ISSN 2545-4366
www.e-mja.com

MJA

Macedonian Journal of Anaesthesia

A Journal on Anaesthesiology, Resuscitation, Analgesia and Critical Care

Number 1. April, 2017

Journal of the Macedonian Society of Anaesthesiologists
and Macedonian Society of Critical Care Medicine

Publisher:
Department of Anaesthesia and Reanimation, Faculty of Medicine,
"Ss. Cyril and Methodius" University, Skopje, Macedonia

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Proofreading Daniela Nacevska Stojcevska

Printed by ASKOLOR

CONTENT

ANAESTHESIA IN THE NEW ERA OF PERSONALIZED / PRECISION MEDICINE

Recently, we have seen a change in the understanding of the concept of practicing clinical medicine. It seems that the time of characterizing patients with similar signs and symptoms in groups and subgroups, in order to manage their treatment and ignoring heterogeneity in terms of their age, gender and comorbid conditions, is slowly passing by. Patients with similar symptoms may have different illnesses, with different causes; and similarly, medical interventions may work well in some patients with a disease, but not in other ones with apparently same disease. If we think of our patients as individuals and not as a disease, we will have greater success in their treatment avoiding harm and increasing benefit.

We have to take into consideration that each patient has his unique genetic profile. The development of the molecular biology, as a cornerstone of determination genetic variability in patients' responses to huge number of treatments, has crucial role in this setting. The path to personalized medicine has been opened focusing on the single individual.

Researchers have discovered hundreds of genes that harbor variations contributing to human illness and have begun to target the molecular causes of some diseases. In addition, they are developing and using diagnostic tests based on genetics or other molecular mechanisms to predict better the patients' responses to targeted therapy (1).

Genomic medicine, which refers to the use of information from genomes and their derivatives (RNA, proteins, and metabolites) in order to guide medical decision making is a key component of personalized medicine (2). Thus, personalized medicine became a rapidly advancing field of health care that is informed by each person's unique clinical, genetic, genomic, and environmental information.

If it is accepted that in critical care the success of personalized medicine depends on having accurate diagnostic tests, that identify patients who can benefit from targeted therapies and can predict outcomes, then what is the situation with the anaesthesia? In anaesthesia the word "precision medicine" is more applicable, as here the focus is on identifying which approaches will be effective for which patients, based on genetic, environmental and lifestyle factors. Therefore preferred term in anesthesia is "precision medicine" instead of "personalized medicine".

It is not too much to say that the concept of personalized anaesthesia is not quite new. In the history of anaesthesia there are few examples where pharmacogenomic has implications for anaesthesia. For example, prolonged apnea after suxamethonium due to the inherited deficiency of pseudocholinestrase was the base of huge number of researches, such as the research that showed that low pseudocholinesterase activity might be risk factor for succinylcholine induced hyperkalemia (3), or the appearance of malignant hyperthermia due to gene mutations.

Furthermore, we can look in the theory of molecular anaesthesia. Because there are still controversies regarding this theory (4, 5), to confirm this concept, the invention of link between molecular anaesthesia and novel cellular and molecular mechanisms is very important.

The advantage of anaesthesia lays, beside on a rapid development of technology, on these new researches on possible interactions of the newly discovered molecules and interaction mechanisms of anaesthetic drugs with organ systems. An inseparable part of these advances is a targeted postoperative treatment. New approaches using biology systems will allow personalized and precise perioperative and postoperative treatment of our patients. The three parts of this link will enable patients to be treated and monitored more precisely and effectively and in ways that better meet their individual needs. Randomized clinical trials are needed to reach this goal. One of the reasons behind the lack of effective new therapies relates to problems in performing randomized clinical trials in the very heterogeneous patient populations. Performing randomized controlled trials in such mixed groups of patients will almost inevitably result in an inconclusive result as some patients in each group will respond to the therapy and others will not (6). Therefore, true precision medicine, in which medical treatments will be customized to an individual's molecular and genetic make-up, can be reached by our ability to identify subgroups within subgroups that will increase until we reach the point at which each subgroup consists of just one patient (7, 8). So, we expect to see more efficient clinical trials based on more thorough understanding of the genetic basis of disease. We also anticipate that some previously failed medications will be recognized as safe and effective and will be approved for subgroups of patients with specific genetic markers (1).

Personalised medicine in critical care has made significant progress with gene-based therapies. Novel approach like genetic make-up or genetic profile of an individual is a big challenge for precise medicine in anaesthesia. We are ready to hear what authors have to say in this field.

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 ISSN 2545-4366 | UDC : 616-001-089.5-032:611.82

OUR EXPERIENCES OF LOW DOSAGE SPINAL ANESTHESIA IN EMERGENCY TRAUMA PATIENTS

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ABSTRACT

Background: Nowadays, spinal anesthesia (SA) for trauma and orthopedics low limb surgery becomes a standard procedure because of its simplicity and fewer complications versus general anesthesia (GA). The development of peroperative hypotension and bradicardia during SA are common side effects, and they can be found in less than 30% of the cases (mostly in emergent cases and geriatric population) (1). Low dose SA with its quick onset and few complications seem to be an alternative for those patients. There are only few data about its use in emergent trauma patients (2, 3, 4).

The aim of the study was to compare the effects of standard spinal anesthesia (SSA) vs. LDSA in emergency trauma cases and to analyze its efficiency, peroperative clinical manifestation and side effects.

Design: A prospective randomized study.

Settings: University Clinic of Trauma & Orthopedics, Anesthesia, Reanimation, & Intensive Care and Emergency Medicine, Clinical Center "Mather Theresa", Skopje, R. Macedonia.

Patients and methods: One hundred healthy patients (ASA I/II) accepted as emergency cases undergoing low limb surgery (n=100) were randomly divided into two groups: anesthetized with standard spinal bupivacaine anesthesia (SSA) and low dose spinal anesthesia (LDSA): SSA (n=50) and LDSA (n=50). All patients for low dose spinal anesthesia were administered single dose of bupivacaine (10-12 mg according BMI) with 20 μg Fentanyl. The patients' hemodynamic (blood pressure, heart rate, ECG), respiratory parameters (respiratory rate, oxygen saturation - SaO_2) and resuscitation interventions (ephedrine/fluids requirements) were measured six times: before spinal puncture (t0) and during anesthesia (t1–t5). Analgesics and low dose spinal side effects in emergent trauma patients were analyzed.

Results: The basic hemodynamic data statistically were without significant differences ($p > 0.05$). A statistically significant hypotension (>30%) was noted in two patients receiving SSA ($p < 0.01$), but not in patients with LDSA. The episodes of hypotension in patients anaesthetized with SSA were found in 20% of the cases and they were short, < 2 minutes, but none in patients

with LDSA. An unsatisfactory block was developed in 4% of the patients anaesthetized with LDSA. LDSA, compared to SSA, leads to more stable hemodynamics of the patients, without compromising the respiratory parameters and less resuscitation interventions ($p<0.01$).

Conclusion: The use of low dosage spinal anesthesia in emergency trauma patients has many advantages, such as stable hemodynamic and respiration parameters and better resuscitation performance. Standard spinal anesthesia with bupivacaine and low dosage spinal anesthesia can be used safely for emergent surgery of low limbs in healthy patients.

Key words: emergency surgery of low limbs**,** low dose spinal anesthesia, hypotension, resuscitation with ephedrine and fluids, spinal anesthesia.

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Introduction

The importance of regional anesthesia for managing trauma patients has been demonstrated in many challenging situations and environments as natural disasters and military conflicts. Neuraxial spinal block in emergency trauma patients, undergoing surgical bone fixation or external fixation, is a challenging anesthesia approach with several advantages. The usage of SA reduces the peroperative bleeding, and the undesirable postoperative complications (1). Spinal anesthesia is frequently accompanied by hypotension (>20-30 % fall from baseline) (2). Without a pharmacological prophylaxis (excessive fluid load, low dose spinal anesthesia or vazopressors), the incidence of hypotension can exceed up to 50-60% (3).

It was shown that LDSA used in trauma patients with a single fracture of the low limbs can produce a stable hemodynamic and is suitable, especially when hypovolemia has been corrected before the establishing of the spinal block (4). The problem appears with the emergency trauma patients that are in shock and should be immediately operated.

The use of crystalloid or colloid for treatment of peroperative hypotension during spinal anesthesia does not prevent the cardiovascular complications in emergency trauma patients. The use of vasopressors is an obligation. However, side effects such as hypotension, bradycardia, urinary retention, post spinal headache or neurological injuries are also common in standard spinal anesthesia (SSA). It is well known that the volume, dose of injected drug, speed of injection and the height of subarachnoid block could enhance those complications (5).

In 2008, it has been shown that lowering the dose of local anesthetic with supplementary analgesia (low dose spinal anesthesia -LDSA) is a safe method for surgery of low limbs of elderly trauma patients (6,9). This is based on spinal injection of small dose of local anesthetic, reduced to half, combined with small dose of opiod as an adjuvant. This combination of low dose of local anesthetics and opiod can reduce the side-effects without compromising the quality of analgesia (10).

The studies on LDSA for surgical procedures on healthy patients, American Society of Anesthesiologists (ASA) physical status I and II, undergoing emergency surgery of fractured bones in low limbs are relatively unexplored and few data exists about its use, which was an initial challenge to do this study.

Prospective randomized study was done with an aim to compare the effects of standard spinal anesthesia (SSA) vs. LDSA in emergency trauma cases and to analyze the efficiency, peroperative clinical manifestations and side effects.

We hypothesized that low-dose bupivacaine with intrathecal fentanyl may provide more beneficially effects on the quality of the spinal block in patients undergoing emergency single fracture repair.

Material and method

This randomized prospective trial was conducted at University Clinic of Trauma & Orthopedics, Anesthesia, Reanimation, & Intensive Care and Emergency Medicine, in tertiary medical centre "Mother Teresa" in Skopje, the Republic of Macedonia, in the period of two years (2013- 2015). Ethical approval for this study was provided by the Institutional Ethical Committee of the Clinic of Anesthesiology at Medical Faculty, Skopje, Macedonia.

The study included all healthy patients with fracture of low limbs for emergency fracture repair, who voluntarily collaborated in the study.

Patients with polytrauma (neurotrauma or back damaged) were excluded from the study, as well as the patients with morbidities, or development of circulatory disturbances during the preparation for anesthesia.

After obtaining written information consent from each patient, we enrolled the total of one hundred healthy patients ASA physical status I and II, undergoing emergent surgery of fractured bones of low limbs (n=100). According to the type of spinal anesthesia, they were randomly divided in two groups. Patients who received standard dose bupivacaine spinal anesthesia (SSA) were in group A(n=50) and those who received low dose bupivacaine spinal anesthesia (LDSA) were in group B(n=50).

An hour before the anesthesia, for all patients a routine pre-anesthetic check-up was done (physical examination of health condition, ASA evaluation and routine lab investigations).

All emergency patients with fractured bones, an hour prior to surgery received analgesia (NSAID) and light sedation with diazepam 5 mg. All enrolled patients fasted (no food and water) 6 hours prior the surgery. After the entrance in the preoperative area electrocardiography, non-invasive blood pressure (BP), heart rate (HR), respiratory rate (RR) and oxygen saturation (pSO2), started to be monitored and continued during the surgical procedure. Baseline Arterial Blood Pressure (BP) and Hearth Rate (HR) were measured and an intravenous line in cephalic vein was secured. Prior the procedure, baseline BP and HR were obtained (t0). The hemodynamic parameters were measured and documented five times at 2.5 or 5 minutes intervals from t1-t5.

A preload of IV infusion of 500 mL of lactated Ringer's solution was infused over a period of 20 minutes. During the surgical procedure, the amount of the infused lactated Ringer was maintained according the BP.

Spinal anesthesia was administered in lateral laid position using 26-27 G Braun Pencam needle. SSA (Group A) received an isobaric solution of 17 mg 0.5% bupivacaine in 3.2 ml at the level L3-4 and patients were made supine immediately. Patients for low dose spinal anesthesia (Group B) were administered intrathecally (L3-4), a single dose of isobaric 0.5% bupivacaine (10 - 12 mg) with 20 μg fentanyl, and saline up to 3.2 ml.

The upper sensory level was checked at 5 minutes, using loss of cold sensation to ice.

A protocol list for all enrolled patients (total n=100) was maintained. A blind researcher noted five times the patients' blood pressure, heart rate, respiratory rate, ECG, pSO2, ephedrine/fluids requirements and side effects. They were measured before spinal puncture (t0), during anesthesia: t1–t2, each 5 minutes after the spinal puncture, t3 – after 15 minutes, t4 - after 25 minutes, t5 -after 40 minutes and t6- at the end of the surgery. Analysis of the effects and side effects of spinal and low dose spinal anesthesia on patients' hemodynamic and level of analgesia were done.

