acetaminophen use follows its safe pharmacokinetic profile, modulatory effect on endocannabinoid system and NMDA receptors, serotonergic pathways3.

Methods: Following ethics committee approval and signed ICF the prospective randomised double-blind pilot cohort study included 38 consecutive American Society of Anesthesi¬ologists (ASA) I and II patients, both gender, age 20-80 with unilateral uretheral stones scheduled for uretheroscopic lithotripsy. Included patients met all inclusion and none exclusion criteria. Demographic data and history of previous surgeries and URSL were obtained on admission to the hospital for all patients. Routine biochemistry analysis, blood count, urinalysis, and urine culture were performed preoperatively. Prophylactic antibiotics were injected intravenously in all patients. Patients were told that the pain scores would be recorded once prior and three times after the procedure according NRS. Included patients were randomly allocated into two groups using random allocation software. S-group (Study group) took 1g (100ml) Acetaminophen i.v. 30 minutes before induction of anesthesia in original bottle. C-group (Control group) took the 100ml 0.9% NaCl. The solutions were prepared and code labeled by an anesthetist and anesthetic nurse who were in¬volved in neither anesthesia administration nor in follow-up. Uretheroscopic lithotripsy was performed under general anesthesia with volatile anesthetics followed with supraglotic device placement. Fentanyl was administered intraoperatively and NSAID on request postoperatively for pain management. Pre-emptive effect of Acetaminophen was assessed measuring intraoperative fentanyl consumption, postoperative NRS scores -1h, 4h, 24h after surgery (NRS 1-3) and postoperative analgesia requests. Data were analized using EZR Statistic Softver.

Results: C-group of patients reported significantly higher NRS 0 (X214.7, p 0.005) as well as significantly higher fentanyl consumption (X2 20.36, p 0.0001) compare to

the S-group. No found difference in procedure duration between groups (T-test 1.45, p 0.154) nor in postoperative analgesia consumption (X2 0.877, p 0.349). C-group of patients reported higher pain scores only 24h after procedure (X2 19.78, p 0.0001) compare to the S-group. NRS 0 strongly corelated with NRS 3 (p 0.00038), fentanyl consumption (p 0.001) and ASA score (p 0.028) among study population. Only in S-group of patients NRS 2 strongly corelated with NRS 3 (p 0,021).

Conclusion: Pre-emptive use of Acetaminophen 1g could significantly reduce pain scores 24h after procedure additionally supported with postoperative NRS reduction in S-group of patients. Futher research is needed for substantial conclusion.

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Tapentadol IR- a new therapy protocol in acute pain control after Extracorporal Shock Wave Lithotripsy

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Introduction: Initially ESWL procedure (Extracorporal Shock Wave Lithotripsy) used to be performed under general anesthesia, but nowdays the technical improvements made it possible without the general anesthesia 1. Still, ESWL is considered a painful procedure. Pain affects the outcome of ESWL due to involuntary movements caused by pain. Still, there is no standard analgesia protocols for ESWL 2,3. The aim of the study was to determine the severity of acute pain related to the ESWL using two comparative preventive analgesia protocols with Tramadol/Ketoprofen and Tapentadol.

Methods: A clinical prospective cohort randomized study included 200 patients of both genders, aged 18-80 years who fulfilled all inclusion and nonne exclusion criteria. Before randomization procedure, sociodemographic data, previous surgeries and comorbidities were recorded. The subjects were randomized into two groups: Group I – received a combination of Ketoprofen 100mg/Tramadol 50mg i.m., 30 minutes before the procedure; Group II reeceived Tapentadol IR 50mg orally, 1 hour before the procedure. Pain intensity score according NRS and complications were recorded before, during and at the end the of procedure. In the statistical analysis, parametric and non-parametric tests were used, and the difference was expressed through two levels of significance.

Results: No difference was found in preoperative characteristics of patient population as well as stone dimensiones and localisation ($p > 0.05$). A statistically significant increase in pain score before and during procedure occurred within each group (0.82 to 3.39 vs 0.68 to 3.85, $p<0.05$) with no difference between groups. In group II, 14% of patients had severe pain during the procedure (compare 3% of group I). It was noted that nausea occurred twice as often in patients with severe pain. In the severe pain subgroups of each group of patients, nausea was present in 42% of patients of group II, which is significantly higher compare to 5% of group I (both group overall incidence 21%). All of them were diagnosed renal postition of stone.

Conclusion: Eventhough, both protocols ensure average low pain intensity score during procedure (3.39 vs 3.85) with no difference in subsequent pain measurements between groups, tapentadol group reported frequently severe pain score followed with nausea might be related to stone position.

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THE BEST POSTER PRESENTATION-THE THIRD PLACE

Effect of ketamine administration on perioperative pain control in burn patients

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Introduction: Accompanying pain in burn disease is very complex and represents a challenge for the team dealing with the treatment of this disease. The aim of this study was to examine the effect of intraoperative administration of ketamine on perioperative pain control.

Methods: In the retrospective observational studies, 165 patients of both genders, older than 16 years, with IIa and IIb degree burns, and combined burns, were included. Patients were bandaged in the operating room, in general anesthesia, in the period between the 3rd and 5th day after the occurrence of the injury (after hemodynamic stabilization, before the planned operative treatment). We divided burns into smaller and larger than 20%. In relation to the applied type of intraoperative analgesia, two examined groups were formed: group 1-without ketamine 44% of patients, group 2-with ketamine 56% of patients. During dressing of the patients, fentanyl and propofol were prescribed (in both groups of patients), in a dose determined by the individual requirements of the patients. The influence of the administration of subanesthetic doses of ketamine (0.25-0.5mg/kg body weight) on the intraoperative requirements for opioid analgetics (fentanyl) was examined in relation to the depth of the burn, surface of the burn, the age, the gender of patients, the duration of the operation-dressing, the duration of anesthesia. Postoperatively, in the Intensive Care Unit, standard hemodynamic and laboratory variables, the intensity of pain based on the Numerical Pain Rating Scale during 1h, 3h, 6h, 12h, 24h was registrated postoperatively. NSAIDs and paracetamol were used for postoperative analgesia. The influence of intraoperatively given ketamine for the needs of postoperative analgesia, tramadol, that was prescribed in a dose of 100mg, was examined, wich was repeated on the patients request when pain intensity on the NPRS was >4.

Results: The results of the studies showed that patients with different extents of burns received significantly lower doses of opioids if ketamine was applied at the same time in a subanesthetic dose. Statistically, in relation to the gender and the age of

examined groups, significant difference was not recorderd. The average age of patients from the group that received ketamine was 46.03 years±19.59. Statistically, highly significant difference was registred in relation to the age of the patients between the examined groups of patients ($p=0.001$). Ketamine was equally represented in all studied groups of patients, divided in relation to the size of the burns. The average values of fentanyl and propofol were significantly lower in the ketamine group and high statistical significance was registered ($p<0.01$). Administration of ketamine intraoperatively did not affect the reduced consumption of tramadol in the postoperative period.

Conclusion: Intraoperative administration of ketamine in subanesthetical doses significantly reduced intraoperative consumption of opioid and propofol in all patients, observed in relation to the size of the burn. The need for postoperative administration of tramadol was equal in both studied groups of patients. Intraoperatively administered ketamine had no positive effect on postoperative pain control.