Hypotension was defined as 20-30% decrease in Systolic Blood Pressure (SBP) from the baseline value or absolute value lower to 95 mm Hg, and it was treated with ephedrine i.v. (5 mg every 2 minutes if needed); Episodes of bradicardia (HR<50 min) were solved with 0,5 mg atropine or more if required.

Statistics: Data were statistically analyzed. Mean and standard deviation of the variables were obtained, the differences of the variables and data were compared to the test of Differences ($p<0.05$ was statistical significant difference). The Mann-Whitney U test was used to compare the grouped parameters.

Results

Demographic data of all participants in this trial are presented in Table 1. Demographic data are presented as mean ± standard deviation (M±SD) for all variables and the differences were obtained.

Table 1. *Demographic data of the patients undergoing the study groups (M±SD).*

Parameters	Group A (n=50) (SSA)	Group B (n=50) (LDSA)	p
Gender (M/F)	43/7	26/24	/
Age (years)	45.9±7.3	47.4±14.4	0.8396
Height (cm)	176.1±9.8	171.01±7.0	0.2153
Weight (kg)	89.3±20.3	71.07±5.4	0.0770
Type of surgery	Fixation of the low limb fracture	Fixation of the low limb fracture	

**p<0.05 significant difference*

In demographic data no differences were observed between the groups A and B ($p>0.05$). There was difference in gender between Groups A and B, the majority of the patients were male (69 vs. 31).

In the study, we evaluated and compared the received 5 times data with the baseline values, and an inter group evaluation (spinal vs. low dose spinal anesthesia).

Because the Systolic Blood pressure is more precise indication for hypotension, Table 2 presents the obtained results of the non - invasive measurement of SBP and the variation in 6 times.

Table 2 *Systolic blood pressure in the study groups (M±SD).*

Groups Time	Group A (n=50) (SSA)	Group B (n=50) (LDSA)	p
t0	138.12±15.46	138.10±22.8	0.9755
t1	103.25±2797	119.7±17.2*	0.0006
t2	114.64±21.57	115.8±17.0	0.7582
t3	119.64±13.86	112.2±10.3*	0.0032
t4	112.72±17.8	112.5±11.3	0.9467
t5	118.7±17.00	116.1±13.6	0.4005

The differences of SBP in the groups (from the baseline values)

	A-SSA	*B-LDSA*
t0/t1	*p= 0.0000;*	*p=0.00*
t0/t2	*p= 0.0000;*	*p=0.0000*
t0/t3	*p= 0.0000;*	*p*

**p<0.05 significant difference*

There were observed episodes of hypotension in the Group of patients anesthetized with SSA (Group A). After 5th minute of the application of SSA, the Systolic Blood Pressure (SBP) dropped down more than 30 mm Hg from the baseline ($p<0.05$). The decrease of SBP in the LDSA group was less than 30 mm Hg from the baseline. The intergroup analysis shows an insignificant decrease of the SBP in the group of patients anesthetized with LDSA (Group B).

In the Table 3 are given the results of the measurements of the heart rate, respiratory rate and oxygen saturation.

Table 3. *The Heart and Respiratory rate and SpO_2 of the studied groups (M±SD).*

Time	HR/min			RR/min			SpO2 in %		
Groups	A (n=50)	B (n=50)	p	A (n=50)	B (n=50)	p	A (n=50)	B (n=50)	p
t 0	82.3±19.3	84.8±12.8	0.4471	14.3±1.3	14.2±3.4	0.8464	98.1±1.7	98.3±1.1	0.4866
t 1	92.02±12.92*	80.1±13.8	0.0000	13.5±2.2*	14.6±2.0	0.0103	99.2±1.3	99.7±0.4	0.0108
t 2	84.64±14.57*	77.5±10.1	0.0054	15.6± 3.5	14.9±2.2	0.2341	99.4±0.7	99.7±0.4	0.0099
t 3	77.66±11.7*	72.4±6.4	0.0064	12.0±2.5*	15.0±1.7	0.0000	99.8±0.3	99.5±0.8	0.0147
t 4	76.92±12.2*	70.4±8.0	0.0021	13.7±1.5	14.4±2.2	0.0660	99.8±0.3	99.5±0.5	0.0004
t 5	73.1±8.83	84.8±12.8	0.4855	13.3±1.4*	14.1±1.8	0.0148	99.8±0.3	99.5±0.8	0.0147

**p<0.05 significant difference*

It was observed that there is statistically significant difference in the heart rate in the groups of patients with SSA vs. those anaesthetized with LDSA ($p<0.05$). Episodes of bradycardia

(HR<50/min) were noted in two patients with SSA group. Increased HR in patients with SSA was found in 5, 20 and 40 minutes after puncture, but not in the LDSA group.

In all enrolled patients the measurement of the oxygen saturation of hemoglobin was in the normal ranges. There were insignificant differences between the groups (p>0.05).

The results obtained concerning the RR show differences in t2, t3, and t5 with SSA.

In Table 4, the results present the observed peroperative side-effects and resuscitation interventions in the patients undergoing spinal and low dose spinal anesthesia.

Table 4. *Developed side effects in the study groups.*

Groups	Hypotension >30 mmHg	Bradycardia <50/ min	Duration of hypotension in min	Nausea n / %	Postoperative headache	Insufficient Analgesia VAS 5 (10 min)
A	2 (4%)	2 (4%)	2.7±1.2	/	2 (4%)	2 (4%)
B	1 (2%)	1 (2%)	2.0*	/	/	/
p	0.0921	0.0921	0.0020	/	/	/

Table 5. *The doses of local anesthetics and resuscitation interventions in the groups.*

Groups	Bupivacaine 0,5% (mg)	Fentanyl µg	Atropin/mg	Ephedrine mg (M ± SD)	Infused RL in mL
A	15.8±0.7mg	/	1mg	10 ± 0	1430±412.43
B	11.3±0.9mg	0.02	1 mg	/	1540±135.64
p	/			0.0000	0.0763

**p< 0.05 significant difference*

Discussion

Spinal anesthesia produced efficient sensory and motor blockade with sufficient analgesia and muscle relaxation, enabling good conditions for surgery of lower abdomen, perineum and low limbs. The most important effect of spinal anesthesia is on the vegetative nervous system producing a sympathetic blockade with a partial parasympathetic block. The end result of this is a decreased sympathetic tone with an unopposed parasympathetic tone (11). This imbalance is the reason for many of the expected alterations of normal homeostasis noted with the administration of spinal anesthesia. The primary physiologic alterations are bradycardia, decreased preload and cardiac volume, whose combination produces a reduction of the arterial blood pressure and cardiac output. The doses of the local anesthetic used for SA are responsible for the severity of the developed impaired vital signs. The incidence of hypotension during SA is 33%, although the incidence of bradycardia is 13% with a decrease in cardiac contractility (12).

The classical doses of bupivacaine for standard spinal anesthesia ranges between 15-20 mg and are charged often for per-operative for development of hypotension and bradycardia.

In the last decades, it has been shown that the main factors responsible for the complications in spinal anesthesia are the baricity, volume and the dose of injected bupivacaine; but Sarvela

PJ and Vercaunter MP have shown that the baricity of the local anesthetic was not an important factor (18). In this study, we used plain isobaric 0.5% bupivacaine for SA and isobaric 0.5% bupivacaine with 20 μg fentanyl for LDSA (13).

In course to find out what is the appropriate dose of local anesthetic in SA, in March 2016, a group of authors published the study where the main finding was that the vertebral column length and abdominal girth were strongly correlated with the dosage of intrathecal plain bupivacaine for the loss of pinprick discrimination at T12 and T10 (14). This finding can justify the use of variable doses of bupivacaine in this study.

There are no set criteria on that how low the blood pressure should be allowed to decline after spinal anesthesia. The variations found in different publications can be explained by the different definitions of hypotension. In our study hypotension was defined as 20-30% decrease in Systolic Blood Pressure (SBP) from the baseline value or absolute value lower than 95 mm Hg. It has been found that spinal blockade has some protective effects during the decline in blood pressure. Total body oxygen consumption decreases in response to the extent of spinal blockade, providing a margin of safety (15).

In our study, a statistically significant hypotension (>30%) was noted in two patients receiving SSA ($p < 0.01$), but not in patients who received LDSA. Anticipation of these side effects of SSA is essential. Using an appropriate "dose" of local anesthetics is essential. The use of LDSA is one of the solutions. Opiods applied in subarachnoid space are binned to the opiods receptors in the spinal cord and have a synergistic effect with the local anesthetics. Opiods may be used as adjuvant to neuraxial anesthesia and to improve the quality of the block (20). In this study a small dose of fentanyl (20 μg) was used. Its pharmacokinetic and pharmacodynamic property of a lipophilic opiate with rapid uptake, faster onset and shorter duration of action, makes it a favorable alternative. It was found that the use of low-dose diluted anesthetic can shorten recovery time from spinal anesthesia (16). This minimizes the rostral migration of the drug to the respiratory center, avoiding delayed respiratory depression. In our previous study, we found that the low doses that are used in obstetric LDSA, are not affecting the newborn (9).

The findings of our study proved that LDSA enabled stable hemodynamic in emergent trauma patients. SBP in patients of SSA group dropped after 5 minutes for 30% and lasted 2.7±1.2 minutes, compared with LDSA were the drop of SBP was insignificant 10-15% and existed for 2.0±0 minutes ($p<0.05$) Table 6.

Heart rate may decrease during a high block due to blockade of the cardio accelerator fibers (T1-T4). Heart rate may also decline as a result of a decrease in SVR, decreased right atria filling, and decrease in the intrinsic chronotropic stretch receptor response (17-18). In this study bradycardia was defined as decrease in heart rate to less than 50 beats in minute. We found that bradycardia in patients anesthetized with SSA developed in 2 out of 50 patients or in 4%, but none in LDSA patients. It is a significant difference between the findings in SSA vs. LDSA group ($p<0.002$).

Volume loading the patient with 10-20 ml/kg of crystalloid fluid or appropriate amount of colloid immediately prior and during the administration of a spinal anesthetic may be helpful (27). In this study the pre load of fluids was with infusion of Ringer lactate in doses of 5-10 ml/kg body weight, where the patients' cardiac function and medical history were taken into account prior to this measure. Generally, the analgesic and motor effects of spinal anesthesia are developed for 10-15 minutes after the administration, but the signs of hypotension and bradycardia in this study were developed earlier (5 minutes). Bradycardia in the SSA patients was found in two cases and was rapidly treated with atropine (0.5 – 1 mg/i.v.).

The hypotension found in two patients in group (A) was treated successfully with ephedrine 5 mg every 2 minutes as required. A significant difference was observed between the amount of Ephedrine used in SSA vs. LDSA ($p<0.05$).

In this study, the amount of infused Saline or Ringer lactate used for resuscitation of hypotension, varied from 1.430±412.43 ml in SSA, respectively 1.540±135.64 ml in the LDSA Group, without statistical significance ($p>0.05$).

There are some studies where it was found that crystalloid was inconsistent in preventing hypotension and that colloid was significantly better for pre-loading (18-22). In our study we also used colloids if the hypotension was severe.

Spinal anesthesia provokes a minor alteration in pulmonary functions. Even with high thoracic levels of blockade, tidal volume is unchanged. There is a slight decrease in vital capacity, as a result of relaxation of the abdominal muscles during exhalation (23). Even when low dose spinal anesthesia (LDSA) was administered by using small dose of opiod (20 μg fentanyl), the signs of respiratory depression were not observed. The respiratory rate in all studied patients was in the normal range, and the hemoglobin saturation with oxygen was without any withdrawal ($p>0.05$).

Nausea and vomiting are quite rare during spinal anesthesia and most often associated with hypotension (24-26). In our study we do not observed any nausea or vomiting among the studied patients.

After spinal anesthesia it may be seen some neurological symptoms (ridiculer symptoms, pain, burning sensation, dysesthesia and paresthesia), that are rare when bupivacine is used (27-35). In our study such adverse sensation were not observed.

Conclusion

Standard spinal anesthesia with bupivacaine and low dosage spinal anesthesia can be used safely for emergency surgery of low limbs in healthy patients. The use of low dosage spinal anesthesia in emergency trauma patients is a method of choice with many advantages. It provides stable hemodynamic and respiration parameters of the shocked trauma patients and better resuscitation performances. Low-dose spinal anesthesia is an optimal technique.

We recommend fentanyl as an adjuvant to bupivacaine in spinal anesthesia for surgery of low limbs as it provides more effective and prolonged analgesia with better hemodynamic stability when compared to plain spinal anesthesia.

Conflict of interest

None declared.