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Difference between long-acting local anesthetics while performing axillary nerve block

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Introduction: Ultrasound-guided axillary blocks are a standard anesthetic technique in upper limb surgery. In addition to providing adequate anesthesia, they also provide postoperative analgesia. Today, long-acting local anesthetics such as bupivacaine and levobupivacaine are most commonly used. Comparison and analysis of the efficacy of local anesthetics levobupivacaine and bupivacaine when performing axillary block, time intervals necessary for achieving complete axillary block, as well as their effect on the consumption of analgesics in the first 72 hours postoperatively.

Material and methods: Patients who received axillary nerve block guided by ultrasound as the main anesthetic technique were divided into two groups. A group of 64 patients was administered levobupivacaine as a local anesthetic, while a group of 63 patients was administered bupivacaine.

Results: There were no significant differences in demographic characteristics among the groups. An adequate axillary block was achieved in approximately the same number of patients ($p=0.675$), however there were significant deviations in the patients in which an adequate block was not achieved. Larger number of patients in the levobupivacaine administered group had an inadequate block in the first 30 minutes from the start of surgery ($p=0.017$). The postoperative requirement for opioid and non-opioid analgesics between the groups did not differ statistically on any postoperative day ($p\geq0.05$).

Conclusion: It can be concluded that both levobupivacaine and bupivacaine are equally effective in providing postoperative analgesia, without major differences in the consumption of non-opioid and opioid analgesics. The main difference between levobupivacaine and bupivacaine was reflected in the time intervals necessary to achieve an adequate axillary block, where in the group with levobupivacaine needed more than 30 minutes before the start of surgery.

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Significance of perioperative use of lidocaine in pain therapy in laparoscopic colo-rectal surgery

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Introduction: To examine the significance of the analgesic effect of continuous intraoperative infusion of lidocaine in order to reduce the amount or dose of opioid and non-opioid analgesics in the perioperative period in patients undergoing colo-rectal laparoscopic surgery.

Methods: Thirty patients undergoing colorectal surgery in OET anesthesia, participated in this study. 15 patients received lidocaine (lidocaine group LG) with 1, 5 mg/kg intravenous bolus in 10 min followed by a 1, 5 mg/kg/h IV infusion, 30 min before before gas insufflation and stopped 60 min after after the surgery is over. Second (control group GA), were administered postoperatively for analgesia in combination tramadol and ketorolak. For both groups propofol 2–2.5 mg/kg will be used to induce anesthesia, and fentanyl 1.5 μg/kg IV will be used to maintain anesthesia and sevoflurane 1-2 vol/%, oxygen:air ratio 1:1. For intubation and maintenance of relaxation we will use rocuronium of 0.1-1mg/kg. Postoperative pain score were evaluated by using visual analog scale score of 0 to 10, every 2 h until the first postoperative day and then every 4 h next 72 h. If pain intensity ≥ 4, analgesia was started. Monitored the amount of administered analgetic and metabolic response (leukocytes, CRP and glucose) were measured 3 h after end of operation and next three days.

Results: At the first measurement patients from LG, by the VAS scale incited a pain score between 3 and 6 and received their first ketorolac. From 15 patients in 6 was added and tramadol (statistically significant, $p < 0,05$). In GA group, the intensity of pain by the VAS scale was between 5 and 9, and docked by tramadol. Application of tramadol was significantly reduced in the LG (40%), And in the later period during movement use of tramadol was significantly reduced in the LG (50 mg ± 25 vs. 200 ± 50). The value of Le, CRP and blood glucose levels were some lower in the LG, but the difference was not statisticaly significant.

Conclusion: Perioperative continuously intravenous lidocaine reduces the systemic use of analgetics in the treatment postoperative pain durig colo-rectal laparoscopic surgery. For this reason, this old method has a new approach.

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THE BEST POSTER PRESENTATION-THE SECOND PLACE

The impact of depression and anxiety on acute musculoskeletal pain

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Introduction: The interdependence of chronic pain and levels of depression and anxiety is well established. However, the exact impact of depression and anxiety on acute pain is still being studied. Our study aimed to evaluate the relationship between acute musculoskeletal pain intensity, depression and anxiety.

Methods: A total of 105 athletes (53 men and 52 women, age 35.0 [35.0 – 44.0] years) participating in the outdoor endurance events were included. Subjects were asked to evaluate the intensity of pain and physical activity during the event and training on an 11-point Likert scale. The Patient Health Questionnaire-9 (PHQ-9) was used to assess depression. Generalized Anxiety Disorder-7 (GAD-7) questionnaire and a three-dimensional Anxiety Sensitivity Index-3 (ASI-3) were used to assess anxiety.

Results: Forty-two (40.0%) subjects showed at least a mild level of depression. According to ASI-3 and GAD-7 scales, 15 (14.3%) and 25 (23.8%) participants showed at least mild anxiety, respectively. During the endurance event, participants reported a maximum pain of 4.0 [1.5-7.0] and an average pain of 2.0 [1.0-4.0]. Positive correlations between PHQ-9, GAD-7, and cognitive concerns domain of ASI-3 scores with both maximal (Kendall tau b coefficients: 0.178, 0.114 and 0.163, respectively, $p < 0.05$ for all) and average pain (Kendall tau b coefficients: 0.190, 0.182 and 0.245, respectively, $p < 0.05$ for all) experienced during the event were observed. Maximal and average pain during the event also correlated with the activity intensity and pain levels during training ($p < 0.05$ for all). PHQ-9 scores, maximal pain during training and the activity intensity during the event predicted the maximum pain intensity during the event (R2 0.398, $p < 0.05$, Standardized Beta 0.250, 0.421, and 0.311, respectively).

Conclusion: During the endurance event, subjects experienced mild to severe acute musculoskeletal pain. The intensity of the acute musculoskeletal pain was

positively correlated with both depression and anxiety levels and also with physical activity during the event.

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THE BEST POSTER PRESENTATION-THE FIRST PLACE

Could Artificial Intelligence Replace Fieldwork in Pain Research?

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Introduction: The introduction of open Artificial intelligence (AI) models caused a significant dissonance in the scientific community. Data acquisition and analysis are among the most controversial aspects of AI use in pain research. While it could save considerable resources, the quality of the acquired and processed data is still controversial. Our study aimed to assess if an AI model could produce data on the intensity and localization of acute musculoskeletal pain in athletes comparable to data acquired by field researchers.

Methods: The study included 52 rock climbers (33 male and 19 female; 29.00 [24.00 - 35.75] years old) who underwent 2-hour indoor training. Athletes were asked to complete a questionnaire to assess the localization and intensity of acute musculoskeletal pain during physical activity. The average and maximal pain was assessed using a numeric rating scale (NRS). An AI deep learning model developed using Generative Pre-trained Transformer 3.5 architecture (ChatGPT 3.5) was instructed to search the entirety of the internet but also separately scientific databases and the five most popular chatrooms where athletes discuss pain during physical activity to provide the answers to the same questions as in questionnaire.

Results: Most climbers identified the back of the forearm (n=10 (19.2%)) and toes (n=9 (17.3%)) as the primary localization of the pain. The average pain intensity was 4.00 [3.00 - 5.00], and the maximum pain intensity was 7.00 [5.00 - 8.00]. ChatGPT also identified the forearm and toes as the primary localization of the pain in climbers but was unable to provide the exact proportions. It also stated that it could not produce the numeric expression of the average and maximum acute musculoskeletal pain intensity in climbers as, so far, such research still needs to be performed.

Conclusions: The AI model was not able to provide data on the intensity and localization of acute musculoskeletal pain in athletes comparable to data acquired by field researchers. However, it confirmed the novelty of our research.