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НАШИ ИСКУСТВА СО НИСКО ДОЗНА СПИНАЛНА АНЕСТЕЗИЈА КАЈ ИТНИ ТРАВМАТОЛОШКИ ПАЦИЕНТИ

АПСТРАКТ

Вовед: Денес, спиналната анестезија (СА) е стандардна процедура која се користи при хируршките интервенции на долните екстремитети во травматологијата и ортопедската хирургија, особено поради нејзиното едноставно изведување и ретките компликации, наспроти општата анестезија (ОА). Појавата на пероперативна хипотензија и брадикардија за време на СА се чести несакани ефекти, кои се јавуваат кај помалку од 30% од случаите (најчесто кај итни случаи и кај геријатриската популација) (1). Алтернатива за овие пациенти, може да биде СА со ниски дози на локален анестетик, кој има брз почеток на дејството и помалку несакани ефекти. Постојат мал број на студии за СА со ниски дози (НДСА) кај итни травма пациенти (2,3,4).

Цел на студијата беше да се споредат ефектите од стандардна спинална анестезија (ССА) наспроти спинална анестезија со ниски дози (НДСА) кај итни травматолошки пациенти, и да се анализира нејзината ефикасност и пероперативната манифестација на несаканите ефекти.

Дизајн: Проспективна рандомизирана студија.

Поставеност: Универзитетска клиника за травматологија, ортопедија, анестезија, реанимација и интензивно лекување и ургентен центар, Клинички центар "Мајка Тереза", Скопје, Р. Македонија.

Пациенти и методи: Сто пациенти (ASA I/II) беа примени како ургентни случаи со повреда на долен екстремитет (n=100) и беа рандомизирано поделени на две групи од по 50 пациенти (n=50), зависно од типот на анестезија: Група А (n=50) оперирани со ССА и група Б (n=50), оперирани со НДСА. Сите пациенти со НДСА примаа единечна доза bupivacaine (10-12mg зависно од BMI) и 20 μg Fentanyl. Кај сите пациенти, беа регистрирани хемодинамските параметри (крвен притисок, пулс, ECG) и респираторните параметри (респираторна фрекфенција, сатурација со кислород - SaO_2), како и ресусцитациското интервенирање со ephedrine и надоместокот со течности и тоа во пет временски интервали: пред спиналната пункција (t0) и за време на анестезијата (t1–t5). Исто така, беше анализиран и степенот на аналгезија и несаканите ефекти кај пациентите од двете групи.

Резултати: Хемодинамската анализа не покажа значајни статистички разлики помеѓу испитаниците од двете групи ($p > 0.05$). Статистички значајна хипотензија (>30%), беше нотирана кај двајца пациенти со ССА ($p < 0.01$), но не и кај пациентите со НДСА. Кај 20% од пациентите со ССА беа регистрирани краткотрајни (< 2 минути) епизоди на хипотензија, но кај ниту еден од пациентите со НДСА. Кај 4% од испитаниците од НДСА групата, беше регистриран незадоволителен спинален блок. НДСА во споредба со НДСА, обезбедува постабилна хемодинамика на пациентите, без компромитирање на респираторните параметри и побарува помалку ресусцитациски интервенции ($p<0.01$).

Заклучок: Употребата на ниски дози за спинална анестезија кај травматолошки пациенти за итна хируршка интервенција има голем број на предности, како што се стабилни хемодинамски и респираторни параметри и подобри ресусцитациски перформанси. Стандардната спинална анестезија и спиналната анестезија со ниски дози, може да се користат безбедно кај травматолошки пациенти за итна хируршка интервенција.

Клучни зборови: итна операција на долен екстремитет, ниско дозна спинална анестезија, ресусцитација со ephedrine и течности, спинална анестезија, хипотензија.

 ISSN 2545-4366 | UDC : 616.24-008.64-053.2

MANAGING CRITICAL ILL CHILD WITH ACUTE RESPIRATORY FAILURE

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ABSTRACT

Children with acute respiratory failure (ARF) present the commonest group of critical ill patients for admission in pediatric intensive care unit (PICU). Respiratory developmental differences between children and adults render this susceptible group to altered response to disease process, various clinical manifestations and interventions for respiratory failure. Appropriate decisions for a proactive and life-saving management of the critically ill child with ARF can be provided recognizing three distinctive clinical profiles: mechanical dysfunction of airways, neuromuscular and breathing dysfunction. Beside this, assessment of many physiologic variables of the respiratory system in children with ARF helps in identification of the development of the respiratory failure and serves as a guide therapy for good outcome. Therapeutic modalities and strategies for respiratory failure in children vary depending on the underlying cause. Interventions include supportive and specific therapy. Maintenance of body temperature is of major importance while fluid therapy, monitoring and assessment are additional necessary measures that are undertaken at first. Supportive therapy include securing the airways, oxygen by mask, nasal cannula or head box, proper positioning, nebulization if indicated, and physiotherapy. Specific measures include oxygen therapy and mechanical ventilatory support. Prognosis and outcome depend on the presence of the disease on admission using a number of scoring system, appropriate follow up and adequate therapeutic treatment.

Key words: acute respiratory failure, critical ill child.

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Critically Ill Child: Definition

Critically ill child with acute respiratory failure (ARF) refers to a child who is in a clinical condition which may result in respiratory or cardiac arrest, if not recognized and treated promptly. When a child presents a respiratory disorder, the goal is early recognition of respiratory

insufficiency. Appropriate management depends on an early diagnosis, a clear understanding of the pathophysiology of the disease and clear treatment strategy. Children are particularly sensitive to critical condition of ARF and it is due to the differences between them and adults. Developmental anomalies, inborn errors of metabolism, susceptibility to infections, various accidents and trauma are responsible for the occurrence of ARF.

There are many methods to assess an acutely ill child with ARF. A very simple and quick way of assessment of overall illness is by tree elements: 1. Appearance of the child; 2. Breathing; and 3. Circulatory status. These three parameters comprise "triple pediatric investigation", a very useful tool for recognizing critical ill child (Tab 1).

Table1. *Triple pediatric investigation.*

1. Appearance	2. Breathing	3. Circulatory status
Alertness	Respiratory rate	Heart rate
Distractibility or consolability	Work of breathing	Pulses
Eye contact	Air entry	Skin perfusion
Speech or cry	Pulse oximetry	Organ perfusion
Motor activity		Blood pressure
Color of the skin		
Seizure activity		
Muscle tone		
Pupil size		

Based on the appearance, breathing and circulatory status, physiologic status of a critically ill child with ARF is characterized as: 1. Stable; 2. Respiratory distress characterized by increased work of breathing (IWB); and 3. Respiratory failure characterized by cyanosis, altered sensorium, poor muscle tone and poor respiratory efforts.

Conditions that characterize a critically ill child with ARF requiring rapid cardio pulmonary assessment are:

1. Tachypnea, with respiratory rate of > 60/min in newborn, > 50/min in infants, > 40/min in 1-5 years old child;
2. Bradycardia or Tachycardia with < 80 bpm/min and > 200 bpm/min in newborn, < 80 bpm/min and > 180 bpm/min in 1 month - 8 years child and < 60 bpm/min and > 160 bpm/min in > 8 years old child;
3. IWB and decreased tidal volume;
4. Cyanosis;
5. Altered level of consciousness;
6. Seizures; and
7. Trauma.

Outcome of critical ill child

Numerous of scoring systems have been developed or modified for pediatric application to predict ICU mortality (1). The pediatric risk of mortality score PRISM and the pediatric index of mortality score (PIM) are applicable to a wide range of critically ill infants and children including acute respiratory failure (ARF). Although PRISM performs better, PIM is easier to collect and hence less prone to errors in data collection. The other advantage of PRIM is that it predicts mortality based on admission parameters whereas PRISM is based on the worst variables in the first 24 hours. PRISM is often recording the dying process rather than predicting it. For specific problems, other specialized scores are developed e. g. the modified injury severity scale (MISS) and pediatric trauma score (PTS) for pediatric trauma and the modified Glasgow coma scale for neurological insults.

Compared to the adult intensive care, children with equivalent therapeutic intervention scores have lower hospital mortality (2). While multiple organ failure increases mortality, the prognosis is considerably better than for adults (3). The mortality, entirely attributable to ARF (4%), is lower in PICU than in ICU for adults. Despite of this, the clinical impact of ARF is significant and ARF is independently associated with morbidity, like poor physical post ICU outcome (4).

Acute Respiratory Failure: Definition

Acute respiratory failure is the leading cause of admission to pediatric ICU. Numerous structural and functional factors contribute to the high incidence of respiratory failure, particularly in the newborns, while at children, ARF is frequently a consequence of pathology primarily affecting other organ systems, e.g. congenital heart disease or central nervous system disease, or it is consequence of critical ill conditions after surgery or pediatric trauma.

According to the definition, ARF is present as inadequate gas exchange due to pulmonary and nonpulmonary reasons that lead to hypoxemia, hypercapnia or combination of both. There are 2 types of impaired gas exchange: 1. Hypoxemic respiratory failure, which is a result of lung failure, and 2. Hypercapnic respiratory failure, which is result of respiratory pump failure. In hypoxemic respiratory failure, ventilation-perfusion V/Q mismatch results in the decrease of PaO_2 to below 60 mm Hg with normal or low $PaCO_2$. In hypercapnic respiratory failure, V/Q mismatches results in the increase of $PaCO_2$ to above 50 mm Hg.

Diagnostic criteria for ARF are similar in children and adults. ARF is present if there is one of the following criteria: cardio respiratory arrest; cyanosis (unless there is cyanotic cardiomyopathy); hypoxemia ($PaO_2 < 100$ mmHg) with $FiO_2 = 100$ mmHg or hypercapnia ($PaCO_2 \geq 50$ mmHg). Arterial blood gas analysis is single most important laboratory test for evaluation of respiratory failure [5, 6].

Predisposing Factors of ARF

Respiratory function must be appropriate to the metabolic demands. Oxygen consumption in child is approximately 7 ml/kg/min (3-4 ml/kg/min in the older child and adult). Fever,

illness and restlessness dramatically increase demands; during periods of apnea or respiratory depression, $PaCO_2$ rises at twice the rate of older children and adults. Lower respiratory reserve in children and newborns is due to the following factors: Predisposing factors for ARF are structural immaturity of the thoracic cage (ribcage structure and function alter between 12 and 18 months); infant intrapleural pressure is -1 to -2 H_2O (-1 to -2 kPa) compared to -5 to -10 cm H_2O (-0.5 to -1.0 kPa) in the adult. The consequence is that any impairment can lead to airway closing, atelectasis and intrapulmonary shunting; small airways with increase tendency for obstruction (edema or airways mucus will have more profound effect on airway resistance in the infant).

There are differences between children and adults. Anatomy is different in children. Small upper airways are predicting factor for laryngitis, while small lower airways are responsive to bronchiolotis. The infant's lung structure is different, although the number of alveoli is proportional to body size; the diffusion area is relatively small. Small lungs and short thorax provide sitting position with 45% angle, which is appropriate for prevention of ventilator associated pneumonia. Physiology is different in children (Table 2).

Table 2. *Physiologic respiratory parameters in children.*

Age	$\dot{V}$ (L/min)	$\dot{V}_A$(mL/min)	V_T(mL)	VD/VT (%)	VC (mL)	FRC (mL)	TMILC
Newborn	1.1	385	21	30	120	80	160
6 months	1.4	-	45	30	-	-	-
12 months	1.8	1245	78	30	-	-	-
3 years	2.5	1760	112	30	870	490	1100
5 years	5.5	1800	270	30	1160	680	1500
12 years	6.2	3000	480	30	3100	1970	4000

$\dot{V}$ ventilation/min; $\dot{V}_A$: alveolar ventilation; V_T: tidal volume; V_d: death space; VC: vital capacity: FRC: functional residual capacity; TLC: total lung capacity

Under most circumstances, correct physical examination alone allows one to pinpoint the cause to a particular part of the respiratory system and to make appropriate decisions for a proactive and life-saving management of the critically ill child (7).

Etiology of Acute Respiratory Failure

Causes, symptoms and signs of ARF are different in critically ill children and adults.

The causes for respiratory failure in children include upper airways obstruction (e.g. subglottic stenosis, laryngitis, tracheitis, acute hypertrophic tonsillitis/or adenoid hypertrophy, retropharyngeal / peritonsilar, abscess foreign body inhalation and trauma); lower airways obstruction (e.g. acute viral bronchiolitis, asthma and foreign body); alveolar and pleural disease (pneumonia, pulmonary edema, effusion, empuema, pneumotorax, and ARDS); CNS causes

(injury, trauma, myasthenia gravis, congenital myopathies and muscle fatigue). Acute respiratory failure may also be result of trauma to the brain, spinal cord, chest or abdomen. Duncan, s sign, presence of rhythmic flaring of the alae nasi without accompanying respiratory might be a useful sign to detect high spinal cord injuries in the presence of severe brain injury. Severe pulmonary contusion can occur from blunt trauma, while respiratory failure may be a result of fractured ribs, haemothorax and pneumothorax. Additional causes for ARF might be a ruptured diaphragm or acute gastric dilatation, which may mimic an acute abdomen or exacerbate respiratory failure.