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THE BEST POSTER PRESENTATION-THE THIRD PLACE

Quadratus lumborum block as a part of multimodal analgesia after inguinal hernia repair surgery

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Introduction: The expansion of truncal block techniques, as a part of perioperative pain management was driven by introducing ultrasound into daily anaesthesiology practice. Quadratus lumborum block is an interfascial plain block performed exclusively under ultrasound control. The crucial landmark for block performance is the quadratus lumborum muscle surrounded by fibrous composite of aponeurotic and fascial tissue: thoracolumbar fascia. Local anaesthetic is injected near the quadratus lumborum muscle with the goal of anaesthetizing the toracolumbar nerves. In most cases analgesia is achieved in T7-L1 dermatomes. The studies have shown the effect on postoperative pain reduction usually lasted more than 24 hours. Also, the use of opioid analgesics was reduced in patients who received Paracetamol, NSAIL, and quadratus lumborum block, as a part of multimodal analgesia. The aim of this study was to examine the efficacy of the quadratus lumborum block after inguinal hernia repair surgery.

Materials and methods: This study enrolled 20 patients. The eligibility criteria were: undergoing unilateral inguinal hernia repair surgery, having ASA physical status I, II or III, and not suffering from any chronic pain condition. In ten patients, the block was performed before surgery and non-opioid analgesics were regularly prescribed in the first 24 hours after surgery (QLB group). In the control group (ten patients), only non–opioid anagesics were prescribed without nerve block. Patients whose pain scores where higher than 4 on Numeric scale, recived Tramadol as a rescue analgesia in both groups. The block was performed before surgery with ultrasound-guided single shot technique, in plane. We used 0,3ml/kg 0,25% Bupivacaine. The outcomes of our study were differences in postoperative pain after 1h, 6h, 12h, 24 h and opioid consumption. We also evaluated the consumption of fentanyl intraoperatively.

Results: We evaluated the postoperative pain scores at 1h, 6h, 12h, and 24 hours after surgery. Pain scores in QL group were significantly lower than in control group.

Table 1. Pain scores on Numeric scale in QLB group and control grup 1h, 6h, 12h, and 24h after inguinal hernia repair surgery

Hours after surgery	QLB group N=10 ($\bar{x}$ ± SD)	Control group N=10 ($\bar{x}$ ± SD)	p value
1h	1,0±1,05	4,55±2,19	p < 0.001
6h	1,1± 0,74	4,55±1,83	p<0.001
12h	0.65±0.67	4.2±1.13	p< 0.001
24h	0.35±0.47	3.3±1.89	p<0.001

QLB – Quadratus lumborum block, $\bar{x}$ - mean, SD – standard deviation, p value for Mann-Whitney U test

In the QLB group there was no need for opioid analgetics. In the control group five patients (50%) received opioid analgesics. There was significantly lower opioid consumption during general anaesthesia in QLB group compared to the control group (Fentanyl dose in the QLB group was 3,17 mcg/kg ±0,77, Fentanyl dose in the control group was 4,18mcg/kg±0,93).

Conclusion: Our results indicate that quadratus lumborum block, as a part of multimodal analgesia, provides adequate postoperative analgesia for adult patients undergoing inguinal hernia repair surgery.

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Influence of demographic factors on development of chronic post-surgical pain in urologic patients: a pilot study

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Introduction: According to standardisation in 2019 after the inclusion in the new International Classification of Diseases, Eleventh Revision (ICD-11), chronic post-surgical pain or post traumatic pain (CPSP) is defined as presence of pain related to surgery or tissue injury that persists beyond the healing process and lasts ≥3 months, also when other causes of pain (e.g. pre-existing pain conditions, infection, malignancy) are excluded. Chronic post-surgical pain can often show characteristics of neuropathic pain and has important negative impact on patients' quality of life that constitutes significant economic and healthcare burdens.1 The wide variability in the incidence can differ depending on the type of surgery (5–85%) and by different methods of data collection and variable definitions of CPSP. Risk factors for CPSP have been identified in periods before, during and after surgery and include genetic, demographic, psychosocial, pain, clinical and surgical factors. 2 The early identification of risk factors can allow risk stratification and the implementation of different treatment strategies for prevention CPSP. 3.

Methods: A pilot observational prospective cohort study was conducted in Urology Clinic, University Clinical Centre of Serbia in period from 2021/2022 that included 30 patients undergoing urology surgery. A questionnaire included preoperative demographic, social, psychologic factors and expectation of pain on NRS scale from 0 to 10, (where the 0 is condition without pain and 10 the worst pain), intraoperative anaesthesiology and surgical factors, pain intensity in rest and during the movement on NRS scale from 0 to 10 in 1h, 8th and 24 hours postoperatively, usage of opioids, existence of nausea, vomiting, weakness, vertigo and influence of pain on breathing, sleeping and walking in same time intervals. Patients were interviewed via phone survey for pain intensity in rest and during movement on NRS scale from 0 to 10 and physical and mental condition 3 months after surgery. Also, neuropathic component of pain is assessed through Pain Detect, validated questionnaire that is translated into Serbian language.

Results: 73,3% of patients were male and 26,7% female. Mean age was 60.6 ± 12.5 and mean BMI was 27.6 ± 4.7. Most patients were married 70%, 16.7% single, 10% widowers and 3,3% divorced. Employed and retired patients had both of 43,33% and

13,33% were unemployed. Twenty of thirty patients (66,67%) described post-surgical pain after 3 months in rest and neuropathic component of pain was negative in 86,67% and unclear in 13,33% of patients. Influence of gender, age, BMI and working status did not affect development of CPSP. However, there is moderate negative correlation between level of education and presence of acute pain (in rest and during movement) on NRS scale 24 hours after surgery that is statistically significant. A moderate positive correlation is showed between CPSP after 3 months (in rest and during movements) and marital status that is statistically significant.

Conclusion: Patients with higher level of education experience less pain on NRS scale 24 hours after surgery. When CPSP is present, married patients showed less pain on NRS scale in rest and in movement after 3 months comparing to single patients.

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Is the obturator nerve block satisfactory to surgeons?

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Introduction: The operating program frequently exceeds the institutions' capacity. In these situations, we frequently expedite processes in order to finish the program on time. Transurethral resection of lateral wall bladder tumors (TUR-BT) requires an obturator nerve block to prevent complications and make the procedure more comfortable. This study's objective was to evaluate the properties of obturator nerve blocks.

Material and methods: A prospective observational evaluation was conducted following approval by the hospital's Ethics Committee and patients' signed informed consent. Twenty consecutive TUR-BT patients with localization on the lateral bladder wall received an obturator nerve block, while patients without lateral bladder wall localization received only general anesthesia with a laryngeal mask or only spinal anesthesia. Following general anesthesia with a laryngeal mask or spinal anesthesia, the obturator nerve block was carried out. Under ultrasound guidance, the nerve's location was determined using the in-plane technique, a syringe was inserted, and 5 mL of lidocaine 2% and bupivacaine 0.5% were injected into the anterior and posterior branches of the obturator. The duration of the operation, the severity of the motor obstruction, and the time required to perform an obturator block were all recorded. During the procedure, the level of contentment of the surgeon was monitored. Additionally, the patient's level of satisfaction and any prospective problems were recorded.

Results: Time to perform anesthesia lasted (minutes) mean ± SD: 6.5±3.2 in general anesthesia patients, 7.2 ± 3.8 in spinal anesthesia patients, 10.8 ± 0.5 in general anesthesia with obturator block, and 12.0 ± 0.3 in spinal anesthesia with obturator block. Block performance time (min) mean ± SD was 5.0 ± 0.8. Onset time until nerve block was (min) mean ± SD: 9.2 ± 3.7. In 2 patients (10%), we had reduced spasm, and in 18 patients (90%), we had complete motor blockade. In the obturator block group, surgeons had excellent satisfaction rates of 95%. The mean surgical time did not differ between the groups. Patients satisfaction was excellent in all patients. We did not have any complications.

Conclusion: Our data shows that there was a variation in the appropriate period to provide anesthetic during the obturator's motor nerve block. Despite the longer procedure duration for the obturator nerve block, patient satisfaction and tumor removal

rates decreased. The length of the obturator blockade is unimportant in this therapy; therefore, the beginning of the procedure, avoiding problems, and the surgeon's satisfaction is the primary issues.

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Analgesic efficacy of tramadol/metamizole combination-bolus doses compare to continous infusion

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Introduction: Promptly and adequately treating acute postoperative pain can reduce the risk that it will transition into chronic postoperative pain. [1] Combined administration of certain doses of opioid compounds with a non-steroidal anti-inflammatory drug can produce additive or supra-additive effects while reducing unwanted effects. [2] Tramadol and metamizol are very commonly used postoperatively for tretment of acute pain (bolus doses). Infusion of tramadol provide safe and more effective acute pain relief. [3] The aim of this study was to compare analgesic efficacy of tramadol/metamizole combination-bolus doses vs. continous infusion.

Methods: The prospective cohort pilot study included all patients undergoing surgery (radical nephrectomy with lumbotomy approach). Patients suffered from diabetes mellitus with polyneuropathia, depressive disorders, advanced renal failure, hematology disease, peptic ulcer, drug abuse or chronic opioid use, medicament allergic reaction, MOCA <25, BMI≥ 25kg/m2 were exluded. Following the same premedication with midazolam, anaesthesia induction was with propofol, fentanyl and rocuronium for intubation. Anesthesia was maintained with O2/Air/Sevo mixture and fentanyl and rocuronium boluses. Preoperatively, all patients were randomized into two groups in double-blinded manner. Group I received intermitent iv boluses of tramadol 100 mg QID and metamizol–Na 2500 mg BID. Analgesia started with tramadol 100 mg followed by metamizol 2500 mg after 120 minutes. Group II received the 500ml of normal saline solution with tramadol 300 mg (0,6 mg/ml) and metamizol 5000 mg (10 mg/ml). Infusion rate was 200 ml/h first 30 minutes followed with 17 ml/h infusion rate for maintenance until end of infusion. For both group of patients administration of analgesia started 15 minutes after anesthesia recovery. Preoperative patient related data were compared between two groups as well as pain scores, intraoperative analgesic and rescue medication consumption. According NRS, if pain intensity score was ≥ 3/10 in rest or ≥5/10 in movement, both group of patients received 1mg iv rescue dose of morphine sulfate every 15 minutes untill pain reduction.

Results: The pilot study included 20 patients both gender (60% male, 40% female), age 68±10.49, BMI 25.71±2.51. No difference was found regarding preoperative

characteristics between groups except experience with previous surgeries (p 0.004). No difference was found regarding intraoperative data: fentanyl consumption (p 0.49), surgery duration (p 0.26), NRSawake (p 0.78). Group I achieved adeqate pain control within 12 hours, by receiving morphine within the whole 12-hour period. Group II achieved adequate pain control within 8 hours by average receiving 1-2mg of morphine within first 4 hours. Statistical difference was found regarding morphine consumption within 8th and 12th hour respectivelly (p 0.05; p 0.058) as well as NRSrest in 12th hour (0.013) between groups. We found strong correlation between age and total morphine consumption (rS 0.48, p 0.03), NRSawake (rS 0.56, p 0.009). BMI correlate with fentanyl consumption (rS 0.44 p 0.05), NRS 8th and 12th respectivelly ($p < 0.004$, rS 0.56, rS 0.44).

Conclusion: Continuous regimen of tramadol/metamizol administration with lower dose of tramadol were superior over bolus regimen in pain control with less resque analgesia consumption.

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Use of opioids for adults with cancer and non-cancer chronic pain – one center experience

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Introduction: Opioid use for both cancer pain and non-cancer pain has been rising globally. For moderate-to-severe cancer pain, opioids have been included as a first line treatment. Opioids have become popular as a second or third line of treatment for non-cancer pain. The United States and Canada have among the greatest global opioid consumption rates. The number of opioids prescriptions for treating chronic pain in our nation is unknown. The aim of this study was to investigate the prevalence of opioid prescriptions among patients with cancer and non-cancer pain in our center for pain therapy.

Patients and methods: We conducted a cross-sectional study of opioids prescription for chronic pain from January 2021 to December 2022, in the Department for Pain Therapy in Clinic for Digestive Surgery-The First Surgical Clinic, University Clinical Center Serbia. We collect data from patients' medical records. Opioid and opioid-combination drugs were selected within classes of opioids that are indicated to manage pain: fentanyl, tapentadol, tramadol, oxycodone, morphine and hydromorphone. Also, we investigate management of pain with non-opioid drugs: gabapentins and non-steroidal anti-inflammatory analgesics (NSAIA). We observed opioids use in two groups of patients: CP group (patients experienced pain due to cancer) and NCP group (patients suffered from non-cancer pain).

Results: 272 patients (181 from CP group and 91 from NCP group) were included in the study. There was statistically significant difference in opioids use between CP and NCP group ($p<0.001$). 91(33.5%) patients were used fentanyl for pain relief with a statistically significant difference in fentanyl use between the CP and NCP group ($p<0.001$; 87(39.4%) vs. 4(7.8%)). In 126 (46.3%) patients, tapentadol was prescribed with a statistically significant difference between CP group and NCP group ($p<0.001$; 90(40.7%) vs. 36(28.6%). In 37(13.6%) patients, oxycodone was recommended, with a statistically significant difference between CP group and NCP group (p-0.005; 13.2% vs. 0.3%). Among 29(10.7%) patients who used tramadol there was no significant statistical difference between CP and NCP group (p-0.802; 10.4% vs. 11.8%). There was statistically

significant difference in morphine use between CP and NCP groups (p<0.001; 40.7% vs. 9.8%) among 95(34.9%) patients. Hydromorphone was prescribed in 7(2.6%) patients.

Gabapentin as a non-opioid drug was prescribed in 58(21.32%) patinets. More patientsin the NCP group had taken gabapentin, but without significant difference between groups (p-0.126; 5.5% vs. 12.9%). There was not statistically significant difference in NSAIA between CP and NCP groups (p-0.379; 3.3% vs. 15.4%).

Conclusion: Although the use of opioids may be widespread in some nations, it was less than 50% in our study group, with higher prevalence in the group of cancer patients.

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Perioperative pain management in minimal invasive aortic valve surgery

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Introduction: The term minimally invasive valve surgery refers to a series of procedures that use direct, nonsternotomy, thoracoscopic, or robotic approaches that are specifically designed for cardiac surgery and have a smaller incision than the conventional midsternotomy approach. These procedures aim to reduce morbidity and speed recovery, thereby increasing patient satisfaction. This procedure is performed under general endotracheal anesthesia or analgesia conditions, and a blockade at the level of the erector spinae muscle is often used for intraoperative and postoperative pain control. The aim of this work was to reduce morbidity and accelerate recovery in patients undergoing aortic valve replacement.