Clinical Manifestation of Acute Respiratory Failure

Symptoms of ARF are different in children and adults. Three distinctive clinical profiles have been suggested in children: mechanical dysfunction of airways, neuromuscular and breathing dysfunction. Tachypnea, exaggerated use of accessory muscles, intercostals, supraclavicular and subcostal retractions are common clinical manifestation of respiratory distress, but in young infants' lethargy, apnea, bradycardia and hypotension may be the first signs of hypoxia. The older child with acute hypoxia, like the adult, demonstrates tachycardia, hypertension, mental confusion and restlessness prior to CNS and cardiovascular depression. Stridor is frequent with upper airway obstruction (laryngitis).

Monitoring of Acute Respiratory Failure

Respiratory monitoring is routinely used in pediatric patients with ARF and mechanical ventilation. Today, modern technology allows bedside assessment of many physiologic variables of the respiratory system in children requiring assisted ventilation. Evaluation of the respiratory status in ventilated patients helps in better understanding of the pathophysiology of the disease, indication of the course of the disease, optimizing ventilator settings, and assessing the effectiveness of treatment modalities (8). Ideal pediatric respiratory and hemodynamic monitoring should be non-invasive and painless, with minimal risk for the child, in order to provide specific information relevant to children's status that will be understandable and reproducibility, to have adequate alarms and to be easy to maintain. Obligatory, monitoring and investigations include pulse oximetry, arterial blood gases, central venous pressure, measurement of cardiac output, capnography, temperature monitoring, RTG of the lung, vital capacity and maximum inspiratory force.

The following parameters are important in evaluation of ARF: 1. PaO_2; 2. $PaCO_2$; 3. Alveolar-Arterial PO_2 Gradient:

P (A-a) O_2 Gradient = PIO_2 – $PaCO_2$ / R where PiO_2 = partial pressure of inspired air, R = 0.8; and 4. Hyperoxia test.

1. Normal values of PaO_2 depend on position of the patient during sampling and the age of the patient:

PaO_2 (Upright) = 104.2 - 0.27 x age (yrs)

PaO_2 (Supine) = 103.5- 0.47 x age (yrs)

2. Normal values of $PaCO_2$ are unaffected by age and positioning and are 35-45 mm Hg.

3. Alveolar – arterial O_2 gradient is a sensitive indicator of disturbance of gas exchange. It is useful in differentiating extra pulmonary and pulmonary causes of respiratory failure. Normal P (A-a) O_2 gradient is 5-10 mm Hg**.** For any age, an A-a gradient > 20 mm Hg is always abnormal. Causes of hypoxemia (low PO_2) are hypoventilation, low ventilation-perfusion (V/Q) mismatch and R/L shunt. It is not possible to predict PaO_2 and $PaCO_2$ accurately using clinical criteria. Thus, the diagnosis of respiratory failure depends on the results of arterial blood gases studies.

Therapeutic Modalities and Strategies

Therapeutic modalities and strategies are different between children and adults. In children there is need for more attention for comfort, ARF mortality is lower and in terms of mechanical ventilation - high frequency ventilation is more appropriate, while non invasive ventilation is more suitable, if acceptable. The most important difference is between a pediatric intensive care unit (PICU) and Intensive care unit (ICU) in terms of the nurse: patient ratio which in children must be 1:1.

Treatment of the critically ill child should be performed in the PICU with minimum standards to address the outstanding problems in this group of patients. General hospitals should have the conditions for urgent resuscitation of children prior to early transport to a specialized PICU (10). Unless unavoidable, critically ill children, particularly those requiring mechanical ventilation, should not be cared for in an adult ICU for longer than 24 hours (according to the American Academy of Pediatrics, the Society of Critical Care Medicine, the British Pediatric Association and the Australian Society of Pediatrics).

Interventions in ARF in children include supportive and specific therapy. Maintenance of body temperature is of major importance, while fluid therapy, monitoring and assessment are additional necessary measures that are undertaken at first. Supportive therapy include securing the airways, oxygen by mask, nasal cannula or head box, proper positioning, nebulization if indicated, and physiotherapy.

Specific measures include oxygen therapy and mechanical ventilatory support. In hypoxemic/non hypercapnic respiratory failure, the major problem is low PaO_2. If it is due to low V/Q mismatch, then oxygen therapy is proposed. If it is due to pulmonary intraparenchymal shunts (e g. ARDS) then assisted ventilation with PEEP may be needed. If it is due to intracardic R-L shunt, O_2 therapy is of limited benefit and surgical treatment is needed. In hypercapnic respiratory failure, key decision is whether mechanical ventilation is required or not. However, in acute respiratory acidosis mechanical ventilation must be strongly considered. In chronic respiratory acidosis, child should be followed closely and mechanical ventilation is rarely required. In acute or chronic respiratory failure, the trend of acidosis over time is a crucial factor.

Indications for mechanical ventilation include PaO_2 < 55 mm Hg or $PaCO_2$ > 60 mm Hg despite 100% oxygen therapy; deteriorating respiratory status despite oxygen and nebulization therapy; anxious, sweaty lethargic child with deteriorating mental status and respiratory fatigue.

Mechanically ventilated pediatric patients represent a complex and diverse population, and respiratory practice is largely guided by a combination of limited pediatric data, anecdotal experience and opinion. These guiding factors lead to extremely variable respiratory management. Among these mechanically ventilated patients, those with acute lung injury or acute respiratory distress syndrome (ARDS) represent an important subset in which substantial controversy exists (11).

Noninvasive ventilation (NIV) with continuous positive airway pressure (CPAP)/BIPAP and invasive ventilation with synchronized intermittent mandatory ventilation (SIMV), assist control (A/C) and PAV modalities are basic strategies for mechanical ventilation. Other approaches to mechanical ventilation as high frequency ventilation (HFV), permissive hypercapnia, prone positioning, inhaled nitric oxide (NO) and extracorporeal membrane oxygenation (ECMO) are also proposed (12).

HFV improves the occurrence and treatment of air-leak syndromes associated with pediatric acute lung injury minimizing the possibility of barotraumas to airways and it is used if conventional ventilation fails to improve gas exchange. There are 3 types of HFV: Oscillatory, Jet and Flow interruption. Very small tidal volumes are used (<1ml/kg) with very rapid rates (150-1000 bpm) and lower mean airway pressures.

Permissive hypercapnia allows the $PaCO_2$ to rise into the 60-70 mm Hg range, as long as the patient is adequately oxygenated (SaO_2 > 92%), and able to tolerate the acidosis.

This strategy is used to limit the amount of barotraumas and volutrauma to the patient.

Prone positioning reduces compliance of the thoracoabdominal cage by impending the compliant rib cage and in that way improves oxygenation and reduces ventilator induced lung injury. However, the outcome may not be improved.

NO improves V/T matching by enhancing pulmonary blood flow to well ventilated parts of the lung and improves oxygenation by reducing increased pulmonary vascular resistance (13).

By ECMO, blood is removed from the patient, passed through an artificial membrane where gas exchange occur, and returned to the body by either the arterial or venous gas system (14).

Conclusion

Children with ARF are great challenge for critical care clinicians that must be experts in anatomy and physiology in this population and must rely on the guidelines for follow up and treatment.

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МЕНАЏИРАЊЕ НА КРИТИЧНО БОЛНО ДЕТЕ СО АКУТНА РЕСПИРАТОРНА СЛАБОСТ

АПСТРАКТ

Децата со акутна респираторна слабост (АРС) претставуваат најчеста група на критично болни пациенти кои се примаат во педијатриските единици за интензивна нега (ПЕИЛ). Разликите во респираторниот развој помеѓу децата и возрасните се причина за изменет одговор при развојот на респираторната инсуфициенција, за различни клинички манифестации и интервенции. Адекватни решенија за активен и животоспасувачки третман кај децата со АРС може да се обезбеди со препознавање на три карактеристични клинички профили: механичка дисфункција на дишните патишта, невромускулна и дишна дисфункција. Проценката на многу физиолошки промени на респираторниот систем кај децата со АРС помага во идентификацијата на развојот на респираторната слабост и служи како водич за терапија со добар исход. Терапевтските модалитети и стратегии за респираторна инсуфициенција кај децата вариираат во зависност од основната причина. Интервенциите вклучуваат супортивна и специфична терапија. Одржувањето на температурата на телото е од голема важност, додека терапијата со течности, монторингот и испитувањето се дополнителни неопходни мерки кои се преземаат во прв план. Супортивната терапија вклучува обезбедување на дишните патишта, кислород со маска, назална канила или кислороден скафандер, правилното позиционирање, небулизација ако е индицирано и физикална терапија. Посебните мерки вклучуваат кислородна терапија и механичка вентилација. Прогнозата и исходот зависат од степенот на болеста при прием, при што се користат голем број на системи на бодување, соодветно следење и соодветен терапевтски третман.

Клучни зборови: акутна респираторна слабост, критично болно дете.

 ISSN 2545-4366 | UDC : 617.741-004.1-089.168.1-085.214.24

EFFECTS OF PROPOFOL ON THE LEVEL OF POSTOPERATIVE BEHAVIORAL CHANGES IN CHILDREN WHO UNDERWENT CATARACT SURGERY

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ABSTRACT

Introduction: The appearance of agitation and behavioral changes in children after sevoflurane anesthesia is common, especially in short-term interventions such as ophthalmic operations. Usage of sub-hypnotic doses of propofol before termination of sevoflurane has been reported that may provide effective sedation and reduce the incidence of severe agitation. The aim of this study was to determine if switching from sevoflurane to propofol (in subhypnotic doses) before the ending of surgery reduces the incidence of agitation-delirium in children after cataract surgery.

Material and methods: 60 children aged 3-7 years, with ASA (American Society of Anesthesiologists physical status) I/II, undergoing cataract surgery were randomly divided into two groups. Group P (n=30) included children in whom 3-5 minutes before the ending the surgery sevoflurane was terminated and propofol 25μg/kg/h was started. The control group (n=30) were patients in whom sevoflurane anesthesia was maintained till the end of the surgery. In all children we evaluated the time of un-operated eye opening (on verbal command), the children's behavior changes and pain. Behavior was assessed with the help of five degree Watch scale (score 1(awake), 2, 3,and 4 (agitation). The degree of pain was followed by visual analogue scale (VAS scale) during the first hour at 30 minutes period. We additionally recorded the need for additional interventions (additional midazolam) during this time.

Results: Agitation occurred in significantly larger number of children in group S compared to group P. Percentage differences for the scores of the ED were significant between the groups for score 4 and score 1. Pain evaluation didn't show any difference between the groups. In group S, 60% of the children had need for giving additional midazolam.

Conclusion: Giving subanesthetic propofol doses 3-5 minutes before the ending of the surgery effectively reduces occurrence of agitation in children after cataract surgery.

Key words: sevoflurane, propofol, postoperative agitation-delirium.

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Introduction

Congenital cataract operations in children are short timed, but painful and it is necessary for the children to have general anesthesia. After completing the operation, the eye is protected with antibiotic ointment and is closed with sterile gauze. The first attempts as well as the followed attempts to open the eyes, are considered to be the main reason for discomfort and anxiety in young children (1,2).

Behavior changes, postoperative agitation or delirium (emergence delirium - ED) in children occurs after emerging from anesthesia. This is a transitory state of impaired mind, when child is angry, cries out with no reason, has uncontrolled movements, has unusual hypersensitive towards everything, becomes aggressive and in many occasions attacks somebody physically. This, stress reaction presents potential risk from self-hurting, hurting the stuff and the parents (1)].

ED is considered when one or several of the previously described reactions are present. For evaluation of behavior changes in children several scales are proposed. Pediatric Anesthesia Emergence Delirium (PAED) measures the degree of delirium, but this scale is difficult for routine use, as well as the scale of Cravero. Watch scale, on other hand is simple for clinical use, and thus has a higher sensitivity than the previous two (3).

Anesthesia history presents data for increased incidence of ED, with the introduction of modern short-acting inhaled anesthetics, primarily sevoflurane (2.4). It is also observed that ED after sevoflurane is common in pre-school children compared to children over 7 years. Additionally the region of the surgical intervention is recognized as a risk factor for ED (1).

ED is more common in children undergoing otolaryngology and ophthalmology procedures, compared to urological and abdominal operations (5). Some authors say that pain is an important risk factor for ED occurrence, especially when some part of the head is operated. At the same time, there is evidence that report that lager number of children are developing ED after sevoflurane anesthesia in painless procedures, (such as diagnostic MRI), compared to those who received propofol and midazolam (4).