Material and Methods: In this phase, the prospective study included 10 patients who underwent minimally invasive valvular surgery (MIVS) from October 2022 to April 2023. All patients were operated in general endotracheal anesthesia and under conditions of extracorporeal circulation with mild hypothermia and systemic heparinization. The surgical approach was via an anterior right thoracotomy at the level of the second intercostal space. The erector spinae muscle blockade was performed before general endotracheal anesthesia was introduced. This is a paraspinal fascial blockade in which a local anesthetic is injected between the tip of the processus transfersus of the thoracic or lumbar vertebra and the anterior fascia of the erector spinal muscle. We used 20 ml of 0.25% Levobupivacaine .The block targets the dorsal and ventral ramus of the thoracic and abdominal spinal nerves to provide analgesia for a variety of surgical procedures and pain conditions.

Results: 10 such procedures were performed in the last six months at the Clinic for Cardiac surgery of University Clinical Center of Serbia. Patients were extubated on the table. The patients breathing was stable during the whole period. Compared with patients who underwent sternotomy, they required fewer analgesics postoperatively. They could be discharged home on postoperative day 4.

Conclusion: The results of this work have shown that blockade of the erector spinal muscle reduces the need for postoperative analgesics and accelerates postoperative recovery in patients who have undergone MIVS.

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OW.16. BISOP. 2023

Perioperative pain management in patients submitted to minimally invasive direct off-pump coronary artery bypass grafting surgery

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Introduction: To achieve the maximal benefit for the patients, different techniques that avoid sternotomy, cardiopulmonary bypass and cardioplegia have been developed. These varied approaches are collectively referred to as "minimally invasive direct off-pump coronary artery bypass grafting – MID-OPCABG" techniques. These procedures aim to reduce morbidity and speed recovery, thereby increasing patient satisfaction. Objective of this work was to illustrate the advantages of combined analgesia (systemic and local) in MID-OPCABG patients, promoting their fast recovery.

Material and Methods: In this phase, the prospective study included 50 patients who underwent MID-OPCABG during the last 10 mounths. All patients were operated in general endotracheal one-lung ventilation (Carlens) anesthesia. In 10 patients we applied Serratus Anterior Plane Nerve Block with 0.5 % levobupivacaine. The surgical approach was via small left thoracotomy (5cm) within the 4th or the 5th intecostal space, just below the mamilla. Revascularisation was achieved by left or both internal thoracic arteries alowing us to revascularise more than one coronary blood vasels. To diminish postoperative pain arrising from incision and port site, apart form the systemic analgesia (trodone, paracetamol) and previously described Serratus blockade, we have infiltrated the chest woond with local anesthetic (lidocaine) as bolus, continued by infusion 0.125% levobupivacaine 5ml/h for the next 24-48h.

Results: In all operated patients we managed to achieve almost painless procedure alowing early detubation (10 patients on site) and unevetfull intensive care time in terms of complications related to extensive pain. They could be discharged home on postoperative day 4.

Conclusion: The results of this work have shown that this pain control protocol, together with principles of MID-OFCABG, resulted in short hospital stay and fast recovery of operated patients.

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CASE REPORTS

THE BEST CASE REPORT-THE FIRST PLACE

Suprascapular nerve block as the analgesic solution in an anterior shoulder dislocation: a case report

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Introduction: The suprascapular nerve block is an effective method for providing anesthesia and analgesia for the shoulder. The suprascapular nerve contributes to the sensory innervation of the acromioclavicular and glenohumeral joints, as well as motor innervation of the supraspinatus and infraspinatus muscles. Wertheim and Rovenstein were first to describe the landmark-based blockade of the suprascapular nerve to treat severe chronic shoulder pain in 1941. Nerve stimulation and ultrasound guidance help identify and block the suprascapular nerve more reliably.1 This technique has developed as an analgesic alternative to the intersaclene brachial plexus block for shoulder surgery. Its advantage is an absence of ipsilateral hemi-diaphragmatic paralysis that is a frequent side effect of the intersaclene brachial plexus block.2 Suprascapular nerve block was not used in Leskovac General Hospital, Serbia (LGH) until August 2022 when we provided this blockade to facilitate the reduction of an anterior shoulder dislocation.

Case report: A 67-year-old male with a 4-day-old anterior shoulder dislocation was admitted to LGH. His previous medical history included hypertension, coronary artery disease, overweight (BMI 29.2 kg/m2), chronic obstructive pulmonary disease, and diabetes mellitus type 2.

The first choice of treatment is a non-invasive trial of reduction. Reduction can frequently be obtained without analgesia in patients with anterior dislocations (particularly those presenting within 24 hours), recurrent, or relatively non-traumatic. Otherwise, procedural sedation and analgesia are administered to relieve pain and to reduce spasm in the muscles of the rotator cuff. If reposition cannot be achieved, surgical treatment would be required (up to 10%). Old dislocations are more prone to require surgical treatment.

We had to provide short-acting shoulder muscle relaxation that could be easily transformed to anesthesia having in mind all patient's comorbidities. The suprascapular nerve block using 1.0 % lidocaine would be an excellent choice for a non-invasive reduction of a shoulder dislocation since, if needed, block would provide satisfying analgesia on spontaneous breathing that could be complemented with sevoflurane in oxygen/air mixture via laryngeal mask.

Patient received 50 mcg of fentanyl and 2.0 mg of midazolam intravenously and ipsilateral ultrasound-guided suprascapular nerve block was performed using 15 ml of 1.0% lidocaine at holding area. After 20 min patient was transferred to the operating room and successful non-invasive shoulder reduction was done. The shoulder was immobilized. The patient was discharged home after 24 hours.

Conclusion: Suprascapular nerve block could be an effective technique for shoulder dislocation reduction, particularly for elderly patients who are obese, or have cardiopulmonary comorbidities.

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CR.2.BISOP.2023

Postopertive pain control strategy in bilateral total knee arthroplasty - case report

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Introduction: Total knee arthroplasty (TKA) is commonly performed in patients with osteoarthritis to relieve joint pain, increase mobility, and improve quality of life (1). TKA is painful procedure. Adequate postoperative analgesia is mandatory not only to treatment reduce pain, risk of thromboembolism, length of hospital stay, but also to improve patient satisfaction, rehabilitation and overall outcomes (2).

Case report: A 66-year-old woman scheduled for elective simultaneous bilateral TKA, due to end-stage osteoarthritis with marked varus deformities and WOMAC score 56. Standard thromboembolic and antibiotic prophylaxis was started with intravenous (IV) tranexamic acid (10mg/kg) immediately before the procedure. Patient was premedicated by Midazolam 5mg intramuscularly. An epidural catheter was placed at the L3-L4 level and a mixture of 20ml of 0.25% levobupivacaine, 4ml of 2% lidocaine and fentanyl 25μg was given preoperatively. General anesthesia was induced by intravenous administration of fentanyl 3 μg/kg, propofol 2 mg/kg and rocuronium 0.8 mg/kg. Patient received 0.6–1.5 vol% of sevoflurane with fentanyl bolus to maintenance of anesthesia. Surgery was performed under pneumatic tourniquet using medial parapatellar approach first on right leg, then on the left with same size implant components. For postoperative analgesia, 10 ml of 0.25% levobupivacaine was applied to the epidural catheter and intravenous nonsteroidal anti-inflammatory drugs, ketorolac 30 mg. Postoperatively, patient was observed in Intensive Care Unit for forty-eight hours. Pain score was measured by numeric rating score (NRS) and it was 8. Postoperative pain management techniques included intravenously administered NSAIDs (ketorolac 30 mg IV every 8 hours), acetaminophen (1 g IV every 6 hours), opioids (morphine 10 mg intramuscularly), regional analgesia (10 ml of 0.25% levobupivacaine). On the second postoperative day, the program of early rehabilitation with verticalization was started. On the third postoperative day, the epidural catheter was removed and patient was transferred to the ward. Due to NRS was 5, pain therapy was continued with intravenous patient-controlled analgesia, provided by an elastomeric pump, along with oral opioid tapentadol 50 mg every 12 hours. The pump contained acetaminophen 1g, tramadol 100mg, ketorolac 60mg and ondasetron 4mg, total volume 100ml. The pump speed was set at 4ml/h, which provided analgesia for 25 hours. From the seventh postoperative day, when NRS was 3, pain was

controlled with acetaminophen 1 g intravenously every 12 hours. On the fourteenth day after the surgery, the sutures were removed, wounds were bandaged, and the patient was discharged for home. WOMAC score at discharge was 21.

Conclusion: A presented of a multimodal analgesia strategy, our patient had a moderate degree of postoperative pain, which enable early mobilisation and adequate physical therapy with greater satisfaction.

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CR.3.BISOP.2023

Intravenous regional anesthesia (IVRA) in children: A case report

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Introduction: Intravenous regional anesthesia (IVRA), commonly known as "Bier's block", is a safe and effective form of regional anesthesia. IVRA was first developed by August Bier in 1908 for anesthesia of the hand and forearm. It is a regional anesthetic technique that is easy to perform, with success rates up to 98%. IVRA can be the choice of anesthesia for short procedures (less than hour), because of rapid onset of anesthesia, easy administration and cheaper cost with special considerations on its side effects and complications. IVRA has been limited by tourniquet pain and its inability to provide postoperative analgesia.

Case report: We present a case of 17-year-old male who was operated for proximal phalange fracture digitus minimus left hand after a fall injury under Bier's Block or IVRA technique. Because the patient has an acute respiratory infection, we decided to perform a method of regional anesthesia. Electrocardiogram, saturation, and non-invasive blood pressure monitoring of the patient were performed in the supine position. Two intravenous cannulas were placed on the dorsum of both extremities. For sedation was administrated Midazolam 5mg i.v. A doble-cuff pneumatic tourniquet was placed on upper arm of the extremity to be operated on. The cuff was inflated to 250 mmHg after the extremity was properly wrapped using the Esmarch bandage and elevated for two minutes. A local anesthetic mixture containing 10 mL of 2% lidocaine and 30 mL of 0.9% NaCl was administered. Pain was monitored using the Visual Analogue Scale (VAS). The VAS score was 2 at the beginning. The patient did not feel pain in the surgical incision area. Tourniquet discomfort appeared 15 minutes after start, and we resolved it with small dose of remifentanil infusion. At the end of the procedure the patient got 2,5g of metamizole sodium. The patient was taken to recovery room in the postoperative period and observed for one hour. He was hemodynamically stable and did not show any toxic symptoms. His postoperative VAS scores were less than 2, and rescue analgesics were not required.

Conclusion: Intravenous regional anesthesia is a safe, effective, and preferable alternative to general anesthesia in the appropriate pediatric patient and makes recommendations in method of practice to improve its safety.

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CR.4.BISOP.2023

Peripheral nerve catheter for repeated surgical debridement in high risk patients

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Introduction: A peripheral nerve catheter (PNC) is a type of catheter that is placed near a nerve or the group of nerves to provide continuous pain relief, or regional anesthesia during various types of surgeries. The most common use of the procedure is to help control postoperative pain, although catheter nerve blocks effectively treat all types of pain. PNC have several benefits that include improved pain control, decreased use of opioids, and other analgesics, and provide earlier mobilization and recovery. We report a case of PNC placement for repeated surgical wound debridement in patient with congestive heart failure and recent covid pneumonia.

Case report: A 78-year-old female patient was admitted to our hospital with big open wound bellow the knee, size of 25x10cm. She fell and hurt her leg 3 weeks before admission. During that period, she had wound dressing in her home for 10 days, and after that she was hospitalized because of covid respiratory infection. The patient had a history of cerebrovascular insult and mitral valve replacement. She also had congestive heart failure, hypertension, atrial fibrillation and chronic renal failure. On the admission patient was examined by cardiologist, she had signs of heart decompensation, proBNP was 15000, had anemia (Hgb was 81g/L), and because of atrial fibrillation and artificial valve received therapeutic dose of low molecular weight heparin. Patient received blood transfusion, diuretics, broad spectrum antibiotics, bronchodilatators and oxygen therapy via nasal cannula 4L/min. On the day of admission surgeon performed wound debridement in analgosedation with midazolam, fentanyl and propofol, and after the procedure she received paracetamol 500mg q.i.d and diclofenac b.i.d. Patient reported intensive pain, VAS scale 6/10, and tapentadol 50mg was given as a rescue medicine.

For further anesthesia and analgesia plan, opioid consumption had to be minimized because of respiratory compromise. Administration of central neuraxial anesthesia was ruled out because of high risk for hemodynamic instability and epidural hematoma. We chose to perform ultrasound (US) guided continuous PNB (cPNB) of sciatic nerve in popliteal fossa for anesthesia during surgical interventions, and analgesia therapy after that. Insertion of catheter (Braun Contiplex S) was performed under sterile conditions, using 9MHz high-frequency linear US transducer to locate sciatic

nerve right above its division into the tibial and common fibular nerves. Perineural catheter was passed through the needle, place of insertion was covered with transparent drapes. Bolus of 10ml 0,25% Levobupivacaine was injected under US visualization, and after that infusion pump was connected to the perineural catheter with Levobupivacaine solution 0,125% 4-5ml/h. Catheter was left in place for 72 hours, and during that period 2 times we injected 10ml 0,5% Levobupivacain before surgical wound debridement. Analgesia was supplemented with intravenous paracetamol 1 g q.i.d, and metamizole 2.5 g b.i.d. Patient VAS score didn't exceed 3/10, and there was no need for opioid analgesics.

Conclusion: Ultrasound guided cPNB is an excellent anesthetic technique for repeated surgical debridements and effective strategy for pain relief in high risk patients.

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CR.5.BISOP.2023

Pain management during parathyreoidectomy – can CPB helps us?

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Introduction: Primary hyperparathyroidism (HPT) is the 3rd most common endocrine disorder, especially in elderly women (1). In more than 80% of cases primary HPT presents as a solitary adenoma (2). Surgery is the only available curative treatment. Standard anesthetic practice is general endotracheal anesthesia. Ultrasound guided Cervical Plexus Block is a technique that has been applied in parathyroid surgery.

Case reports: Female, 46 years old, obese. Chronic diseases: prolactinoma, Hashimoto's thyroiditis, hypertension, diabetes mellitus, previous deep vein thrombosis.

Female, 73 years old. Chronic diseases: hypertension, osteoporosis. Varicose veins. Systolic murmur.

Female, 62 years old. Previous operations: left shoulder due to leiomyosarcoma, reoperation followed by radiotherapy; metastasectomy in the: right lung, left lung, bowel, scapula and sigmoid colon. Chronic diseases: haemorrhoids, kidney calculus.

Female, 68 years old. Previous operations: lithotripsy x 2, tumor of the oral cavity, right breast (injury), left eye (glaucoma), uterine prolapse. Chronic diseases: hypertension, nephrolithiasis, osteoporosis, glaucoma. Varicose veins.