In anesthetic practice, researchers are studying the causes of ED at the same time with the therapy for ED. It is known that usage of propofol, ketamine, α2-adrenceptor agonist, fentanyl and preoperative analgesia, reduce the incidence of ED and at the same time these drugs are very effective in reducing postoperative pain (1,5,6).

The aim of this study was to determine if switching from sevoflurane to propofol (in sub hypnotic doses) before the ending of surgery reduces the incidence of agitation-delirium in children after cataract surgery.

Material and Methods

The study included 60 children aged 3-7 years, with ASA (American Society of Anesthesiologists physical status) I/II, undergoing cataract surgery at the eye hospital, Skopje. According to the

standards of European Eye Hospital Skopje, all parents bring their children into the operating room and are present in the recovery room right after the surgery. Therefore, in accordance with the ethics committee they are thoroughly informed how awaking from anesthesia can be, how we act and how they can help their children.

Children were randomly divided into two groups. Group P (n=30) included children in whom 3-5 minutes before the ending of the surgery sevoflurane was terminated and propofol 25-50μg/kg/h was started. The control group S (n=30) were patients in whom sevoflurane anesthesia was maintained till the end of the surgery.

After admission in the hospital all children were weighing and received oral premedication with 0.5 mg/kg syrup midazolam and syrup brufen 5ml (100mg) for preemptive analgesia and then they were insert venous line. Children who showed anxiety or crying when entering the operating department were excluded from the study. After entering the operating room the children were put on continuous monitoring of heart rate, ECG, arterial blood pressure, oxygen saturation and capnography.

The standardized anesthesia started with fentanyl in a dose of 2μg/kg and propofol in a dose of 2-3 mg/kg. To facilitate intubation. 0.6-1mg/kg rocuronium bromide was used. After intubation, children were ventilated in controlled manner with oxygen and air (50%: 50%). The parameters of tidal volume and frequency were determined according to the age with a target of end-tidal CO2 of 35-40 mmHg. In all children anesthesia was maintained with sevoflurane up to 5 minutes before the surgery ending. All children received antiemetic ondansetron dose of 0,1 mg/kg.

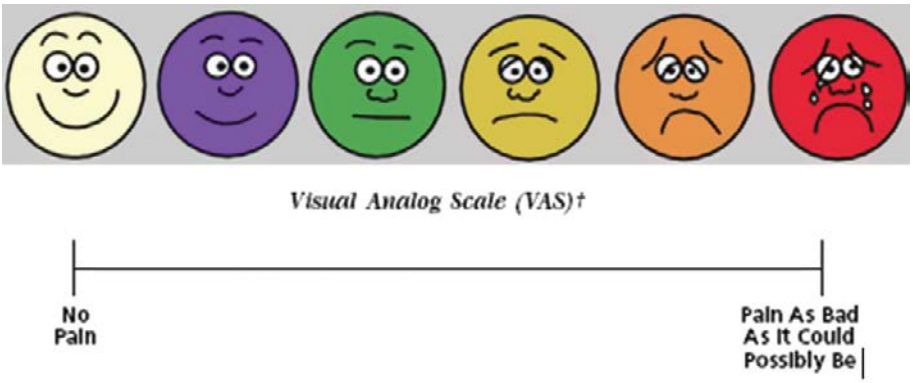
In all children we evaluated the time of un-operated eye opening (on verbal command), the children's behavior changes and pain. Behavior was assessed with the help of five degree Watch scale*. Measurements for Watch scale (0-4 points) was done every 5 minutes during the first 15 minutes. The degree of pain was followed by visual analogue scale (VAS scale**) (Table 1 and 2) (7).

* Watch scale, free access online from Contin Educ Anasth Crit Care Pain (2012) doi: 10.1093 / bjaceaccp / mks051.

Table 1. *Watch scale.*

Behavior	Score
At sleep-sleepy	0
Awake	1
Cry, but can control	2
Crying, but cannot control	3
Agitating and beating around	4

Table 2. *Visual Analogue Scale (VAS scale)*



***Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2539005/15056325 DOI:*

Results

Demographic and clinical data in both groups of patents were homogenic.

Average age in both groups was 3 years while on average children weighted 17.9 kilos in group P and 18.7 kilos in group S. (Demographic and clinical characteristics are shown in Table 2.)

More children in group P were male while more patients in group S were female. Male to female ratio was 16/14 vs.14/16 in respect to the groups.

Most of the children in both groups were classified as ASA I.

Table 2. *Demographic data, length of the operation and time of extubation.*

Variables	Propofol (n=30)	Sevoflurane (n=30)
	Mean ± SD	Mean ± SD
Age (years)	3±3	3±3.3
Body weight (kg)	17,9±3,4	18,7±3,2
Length of operation (min)	25,9±4	26,2±5
extubation time (min)	10±2	11±3

Most of the patients in the propofol group were awake during the first 15minutes.

Contrary to this, in group S, the most of the patients were agitated and were beating around or cried uncontrolled. The percentage of differences for occurrence of agitation+beating and awekeness between the groups was significant.

Incidence of delirium was much greater in the group with sevoflurane (Fischer accuracy test, $p < 0.0087$ sevoflurane group vs propofol group $p > 0.9999$).

In group S, in 60% of the children additional midazolam was given during the first hour.

Table 3. *Watch scale during the first 15 minutes.*

Watch score	Group P (n=30)	Group S (n=30)
minutes 4	5' 10' 15' patient No. 3 pts / /	5' 10' 15' patient No. 15 pts 14 pts 9 pts
3	4 pts 3 pts 2pts	10 pts 7 pts 5 pts
2	9 pts 7 pts 6 pts	5 pts 5 pts 4 pts
1	14 pts 20 pts 22 pts	5 pts 4 pts 12pts

The pain perception according to VAS of 3 was noticed in both groups on 15' and 30th minute. On the 60th minute in both groups VAS of 2 was noticed.

Discussion

This study found out that the incidence of behavioral changes is much greater in children with sevoflurane anesthesia during the procedure compared to those who recievedsubhypnotic doses of propofol at the end of the operation.

Theories that elaborated the possible causes of postoperative delirium include hypoxemia, metabolic disorder and pain or drugs effects (2.5, 8). In this study, all patients were healthy, procedures lasted for a short time, without hemodynamic instability and without registered decline in oxygenation. Also, all patients were without pain because of preoperative given analgesic. So, ED after anesthesia with sevoflurane was not a result of pain, hypoxia or metabolic disorder.

Numerous clinical studies confirm that behavioral changes are common phenomenon in children after anesthesia with sevoflurane or desflurane and the incidence is significantly higher compared to halothane or anesthesia based on propofol (1, 5, 9). Also, agitation is reported to be common in pre-school children compared to children over 7 years (10,11).

The incidence of delirium in children after sevoflurane anesthesia, in the quoted studies, ranged from 23-46%, which is similar to our findings. The incidence behavioral changes after propofol given in a single dose, ranges between 0-9%. In our study is higher, which may be due to differences in the method of giving propofol, continuous or bolus dose. The findings of this study confirmed that propofol is an important factor in reducing postoperative behavioral changes and agitation, after ophthalmological interventions in pre-school children. It should be considered that ophthalmic procedures in children give possible to be followed by a higher incidence of behavioral changes due to the impaired vision and closed eye (1).

Postoperative pain is an expected phenomenon, especially at the same day of (ambulatory) surgery. The combination of pain and discomfort related to the place of operation is a phenomenon also observed in the operations of nose and throat (12).

Conclusion

Giving subanesthetic propofol doses 3-5 minutes before the ending the surgery effectively reduces occurrence of agitation in children after cataract surgery.

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ЕФЕКТ НА ПРОПОФОЛ ВРЗ ПРОМЕНИТЕ НА ОДНЕСУВАЊЕТО ПОСЛЕ АНЕСТЕЗИЈА СО СЕВОФЛУРАН КАЈ ДЕЦА ОПЕРИРАНИ НА КАТАРАКТА

АПСТРАКТ

Вовед: Појавата на агитација и промени во однесувањето на децата после анестезија со севофлуран е вообичаена, особено кај краткотрајни интервенции какви што се офталмохируршките операции. Краткотрајна примена на пропофол во субхипнотски дози непосредно пред прекинување на севофлуранот може да овозможи ефективна седација и намалување на инциденцата на тешка агитација.

Цел: Оваа студија има за цел да определи дали преминување кон пропофол во субхипнотски дози по прекинот на севофлуран ја намалува појавата на агитација-делириум кај децата по операција на катаракта.

Материјал и метод: 60 деца на возраст од 3-7 години, со АСА I или II скор (American Society of Anaesthesiologysts physical status), закажани за операција на катаракта, по метод на случаен избор беа поделени во две групи. Групата П(n=30) вклучуваше деца кај кои 5 минути пред да заврши операцијата севофлуранот беше исклучен и се вклучуваше пропофол на пумпа во доза од 25μg/kg/h и контролна група С, каде анестезијата завршуваше со севофлуран. Кај сите испитаници се регистрираше времето на отворање на неоперираното око на вербална команда, степенот на агитација и степенот на болка. Агитацијата и однесувањето на децата беше оценувано според пет степената Watch скала, а степенот на болка беше следен според визуелната аналогна скала (VAS scale). Дополнително, се регистрираше и потребата за дополнително давање на мидазолам во двете групи.

Резултати: Агитација беше регистрирана кај сигнификантно поголем број деца од групата С. Процентуалните разлики меѓу групите беа сигнификантни во однос на скоровите од Watch скалата за агитација и будни, мирни пациенти, помеѓу двете групи на пациенти. Регистрираната болка не беше различна меѓу двете групи. Поголем број на пациенти од групата С (60%) имаа потреба од додавање на мидазолам во дадениот период.

Заклучок: Субанестетички дози на пропофол непосредно пред прекинување на севофлуранот ефикасно ја намалува појавата на агитација кај деца по операција на катаракта, а при тоа нема значително продолжување на будењето.

Клучни зборови: постоперативна агитација-делириум, пропофол, севофлуран.

 ISSN 2545-4366 | UDC : 616.231-089.819.3:613.25

ENDOTRACHEAL INTUBATION IN MORBID OBESE PATIENTS WITH OBSTRUCTIVE SLEEP APNEA

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ABSTRACT

Aim: The aim of the study is to determine the obstructive sleep apnea as predictive factor for difficult endotracheal intubation in morbid obese patients.

Material and methods: Clinical prospective study. We tested obstructive sleep apnea (OSA) and its severity, as determined by apnea-hypopnea index (AHI); neck circumferential (NC), and body mass index (BMI) in morbid obese patients scheduled for establishing the airway with tracheal intubation.

Polysomnography was used to define the severity of obstructive sleep apnea. The inclusion criteria for the patients were: morbid obese patients, patients with body mass index more than 40kg/m^2 and patients with severe sleep apnea with apnea-hypopnea index more than 30 abnormal respirations/hour during the sleeping time of 8 hours.

Neck circumferential was measured preoperatively. Mallampati score was investigated before induction in anesthesia, while Cormack and Lehane score was notified during the laryngoscopy before the intubation. Mallampati score 3 and 4; Cormack - Lehane score 3 and 4 were defined as difficult intubation scores. Endotracheal intubation was performed in elevated position of the head for 25 degrees.

Results: There was no positive correlation between obstructive sleep apnea, body mass index and neck circumferential with difficult intubation scores Mallampati and Cormack - Lehane score in morbid obese patients scheduled for general anesthesia intubated in elevated head position for 25 degrees. Mallampati score, measured before induction, showed the levels 1 and 2; Cormack - Lehane score, measured before intubation, showed the levels of 1 and 2, too.

Discussion and conclusion: Elevated head position for 25 degrees facilitates endotracheal intubation in morbid obese patients with severe obstructive sleep apnea score. We concluded that obstructive sleep apnea is not a predictive factor for difficult tracheal intubation in morbid obese patients.

Key words: morbid obese patients, obstructive sleep apnea, tracheal intubation.

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Introduction

Obstructive sleep apnea (OSA) is a highly prevalent disease since it could affect 7-15% of the middle-aged population, but most patients are not yet diagnosed for OSA. Middle age, male gender, obesity and arterial hypertension are main risk factors for OSA in adults (1, 2). Obesity changed the anatomical measures of the oropharynx and neck circumferential. Body mass index higher than 40kg/m^2 disables face mask ventilation and oxygenation of the patients that had to be scheduled for general anesthesia with tracheal intubation.