Female, 71 years old. Previous operations: intestine tumor, cholecystectomy, left patella operation (injury), lumbar spine operation 2 times (benign tumor). Chronic diseases: neuroendocrine tumour of intestine, hypertension, asthma, nephrolithiasis, chronic renal failure gr II. Systolic ejection murmur.

Applied technique: The procedure was explained to the patients in detail and written and oral consent was obtained. After identifying the posterior edge of the sternocleidomastoid muscle and skin disinfection, the transducer was placed on the lateral neck, overlying the SCM at the level of its midpoint. Using ultrasound, we identify internal jugular vein, carotid artery and levator scapulae muscle. Using an in-plane approach, needle was inserted until the tip is visualized within the facial plane just deep to the SCM and superficial to the prevertebral fascia overlying the LSM and scalene muscles. After negative pressure aspiration, 2 ml local anesthetic was injected to confirm

appropriate position. A total of 16 ml of local anesthetic was applied, 8 ml for each side. During the operation, the patients were slightly sedated, they did not require additional analgesics, and no side effects of local anesthetics were registered.

The average duration of the operation was 30 minutes. In the postoperative period, all patients were hemodynamically stable with good pain control.

Conclusion: Ultrasound guided regional anesthesia in neck surgery is rapidly expanding and the main advantages of ultrasound technique include a direct view of nerves; local anesthetic (LA) spreading during injection; reduced volume of LA; blood vessels and other structures injury is significantly reduced. It is especially useful in patients with serious comorbidities, in which possible perioperative consequences and risks of general anesthesia can be avoided. It also reduces cost of operation. Based on our first results of the presented cases, we can say that superficial CPB is a safe and simple procedure in order to provide perioperative analgesia in parathyroid surgery. Miccoli et al found similar results in their study (3) where minimally invasive video-assisted parathyroidectomy (MIVAP) conducted under regional anesthesia (RA) compared with the results of or general anesthesia (GA).

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CR.6.BISOP.2023

Everything is easy if We know the Cause

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Introduction: Recreational opioid use is a major health and social problem that affects about 6 million people around the world. Taking this into consideration, it is inevitable that we, as anesthesiologists, will encounter both addicted patients and those who are already on substitution therapy [1]. Methadone and buprenophine are widely used subtitution therapies in opioid addicted regarding its pharmacokinetics properties and receptor selectivity. It is important to emphasize that substitution doses are often insufficient to relieve acute postoperative pain, and it is necessary to combine methadone with other drugs. Despite certain guidelines, there is still no standardized protocol for perioperative acute pain management of opioid addicted patients [2].

Case Report: A 57-year-old male admitted to hospital for seceduled surgical treatment of right kidney carcinoma. He suffered from intense pain in the right half of his abdomen that persisted for 20 days before hospital admission. The former medical records revealded a cerebrovascular insult within 5 months before admission followed with motor function lost of left arm, hypertension, hyperlipidemia, hepatomegaly, splenomegaly, Schwannoma of the right vestibular nerve, radiculopathy of a lumbar region, as well as chronic Hepatitis C infection. The patient denided opioid use anytime in life. After regular preoperative assessment and premedication with atropine and midazolam, it was planned to performe surgery under general anesthesia with intubation. Anesthesia induction was with midazolam, fentanyl, propofol, rocuronium followed with O2/Air/sevoflurane inhalation, and intravenous boluses of fentanyl and rocuronium as needed. Appropriate hemodynamic response to administration of 2.6mcg/kg of fentanyl boluses in 20 minutes intervals during the whole procedure was missing. No complicationes occured during intraoperative procedures. Postoperative analgesia was with continuous infusion of tramadol/ metamizole combination in maximal doses followed with rescue morphine boluses. Just after anesthesia recovery, the patient reported moderate pain intensity. Despite standardized analgesia regimen, the patient permanently reported intense pain of lumbotomy wound, became hypertensive and bradycardic, with no sweating. The patient was not relieved the pain despite additional morphine boluses. Finally, at the end of the day, the patient had confessed opioid consumption and current methadone therapy for years. He reported the last medicine intake two days ago. Also,

he told that he did not bring methadone with himself in hospital because he thought that he would not be operated otherwise. The anesthesiologist on duty had consultation with psychiatrist from the Dependency disease institution who prescribed substitution with methadone 100mg ONCE and opioid restriction. Thirty minutes after the patient received methadone 50mg, the pain disapeared. In addition, the patient kept receiving the analgesic combination of methadone and non-opioids untill ICU discharge. The recovery after surgery was according to plan and on the 6th postoperative day, the patient was discharged from hospital.

Conclusion: Stigmatization and the mistaken belief that opioid addiction is a contraindication for surgery significantly complicate the postoperative acute pain treatment. In order to adequate treatment of postoperative pain, the coordination of hospital team with psychiatrist and the patient is mandatory.

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CR.7.BISOP.2023

Faith, hope, and love. Is there a fourth one?

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Introduction: Medication non-adherence continues to be a major challenge facing the healthcare system. Non-adherence to prescribed pain medication is very common and may result in sub-optimal treatment outcome.1 A relationship between the physician and the patient, based on accessibility, empathic understanding, and constructive communication could play a key role in analgesic outcome. This is particularly relevant in treatment of chronic non-cancer pain which is characterized by high inter-individual variability in therapeutic response.2

Case report: A 65-year-old male patient presented with dull plantar pain, more severe in the left (NRS8) than in the right foot (NRS6). He reported that the first symptoms had appeared two years ago with severe lower back pain that radiated down both legs followed by burning pain in lower legs. Initial CT scan revealed protrusion of L4-L5 and L5-S1 intervertebral discs with a compressive effect on both L5 and S1 roots. EMNG showed symmetrical moderate sensorimotor polyneuropathy combined with mild to moderate chronic bilateral neurogenic lesions of L5 roots. Foot X-ray visualized advanced degenerative changes. Initial corticosteroid pulse therapy led to significant resolution of lower back pain symptomatology. Pharmacological treatment for neuropathic pain (Gabapentin 900mg/day) combined with physical therapy was effective against residual symptoms (NRS3). At the recall appointment patient complained of tiredness, therefore he had intentionally reduced the dose of medication. He reported progression of pain symptoms. As a following treatment, the combination of Gabapentin (400mg once a day), Amitriptyline (25mg twice a day) and polyvitaminic therapy was prescribed. The patient further reported side effects from the medications, such as skin rash, tiredness and loss of libido. On the next appointment Tapentadol 50mg twice a day was prescribed. Although he had significant reduction of symptoms, he stopped taking medications because he reported impaired ability to write, since he was a poet. During the next two years the therapy was adapted several times. All the time he was suspicious about diagnosis, hence he underwent multiple examinations. Some of these were: tests for B. burgdorferi, T. pallidum, serum levels of homocysteine and tumor markers, immunological tests, immunofixation and electrophoresis of serum protein. All the tests were found to be within normal ranges. The patient tried variety of different

therapeutic modalities such as acupuncture and chiropractic, but with limited effect. The current medication therapy includes Gabapentin combined with Tapentadol (50mg a day), NSAID and spasmolytic. The patient kept being suspicious about the efficacy and safety of the prescribed drugs, despite the doctor's advice to adhere to the treatment.