These patients have the episodes of hypoxia during the sleep, because of the low tonus of the pharyngeal muscles, soft palate falls in glottis that produces upper airway obstruction (3). Face mask ventilation and oxygenation during the anesthesia induction are disabled at morbid obese patients. Because OSA may lead to life-threatening problems if undiagnosed, anesthesiologists should be aware of their screening role in the preoperative period. In the postoperative period, early resuming continuous positive airway pressure and installing the OSA patient in a nosupine position could be effective in preventing pharyngeal obstruction.

Material and Methods

50 patients, 30 men and 20 women were included in the study. Preoperative preparation for the patients included: spontaneous respiration measurement in sitting position and body mass index. Patients with body mass index more than 40kg/m^2 were scheduled for polysomnography. Severity of OSA was quantified using AHI and the American Society of Anesthesiologists' OSA severity scale. Obstructive sleep apnea syndrome in adult is defined as an Apnoea -Hypopnoea Index (AHI) of 5 or more per hour of sleep in a context of excessive daytime sleepiness and snoring. OSA is considered as mild with an AHI of 5-15, moderate with an AHI of 15-30, and severe with an AHI greater than 30 (4,5).

Mallampati score was evaluated in sitting position in the preparation room (6). Neck circumferential was measured before intubation. The position of the patients' heads was elevated for 25 degrees from the operating table by the pillow. Cormack – Lehane score was notified during the visualization of the glottis, before intubation (7, 8).

Intubation attempts were limited up to 3; they lasted no longer than 10 minutes. Tracheal intubation was performed with silicone tube without stile.

Mallampati 3 and 4 as well as Cormack – Lehane score 3 and 4 are predictors for difficult intubation.

Results

Our results showed that the mean BMI was 45.0 kg/m^2. The mean AHI was 32.1 (range 0-133). The mean neck circumference was 42cm.

All patients were intubated successfully without aid of rescue airways by anesthesiology residents within 10 minutes and max of three attempts.

There were 10% incidence of Mallampati 3 and 4. The incidence of difficult laryngoscopy, defined as a Cormack - Lehane Grade 3 or 4 view was 6.3%.

There was no correlation between NC and difficult tracheal intubation (odds ratio 1.0, 95% confidence interval 0.93-1.1; p=0.02). Increasing NC was associated with difficult visualization that consume 10 minutes, the edge time for the procedure, but not difficult intubation (p = 0.02).

There was no correlation between the severe OSA (AHI 32.1) and difficult intubation (p = 0.09), or between BMI and difficult intubation (odds ratio 0.99, 95% confidence interval 0.92-1.06; p = 0.8).

There was no correlation between number of intubation attempts and BMI (p = 0.8), AHI (p = 0.81) or NC (p = 0.3).

Discussion and Conclusion

There is no correlation between OSA, BMI, NC and difficult intubation in morbid obese patients. The head position with 25 degrees elevated is the proper intubation position for these patients. This position allows good visualization of the vocal cords that facilitate tracheal intubation.

We conclude that OSA and AHI could not be predictive factors for tracheal intubation in morbid obese patients.

There are many other scales to define OSA like: Epworth sleepiness scale (ESS); STOP-BANG questionnaire is a well-adapted instrument to screen patients for OSA during the preoperative visit (9-12). They all use an AHI index to define severity of the OSA that could be in correlation with difficult intubation.

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ЕНДОТРАХЕАЛНА ИНТУБАЦИЈА КАЈ МОРБИДНО ГОЈАЗНИ ПАЦИЕНТИ СО ОБСТРУКТИВНА СЛИП АПНЕЈА

АПСТРАКТ

Цел: Целта на студијата е да се определи дали обструктивната слип апнеја претставува предиктивен фактор за тешка ендотрахеална интубација кај морбидно гојазни пациенти.

Материјал и методи: клиничка проспективна студија. Го одредувавме степенот на обструктивната слип апнеја (ОСА) според апопнеја-хипопнеја индексот (АХИ); циркумференцијата на вратот (НЦ) и боди мас индексот (БМИ) кај морбидно гојазни пациенти, кај кои требаше да се воспостави дишен пат со ендотрахеална интубација. Полисомнографијата беше користена за определување на степенот на обструктивната слип апнеја. Критериуми за вклучување во студијата беа: морбидно гојазни пациенти со боди мас индекс поголем од 40kg/m^2 и пациенти со силна слип апнеја со апопнеја-хипопнеја индекс поголем од 30 абнормални респирации/час за време на спиење од 8 часа.

Циркумференцијата на вратот беше мерена предоперативно, Mallampati скорот се определуваше пред воведот во анестезија, додека Cormack-Lehane скорот се определуваше за време на ларингоскопија непосредно пред ендотрахеалната интубација. Mallampati скор 3 и 4, како и Cormack-Lehane скор 3 и 4, предвидуваа дека интубацијата ќе биде тешка. Ендотрахеалната интубација се изведуваше во подигната позиција на главата за 25 степени.

Резултати: Не постоеше позитивна корелација помеѓу ОСА, БМИ, циркумференцијата на вратот и тежината на интубацијата определувана според Mallampati и Cormack-Lehane скорот кај морбидно гојазни пациенти воведени во општа анестезија, поставени во позиција за интубација со подигната глава од 25 степени.

Дискусија и заклучок: Подигнатата глава на пациентите за 25 степени ја олеснува ендотрахеалната интубација кај морбидно гојазни пациенти со силна обструктивна слип апнеја. Заклучивме дека обструктивната слип апнеја не претставува предиктивен фактор за тешка ендотрахеална интубација кај морбидно гојазни пациенти.

Клучни зборови: ендотрахеална интубација, морбидно гојазни пациенти, обструктивна слип апнеја.

 ISSN 2545-4366 | UDC : 616.8-009.17-089.5

MYASTHENIA GRAVIS AND GENERAL ANESTHESIA

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ABSTRACT

Myasthenia gravis patients undergoing general anesthesia are real challenge. Several contemporary issues of the disease, as well as the therapy and additional contributing factors interfere with the anesthetics on several levels. Up to day, literature has not proved which type of anesthesia or anesthetics are superior in such patients. The aim of this article is to elaborate and review some of the possible aspects of this disease and their interference with anesthesia that have direct influence on these patients outcome.

Key words: general anesthesia, myasthenia gravis

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Introduction

Myasthenia gravis is a chronic autoimmune disease characterized by destroyed acetocholine receptors at the neuromuscular junction (1). Anesthetic management for these patients in general anesthesia is very challenging.

Many aspects of the disease interfere with the anesthetic management and when all aspects are not carefully elaborated anesthesia may have detrimental outcome.

When myasthenia is elaborated in relation to the surgery, anesthesia and complications, authors have proved that the preoperative therapy, stage of the disease, the histology of the thymus, and the usage of neuromuscular relaxant play major role in the postoperative complications in these patients (2,3,4).

The aim of this study is to evaluate and review all possible implications

(neurological state, preoperative therapy, preoperative assessment, different type of anesthetics used) in myasthenia patients undergoing general anesthesia.

Neurological Aspect of Myasthenia Gravis

First aspect that has to be evaluated in myasthenia patient is the degree of the underlying disease. Myasthenia gravis can be classified by different classifications, but the mostly used is the one proposed by Osserman and Genkis (4). This classification was firstly introduced in the late 1980s and classifies myasthenia patients according to the progression of the disease and the muscle enrollment to several stages where:

- I: Ocular myasthenia,
- IIA: Mild generalized myasthenia with slow progression: no crises, responsive to drugs,
- IIB: Moderately severe generalized myasthenia: severe skeletal and bulbar involvement, but no crises; drug response less than satisfactory,
- III: Acute fulminating myasthenia, rapid progression of severe symptoms, with respiratory crises and poor drug response,
- IV: Late severe myasthenia, same as III, but progression over 2 years from class I to II.

Global burdens of myasthenia show that ptosis, diplopia and blurting are present in nearly 50% of all patients, as sole symptoms, while in around 20% bulbar muscles alone are affected. The age presentation is bimodal, male to female ratio is 4:1 and the mortality rate in these patients after 1980 has drastically decreased (5).

Besides these qualitative scores, additional Quantitative myasthenia scores are present as the one of the Barohn at al., where different features (ptosis, facial muscles activity, swallowing, speech, arms outstretching, vital capacity, hand grip, head lifting and legs stretching) are individually graded (6). In our opinion these quantitative scores are more predictive in terms of anesthesia complications and give the anesthesiologist global knowledge of the patient's state.

However, these burdens confirm that 85% of all myasthenia patients have possibility to develop muscle weakness after anesthesia. Every anesthesiologist should know that the most

of myasthenia published cases, where anesthesiology management is disused, are myasthenia patients undergoing thymectomy. Thymectomy is the first line of therapy for myasthenia patients (90% of the cases are positive for acetylcholine receptors antibodies) and therefore thymectomy is usually done in the early stages of the disease (2, 3).

Anyway, every stage of the disease needs special collaboration between the anesthesiologist, neurologist and surgeon. Furthermore, more advanced stages need special preoperative therapy and physical preparation that might take months in order to reduce the incidence of complications. Every patient with myasthenia should be considered as a high risk patient no meter how minor surgical intervention is.

Myasthenia Gravis Therapy Optimization

According to the progression and the symptoms of the disease, different therapy is used. When the myasthenia therapy is elaborated in relation to the surgery, anesthesia and complications, authors have proved that the preoperative therapy, stage of the disease, the histology of the thymus, the usage of neuromuscular relaxant, play major role in the postoperative complications, as well as in the remission of the myasthenia (increase symptoms after thymectomy) (7).

Preoperative therapy for myasthenia, in general consists of several modalities:

anticholinesterase drugs (pyridostigmin, neostigmine), immunosuppressant (cyclosporine), plasmapheresis and immunoglobulins. Preoperative therapy goals for myasthenia patients are optimization of anticholinesterase therapy, weaning of corticosteroids (to the lowest dose) and if needed, plasmapheresis should be done (to prepare the patient for surgery) (8).

Anticholinesterases increase the synaptic cleft acetylcholine. Different centers have different perspective for taking or omitting these drugs on the day of the surgery. These differences are mainly due to the different experiences from the centers, as well as the possibility of this drug to increase the need for neuromuscular relaxants and additional effects. Anticholinesterases potentiate the vagal responses and hence adequate atropinisation must be ensured. Also, anticholinesterases can inhibit plasma cholinesterase activity with a subsequent decrease in the metabolism of ester local anesthetics, and the hydrolysis of suxamethonium will be decreased (9).

The globally used guidelines is that in the mild cases of myasthenia, half of the anticholinesterases doses should be taken in the morning of the surgery while full dose in moderate to severe forms. Additionally, what should be absolved is that two ampoules of neostigmine (1 mg) are equal to 30 mg pyridostigmin, so if neostigmine is given, the doses should be equilibrated.

For the corticosteroids, minimization is suggested in order to reduce the postoperative wound healing problems, infections and pulmonary complications. If present in the preoperative treatment, these drugs are usually omitted on the day of the surgery (8).

Azathioprine (immuran) decreases the steroid doses, while cyclosporine (immunosuppressant) and immunoglobulins are used months or weeks prior the surgery to optimize the stable state for the patient that lasts for weeks.

Several data suggest that plasmaphereses are mainly needed in more progressive stages of the disease. Preoperatively plasmaphereses preconditioning is suggested at least two weeks pre surgery. Furthermore, it is proven that the preoperative plasmaphereses are more beneficial than postoperative and may allow some discontinuation of the anticholinesterase drugs in surgery patients (9).

However, every strategy concerning the preoperative therapy and the therapy on the day of the surgery is mainly constructed for every single patient in collaboration of anesthesiologist, neurologist and surgeon.

Preoperative assessment

In myasthenia, preoperative comorbidities evaluation and optimization play major role in reducing the postoperative risks.

Respiratory and cardiac enrolment should be carefully investigated and evaluated (10,11). Spirometry in myasthenia patients, may show normal total capacity, but low vital capacity with normal to high residual volume. Cardiologic impairment is usual finding in these patients, especially the presence of arrhythmias, bradycardia and atrial fibrillation, as well as the presence of left ventricular dysfunction. Every therapy chronically taken should be taken on the day of the surgery.

However, some new data propose that train-of four (TOF) stimulation before the surgery, is sometimes a baseline function that should be considered on the awakening (9). Therefore, commonly this is a test plus that should be evaluated in the preoperative assessment.

Myasthenia gravis patients Foundation confirms that the myasthenia patients who need prolonged mechanical ventilation are those who have higher degree of the preoperative comorbidities, patients that are stage IIB and higher, patients who have myasthenia more than 6 years, with vital capacity below 2.9 L and those who take pyridostigmine doses larger than 750 mg/day (9).

Drugs that Might Emphasize the Myasthenia

Some of the medications are reported to cause exacerbations of myasthenia and their use should be excluded in the preoperative and postoperative period (9):

Antibiotics - macrolides, fluoroquinolones, aminoglycosides, tetracycline, and chloroquine;

Antiarrhythmic agents - beta-blockers, calcium channel blockers, quinidine, lidocaine, procainamide, and trimethaphan;

Miscellaneous - diphenylhydantoin, lithium, chlorpromazine, muscle relaxants, levothyroxine, adrenocorticotropic hormone (ACTH), and, paradoxically, corticosteroids.

Anesthesia and Myasthenia

Sedation

According to the literature, preoperative sedatives, anxiolytics or opioids premedication's drugs are commonly used in myasthenia patients, but their usage should be with precaution in

patients with little respiratory reserve (9). If the patient has primarily ocular symptoms, a small dose of benzodiazepine is acceptable.

Monitoring

Anesthetic plan for every myasthenia patient should be individualized and in all patients intraoperative monitoring should be used. All patients should undergo for an intraoperative temperature, ECG, blood pressure, respiratory rate, pulsoximetry, carbon dioxide, and TOF monitoring, that according to the literature are considered as a standard (9).

General Anesthesia Techniques

Several general anesthesia techniques are proposed for myasthenia patients even though none of them are proven to be superior. Some prefer avoiding muscle relaxants and the use of potent inhalation agents, both for intubation and relaxation during surgery. Other prefer intravenous anesthesia with small doses of muscle relaxants, and certainly there are authors who prefer total intravenous anesthesia, but are always reconsidering the cardiovascular instability.

Anesthesia with inhalation anesthetics are reported, but the fundaments of pharmacokinetics and pharmacodynamics of these agents are that they prolong the effect of the neuromuscular blockade which is profound in myasthenia patients (12,13,14).

Isoflurane and enflurane decrease the train of four (TOF) response in myasthenia patients. Theoretically, desflurane and sevoflurane have advantages due to their low blood solubility. Sevofluran has been reported to be safe as a sole anesthetic when used with MAC (Minimal Alveolar Concentration) of 1-2, in myasthenia patient. On the other hand, it has been found that sevoflurane appears to depress neuromuscular transmission sometimes in larger extend than isoflurane (14, 15).

Desfluran has not been extensively elaborated in myasthenia, but normally when this agent is used in non myasthenia patients, the need for muscular relaxants is lower, so theoretically this agent pronounces the neuromuscular block as other inhalation agents (16).

Therefore, if inhalation anesthetics are used for induction and maintenance of anesthesia in myasthenia patient as sole agent and without muscle relaxants, they may be given safely, otherwise reconsideration should be done.

Usage of short acting barbiturates (like thiopental) and non barbiturate agents (like propofol) as induction and maintenance agents are reported to be safe in myasthenia patients. O'Flaherty et al., Stephanson and Srceva M. gave certain theoretical advantage to the propofol due to the short time of action and lesser effect on the neuromuscular junction (17, 2, 18).

Different studies show different results in what maintenance agent is superior in myasthenia patients. Many authors suggest that sevoflurane is suitable as sole maintaining agent, while other give superiority to propofol. All reports confirm that both of the agents can be safely used in myasthenia patients, but direct comparison is impossible. Firstly, because the former

is inhalation, whereas the latter is intravenous anesthetics; secondly, corticosteroid inhibits the synthesis of GABAergic steroids and may lead to antagonistic interference with propofol. Therefore, comparison of their neuromuscular effects requires a deliberate interpretation (18).

The usage of opioids for surgery is common practice. Literature presents studies that opioid usage in myasthenia patients doesn't appear to depress neuromuscular transmission, but may depress central respiratory center when given in supra-therapeutically dosage (9,2).

On the other hand, to our knowledge, no large randomized study is published that show the advantages or disadvantages of the short acting opioid (remifentanil) in combination with propofol as induction or management in these patients. All published studies have showed some advantages for this type of induction in myasthenia patients, in regards of extubation and compared to inhalation anesthesia techniques (19,20). But there are still reports, which show that this combination of induction and maintenance resulted in delayed postoperative arousal (21).

Usage of Muscle Relaxants in Myasthenia Patients

Succinylcholine: Patients with myasthenia show resistance to succinylcholine due to the loss of the receptors, and this relaxant produces muscular block by agonist action. Because of this, usage of succinylcholine in myasthenia patients is not recommended (2, 9, 22) even though it is possible with higher doses administrated.

Additionally, if the patient has cholinesterase depletion after plasmapheresis or due to high pyridostigmine doses, the metabolism of this drug is changed and results in prolonged block.

Non depolarizing muscle relaxants (NDMR): Myasthenia patients are sensitive to NDMR and even small doses might result in respiratory distress. This sensitivity is not always proportional to the neurological state of the disease and literature reports extreme sensitivity in patients with minor symptoms or even being asymptomatic (22-26).

Long-lasting NDMR (pancuronium, doxacuronium) should be avoided in myasthenia patients, while short acting (vecuronium, atracurium, rocuronium, cisatracurium etc.) should be used with special precaution and adequate monitoring.

Literature reveals that the elimination of vecuronim in myasthenia patients is not alerted, that myasthenia patients have similar sensitivity to cisatracurium as the non myasthenia patients. However, increased sensitivity to mivacuronium has been reported (25).

Studies confirm that when rocuronium is given in small doses for intubation no adverse or prolonged block was noticed, while others confirm that rocuronium need extreme conversion and is safe to be given in myasthenia patients only if suggamadex is given. Novel strategies for anesthesia with muscle relaxant especially rocuronium are based on the usage of the suggamadex as a reversal agent (27,28).

Although literature in the past was very critical to the usage of muscle relaxants in myasthenia, resent studies are suggesting that short acting NDMR are safe to use (27). However, myasthenia patients' response to relaxants is difficult to predict so these drugs should be used with precautions.

Usage of Reversal Agents

The usage of agents for reversal of muscle relaxants in myasthenia patients remains controversial. Some argue that the presence of anticholinesterases and antimuscarinics will confuse efforts to differentiate weakness due to inadequate neuromuscular transmission from cholinergic crisis in the recovery room. They prefer spontaneous recovery and extubating when the patient has demonstrated adequate parameters for extubating (head lift, tongue protrusion, arm lifting).As of 2010 several authors, argue that the effect of rocuronium should be reversed in all MG with sugammadex (27). Some older reports show results that reversal of neuromuscular block with neostigmine is not needed in all MG patients, when single dose of rocuronium is given (2).

Postoperative Consideration

Based on the preoperative condition of the patients, the surgery extend, the anesthetics used careful extubation should be planned together with adequate pain control, avoidance of drugs that interfere with the neuromuscular transmission. All myasthenia patients should have at least 24 hours of adequate postoperative monitoring. What should every anesthesiologist reconsider, is the possibility of occurrence of cholienergic crisis. Cholienergic may result from excess acetylcholine due to excess of anticholinesterase drugs. Signs are involuntary twitching, fasciculation and weakness. In this situation, if muscarinic effects are present diagnosis is easily made and in the absence of this signs patient should be allowed to recover clinically with the mechanical ventilation support (29).

Conclusion

Myasthenia gravis is a disease that has many implications and aspects for safe anesthesia administration. Controversies are still open to work on, but different anesthesia induction and maintenance techniques with or without NDR are proposed to be safe. The choice of what anesthesia is still left on the anesthetists' experience and knowledge. Additionally, excessive collaboration between the anesthesiologist, neurologist and surgeon are essential for minimizing the postoperative complications.

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МИАСТЕНИЈА ГРАВИС И ОПШТА АНЕСТЕЗИЈА

АПСТРАКТ

Пациентите со мијастенија гравис кои се оперираат се вистински анестезиолошки предизвик. Многу аспекти на болеста, терапијата и коморбидитетите интерферираат со анестетичките лекови на повеќе нивоа. Литературата сè уште не дава силни докази за тоа кој вид на анестетик или анестезија е супериорен кај овие пациенти. Целта на овој ревијален труд е да се изнесат и елаборираат сите можни аспекти кои имаат можно влијание врз исходот на пациентите кои имаат мијастенија, а се оперираат во општа анестезија.

Клучни зборови: мијастенија гравис, општа анестезија.

 ISSN 2545-4366 | UDC : 616.6-089.168.1-009.7

POSTOPERATIVE PAIN MANAGEMENT IN CHILDREN UNDERGOING UROLOGY PROCEDURES

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ABSTRACT

Postoperative care is most commonly shared between health professionals from different disciplines, who should be suitable qualified and aware of the general principles of pain management in children. Initiation of postoperative analgesia is the obligation of every pediatric anesthetist. In consultation with parents/ tutors and other members of the team, one must plan and organize postoperative analgesia prior to surgery. Children should not be discharged from Postoperative Care Units before adequate pain control is established and ongoing analgesia is available. The most severe pain occurs within 24-72 hours after surgery and may persist several days, even weeks. Analgesia can be given per hours in the early postoperative period and then as required. It is also very important that, prior to discharge from the hospital, patients and their parents/tutors should be given advice on how to assess pain and administrate analgesia at home.

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Review of literature

This review discusses the approaches in the treatment of postoperative pain in various urological surgical procedures in children.

When we speak about circumcision, it is frequently regarded as a relatively minor surgical procedure, even though it may be associated with significant postoperative pain and distress. LA techniques including a regional block or topical application can be effective in the early postoperative period (1,2,7).Caudal and dorsal block analgesia were equivalent and superior to subcutaneous 'ring' block and were demonstrated as a low failure and serious complication rate in all studies (1,3-6). According to some studies, a caudal block increased the time to micturition and incidence of motor block in comparison to dorsal nerve block and subcutaneous 'ring' block, but this finding was not reported in other trials (1,3-9). There is still no information about the

ideal agent, dose, or concentration for a caudal block. What has been shown is that the usage of ultrasound for dorsal nerve block improved the efficacy and decreased the incidence of failed blocks (8). When talking about caudal neuraxial analgetics additives, Ketamine combined with LA increased analgesic efficacy, but also increased motor block in comparison to LA dorsal nerve block (11). Pudendal nerve has also been shown as effective for circumcision (9,10). On the other hand, parenteral opioids provided lower analgesic efficacy and increased postoperative nausea and vomiting. NSAID as a single agent was inferior to dorsal nerve block, but when combined, it could decrease supplementary analgesic use compared to other technique in isolation (7).

Due to differences in clinical practice and evidence base, neonatal circumcision is observed separately from circumcision in elder children, and postoperative pain control after it, in this particular group has not yet been well investigated. There was significant failure rate for all techniques studied (12,13). Usage of LA was superior to either placebo or simple analgesic and sucrose (12). Dorsal nerve block appeared to be more efficient than subcutaneous 'ring' block or topical LA (12). As studies have shown, topical local anesthetic agents efficacy was very dependent on the technique of application and time allowed (12). Caudal epidural analgesia has not yet been studied.

Orchidopexy is generally performed on a day-case basis. Caudal LA using 1ml/kg of 0.125-0.25% bupivacaine or 1-1.5 ml/kg or 1-1.5 ml/kg of 0.15-0.225% ropivacaine was most commonly investigated and it was associated with good efficacy, low failure, and serious complication rate, less supplementary analgesic use and lower levels of stress hormones when compared to ilioinguinal nerve block plus local infiltration (16-18). No difference in time to micturition, motor block or nausea and vomiting between the two techniques has been detected (14). A higher volume of local anesthetic, 1ml/kg, did not improve postoperative analgesia, but it was associated less response to cord traction (17). The addition of ketamine 0.25-1 mg/kg as an adjunction to bupivacaine increased analgetic efficacy of neuraxial analgesia, but was associated with 'short-lived psychomotor effects' at higher doses (19). IV dexamethasone added to caudal block increased analgesic efficacy (20). As a part of a multi-modal analgesic technique, transverse abdominal plane (TAP) block using plain LA, was associated with good perioperative analgesic efficacy with no complication in a small case series (21).