Conclusion: Lumbosacral polyradiculopathy, polyneuropathy of undetermined cause and arthropathy all contributed to the chronic pain in this case. Due to the complex nature of chronic pain, treatment needs an individualized approach. Although adequate treatment focuses on several aspects, such as physical rehabilitation and psychological strategies, medication often remains a cornerstone of chronic pain treatment. Both adherence to the therapy and individualized multimodal approach may have the key role in successful treatment. Medical non-adherence in a chronic non-malignant pain population certainly requires more attention.

Key words: treatment adherence, neuropathic pain, medication non-adherence

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CR.8.BISOP.2023

THE BEST CASE REPORT-THE THIRD PLACE

Are you ready to take the risk for the benefit?

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Introduction: Marshall-Smith syndrome (MRSHSS) is a rare genetic disorder caused by mutations in the NFIX (Nuclear Factor I X; 19p13.13) gene that causes intellectual disability, airway, breathing, and feeding difficulties, unusual facial features, advanced bone maturation, psychomotor, and neurological issues in patients. Cardiovascular and endocrine abnormalities, blue sclerae, hirsutism, progressive kyphoscoliosis, short stature, and osteopenia associated with fractures are all possible symptoms and signs. These patients have a poor prognosis; they commonly die in infancy due to respiratory compromise (upper airway obstruction, respiratory distress due to glossoptosis, laryngomalacia, and choanal stenosis). There are fewer than sixty cases described in the literature, and fewer than fifty children worldwide have this syndrome. We report the first case of a successful operation performed under regional anesthesia with ultrasound-guided peripheral blocks and dexmedetomidine analgosedation in a patient with MRSHSS syndrome.

Case report: An 11-year-old girl was admitted to the clinic for orthopedic gena valgus l.dex surgery. The mother reported that her child had swollen tonsils, trouble swallowing, recurrent respiratory infections, and severe sleep apnea. She occasionally used non-invasive respiratory support while sleeping at home. An otolaryngologist's preoperative examination revealed swollen tonsils and adenoids obstructing the airway and an enlarged epiglottis and laryngomalacia. The patient was premedicated with atropine and dormicum, and non-invasive monitoring we used. We started dexmedetomidine after a single dosage of fentanyl (1 μg/kg); however, the patient suffered apneas in the supine position. We put on a laryngeal mask and performed proper breathing. Then, we injected three peripheral nerve blocks using ultrasound guidance: PENG, n. popliteus, and n. saphenous, with 20 ml of 0.25% levobupivacaine and 10 ml of 1.3% xylocaine.

Conclusion: Due to the limited experience and lack of information in the literature, as well as the absence of a guide to provide safe anesthesia, developing an

anesthesiological strategy for patients with exceedingly rare syndromes is challenging. Complications during induction of anesthesia have been described in the literature as a result of a difficult or impossible vision of the larynx via direct laryngoscopy, as well as cases of upper and lower airway obstruction in which an emergency tracheostomy was required. Peripheral nerve blocks provide adequate postoperative analgesia, minimize opioid use, and promote early postoperative mobility and recovery. Regional anesthetic procedures, such as ultrasound-guided peripheral nerve blocks, are becoming increasingly prevalent, and we strongly recommend them for patients with a potentially difficult airway. In some cases, the risk should be taken for the benefit.

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THE BEST CASE REPORT-THE SECOND PLACE

Emergency abdominal surgery in a child with varicella zoster virus—quick anesthesia decision

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Introduction: With a median age of occurrence between 10 and 11 years, appendicitis is a prevalent illness in children and adolescents that frequently necessitates immediate surgical intervention. The varicella-zoster virus (VZV), which causes varicella (chickenpox), can be fatal to children, adults, and immunocompromised people. We present the first appendectomy case in a patient with varicella zoster virus who underwent regional anesthesia as the sole technique in our clinical experience.

Case report: A 30-kg, 11-year-old boy was admitted to our clinic with appendicitis, which required immediate surgical intervention. The child was diagnosed with chicken pox ten days ago. He was in poor general condition, including dehydration, drowsiness, a high temperature, and bilateral pneumonia. The parents reveal that their second child died from cytomegalovirus (CMV) two years ago. Following a period of accelerated rehydration, we entered the operating room. Due to the patient's general condition and bilateral pneumonia in an advanced stage, we decided on a caudal and transversus abdominis plane (TAP) block and continuous sedation with propofol with spontaneous breathing avoid mechanical ventilation. We used 25 ml of 0,25% levobupivacaine for caudal block and 10 ml of 0,25% xylocaine for TAP block. During the operation, we used non-invasive monitoring, and the patient was stable throughout the procedure. Postoperatively, multimodal analgesia was administered, and the patient was discharged home after three days in good condition.

Conclusion: The use of regional anesthesia in pediatric patients with viral infections is still controversial. We successfully performed ultrasound-guided TAP and caudal block with confirmed appendicitis, reducing pain and the need for further opioid use.

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Painful skin changes of unusual origin

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Introduction: Neuroendocrine tumors (NETs) are rare, slow-growing neoplasms characterized by the ability to secrete hormones, neurotransmitters, neuromodulators, and neuropeptides[2]. The most common primary sites are the gastrointestinal tract (62%) and the lung (23.1%)[2]. The most common sites of tumor dissemination are the liver, lungs, lymph nodes1. Cutaneous manifestations of neuroendocrine carcinoma are rare, with few reported cases in the literature[1].

Case Report: A 58-year-old patient comes for an examination in the outpatient clinic for pain, for the first time, because of the pain he feels in the area of skin changes in several locations. Upon inspection of the medical history, it was learned that the papillomatous changes of the right aryepiglottic fold had been removed two years earlier. The pathohistological findings corresponded to infiltrating squamous cell carcinoma. One year later laryngomicroscopy revealed a cystic change on the right arytenoid. The biopsy indicated a poorly differentiated neuroendocrine carcinoma. The patient underwent a supraglottic laryngectomy. Histopathological findings confirm poorly differentiated neuroendocrine carcinoma. Two years after the reoperation, the patient noticed that hard, painful, and erythematous changes up to 2cm in diameter appeared on the skin of his left hand as well as in the right lumbar area and upper back. A biopsy of the changes verified metastasis of a neuroendocrine laryngeal tumor. During the examination, the patient complains of persistent, pain in the area of skin changes with stabbing characteristics, present even during the night. The pain intensifies upon movement and in certain positions. He is often awakened by pain. The left arm is in a forced position (of reduced functionality), flexed at the elbow joint. He reports pain intensity during the day, 5/10, based on the NRS. The general medicine practitioner prescribed ibuprofen 600 mg BID, which can reduce the pain intensity by about 30%, so the pain medicine specialist indicated the same therapy. On the second visit to the outpatient clinic for pain, the patient reported that the skin changes were more painful and that the prescribed medicine reduced the intensity of the pain by 2 hours. Biopsied skin lesions are less painful than newly formed lesions. The patient reports that his pain intensity is now 8/10 based on the NRS. In addition to the intensification of the pain, a feeling of

burning and stinging appears in the area of skin changes. Targinact 10/5 mg BID was prescribed, and a follow-up examination was scheduled in two weeks. After two weeks, the patient reports a functional disability reduction of the left hand and less pain in the area of cutaneous metastases, better sleep, and better mood.

Conclusion: Cutaneous metastases are encountered in 0.7-9% of all tumor patients, and as such, the skin is an uncommon site of metastatic disease compared to other organs 3. Even though it is a rare entity, skin changes should arouse suspicion of secondary deposits, and diagnostics should be pointed in that direction, even though the site of the primary tumor often remains undetected2. Also, the size of the changes and distribution is not correlated with the intensity of the pain or the functional disorder.

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