Hypospadias surgery may be both relatively superficial and minor suitable for day-case, or more major reconstructive requiring hospital admission overnight or longer, which will influence postoperative analgesia treatment. Caudal LA was most commonly investigated and it was demonstrated as a technique with good efficacy and low failure and serious complication rate (22-25). Most frequently studied was bupivacaine 0.25%, 0.5ml/kg. There were few more comparisons with other local anesthetics and between different concentrations or volumes. According to one study, caudal ropivacaine 0.1% 1.8 ml/kg was more effective with less motor block than ropivacaine 0.375%, 0.5 ml/kg.[27] When talking about caudal neuraxial analgesic additives combined with LA, neostigmine or diamorphine added to caudal bupivacaine increased analgesic

efficacy, but also the rate of nausea and vomiting in two of the studies (26,28). Tramadol added to bupivacaine increased the analgesic efficacy in the first 24 h postoperatively in some studies but did not increase efficacy in other studies, same as clonidine or sufentanil (29-31). In case LA was excluded, ketamine or mixture of ketamine and alfentanil was superior to alfentanil alone, and higher doses of neostigmine increased efficacy, but also postoperative nausea and vomiting (32-33). Summing, further research to identify safety profile, risk/benefit and dose are required, as the use of neuraxial analgesics has not yet been fully studied. According to one study alone, which compared different techniques, tramadol given by the caudal route demonstrated better analgesic efficacy and less postoperative nausea and vomiting than when given intravenously (34). Both intra and postoperatively, epidural analgesia provided good results, regardless of the local anesthetic agent used, bupivacaine, levobupivacaine, or ropivacaine. In one study there was an exclusion rate of 10% (35). Adding fentanyl to ropivacaine increased analgesic efficacy for postoperative epidural infusions at low concentrations of ropivacaine, 0.125% (15). For distal hypospadias repair, dorsal nerve block was shown as effective. Some of the research pointed that placing the block prior to surgery improved analgesic efficacy (36). Spinal intrathecal neuraxial analgesia using hyperbaric 0.5% bupivacaine is effective both intra and postoperatively. Adding morphine to the LA increased the efficacy without increasing side effects in one study (37). Compared with a caudal block alone in one study, paracetamol given alongside, did not improve analgesia in the first six postoperative hours (38). Overall, in clinical practice, a multi-modal analgesia for hypospadias surgery is suggested, with regular supplementary analgesia given in the postoperative period, but there is still no sufficient data to evaluate its use in either early or late postoperative period.

When talking about major urology procedures, including pyeloplasty, nephrectomy, heminephrectomy, bladder augmentation/reconstruction, ureteric reimplantation etc., LA techniques are commonly used. Comparison with parenteral opioid techniques is limited, and less good evidences exist with regard to the optimum analgesic regimen. Epidural LA, using perioperative ropivacaine infusions, have shown good analgesic efficacy with low pain scores and complication rates (42, 43). The addition of fentanyl or sufentanil to ropivacaine, and fentanyl or butorphanol to bupivacaine did not show any difference in efficacy or pain scores between these regimens (39, 42). Postoperative epidural ropivacaine infusions in comparison to regular bolus tramadol or oxycodone plus paracetamol and NSAID did not show any difference in pain scores up to 48 hours, but did increase rescue analgesia between 48 and 72 hours (43). Caudal analgesia with LA plus clonidine or opioid has shown good efficacy in children undergoing uretric reimplantation. No difference has been shown in efficacy or pain scores from adding clonidine, morphine, or hydromorphone to caudal ropivacaine 0.2% plus epinephrine. Patients receiving clonidine experienced fewer side effects [40]. A ‘Single-shot’ intraoperative paravertebral block with levobupivacaine and paracetamol postoperatively, was associated with low pain scores and low opioid use in the early postoperative period in patients undergoing major renal

procedures (41). When talking about wound infiltration, a multimodal analgesic technique using LA infiltration together with opioids, NSAID, and paracetamol was associated with low pain scores in children undergoing pyeloplasty and ureteric reimplantation (44, 45).

To summarize the story, initiation of postoperative analgesia is the obligation of every pediatric anesthetist. Liaising with patients and their families/tutors, surgeons, and other members of the team they should provide postoperative care to ensure that pain is assessed and adequate ongoing analgesia is administered. In order to provide safe, sufficiently potent, and flexible pain relief with a low incidence of side effects, postoperative analgesia should be in accordance with developmental age, surgical procedure, and clinical settings.

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 ISSN 2545-4366 | UDC : 616.383.9-007.43-089.819-089.5

THE ANALGESIC EFFECT OF ULTRASOUND-GUIDED TRANSVERSUS ABDOMINIS PLANE (TAP) BLOCK FOR LAPAROSCOPIC BILATERAL INGUINAL HERNIA REPAIR

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ABSTRACT

Background: Transversus abdominis plane (TAP) block is a (new) regional anesthetic technique that provides analgesia to the parietal peritoneum, as well as the skin and muscles of the anterior abdominal wall, by introducing local anesthetic into the neuro-fascial plane between the internal oblique and the transversus abdominis muscles. Pain after laparoscopic bilateral inguinal hernia surgery can be moderate to severe and can result in prolonged hospital stay, unanticipated hospital admission and delayed return to normal daily activities. We evaluated the efficacy of TAP block in patients undergoing laparoscopic bilateral inguinal hernia repair in a randomized controlled clinical trial.

Material and methods: Sixty patients undergoing laparoscopic bilateral inguinal hernia repair were randomized to undergo standard care (n=30) or to undergo a bilateral TAP block with bupivacaine (n=30). All patients received standard anesthetic, and after induction of anesthesia, the TAP group received an ultrasound-guided bilateral TAP block. Each patient was assessed after operation at 2, 6, 12 and 24 hours after surgery.

Results: Bilateral ultrasound-guided TAP block significantly reduced postoperative visual analogue scale (VAS) pain scores at rest and on moving, reduced ketonal and tramadol postoperative consumption and reduced incidence of PONV in the TAP block group after surgery compared to control group.

Conclusion: Bilateral ultrasound-guided TAP block provides effective postoperative analgesia during the 24 postoperative hours after laparoscopic bilateral inguinal hernia repair.

Keywords: inguinal hernia, laparoscopy, pain, TAP block, ultrasonography.

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Introduction

Transversus abdominis plane block (TAPB) is a (new) regional anesthetic technique which provides analgesia to the parietal peritoneum, skin and muscles of the anterior abdominal wall (1). It was first described in 2001 by Rafi as an analgesic technique for abdominal incisions by using the technique of "loss of resistance" in the lumbar triangle of Petit (2). TAPB technique is a regional anesthesia technique in which a local anesthetic is applied in the space between m.obliquous internus and m.transversus abdominis. The pain of the anterior abdominal wall is transmitted by the anterior branches of thoracolumbar nerves from Th7 to L1 (1). Ultrasound-guided TAPB was first described in 2007 by Hebbard et al (3).

Inguinal hernia repair is one of the most commonly performed surgical procedures worldwide. Open and laparoscopic herniorraphy are both used, but since the evolution of surgical tools and new surgical skills in the 1990's, laparoscopic procedure has become more prevalent. The prevalence of laparoscopies is due to the advantage of fewer complications, decrease in hospital length of stay, speed of recovery, fast return to activities of daily living and work (4). Generally laparoscopic surgeries are known to be relatively less painful, but still require pain management.

Pain after laparoscopic inguinal hernia surgery can be moderate to severe, interfering with return to normal activity. There are some opinions that the inadequate treatment of postoperative pain can be a risk factor for persistent pain after surgery of inguinal hernia (5). Preoperative and postoperative pain following an operation are mostly accompanied by the appearance of chronic pain, and ranges from 0 to 54% of cases (6,7). The study of Nienhuijs et al. indicates that 11% of patients suffer mostly from chronic pain after surgery of inguinal hernia with a mesh and almost 1/3 of the patients have limitations in performing daily activities due to chronic pain (8).

Material and methods

In this prospective, randomized and controlled study were examined 60 male patients aged 20-60 years, scheduled to laparoscopic bilateral inguinal hernia surgery and ASA classification 1-2. Patients were excluded if there was a history of allergy to bupivacaine, ketonal and tramadol, coagulopathy, infection at the needle insertion site and patients with ASA classification 3-5. The study was performed at the University Clinic of TOARILUC - KARIL, Clinical Campus "Mother Teresa" - Skopje, from March 2014 to December 2016. TAP block was performed by one investigator and surgery was performed by one surgeon. Patients were divided into two groups of 30 patients: one group to undergo USG-TAPB with 20ml 0.25% bupivacaine on both sides (TAPB or N1 group) and the other group to receive standard care (control or N2 group). All patients received a standard general anesthesia with standard monitoring. Anesthesia was induced with midazolam 0.04mg/kg, fentanyl 0.002mg/kg, propofol 1-2mg/kg and rocuronium 0.6mg/kg. Anesthesia was maintained with oxygen, air and propofol 50-200microgr/kg/min. Standard monitoring include continuous electrocardiography, noninvasive blood pressure every 5 minutes, pulse oxymetry, heart rate and capnometry. Additionally fentanyl 0.5-1microgr/kg

was injected to control blood pressure and heart rate within 20% of baseline. During the study prophylactic antiemetic were not given.

After induction of anesthesia, the patients from the first group had the TAP block performed under ultrasound guidance on the both sides (right and left), using Siemens Acusion X300 system (Siemens, Germany) ultrasound device and high-frequency (6-13MHz) linear transducer, covered with sterile plastic sheath. The skin was prepared with 10% betadine solution. After draping the needle insertion site, the probe was placed on the anterolateral abdominal wall between the iliac crest and the subcostal margin. After identification of the neuro-fascial plane between the internal oblique and the transversus abdominis muscle, a 22G x 4" 50mm needle mm (B. Braun, Stimuplex, Germany) was advanced by the "in-plane" technique. When tip of the needle reached the TAP between the internal oblique and transverses abdominis muscles, 1 ml of 0.25% bupivacaine was injected into the patients of the TAPB (N1 group). After negative aspiration the entire amount of the syringe was given with occasional aspiration. By giving local anesthetic on the US-monitor was seen the spread of the local anesthetic in TAP space, as a dark oval-shaped hypoechoic fluid pocked at TAP. The opposite side was performed in the same manner. End-tidal carbon dioxide (CO_2) was maintained at 30-35 mmHg. Carbon dioxide infusion pressure was set at 12 mmHg, a mesh was placed and secured with a tacker.

After the operation, patients were transferred to the postanesthesia care unit (PACU) and stayed there for 2 hours. There, the patients were monitored. If the VAS score was over 3, then 100 mg of ketonal was administered, whereas if the VAS score was over 6, then 100 mg tramadol was administered. The presence and severity of pain and postoperative nausea and vomiting were assessed by an investigator blinded to group allocation. These assessments were performed in the recovery suite 2, 6, 12 and 24 hrs after operation. All the patients were asked to give scores for their pain at rest and on moving, and for the nausea and vomiting at each time point. Pain severity was measured using a visual analogue scale (VAS). Rescue antiemetic were offered to any patient who had complained of nausea or vomiting.

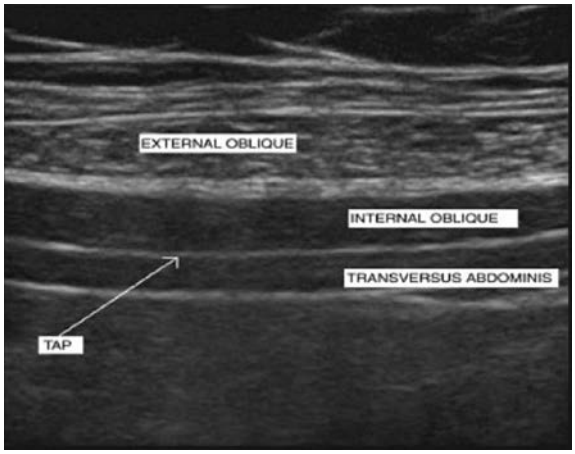

Fig.1: TAP block as seen via ultrasound: we can see the three muscle layers under ultrasound

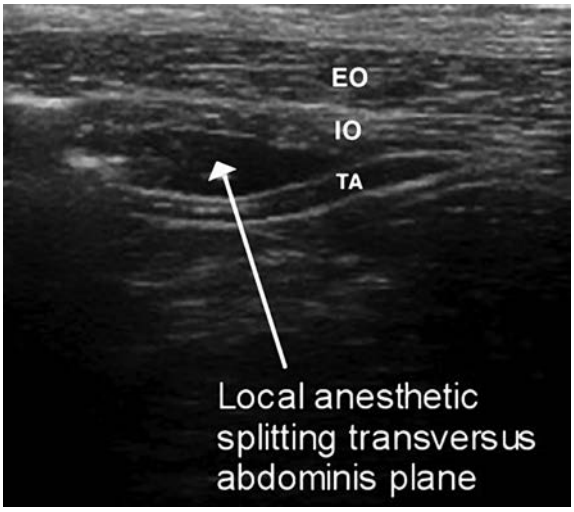

Fig.2: We can see the spreading of the local anesthetic into the TAP between MOI and MTA.

The primary outcome measure in this study was the VAS pain scores at rest and on moving 2, 6, 12 and 24 hours after the operation. The secondary outcome measure included the postoperative opioid consumption. The third outcome measure included the incidence of postoperative nausea and vomiting (PONV). All these outcomes were systematically assessed by a member of the research team blinded to the group allocation.

Results

Sixty patients entered this study. Thirty patients were randomized to receive general anesthesia and bilateral USG-TAPB with 20ml 0.25% bupivacaine (N1) and other thirty were randomized to receive standard care (N2).

In Table 1 average values of VAS score are given in patients who received general anesthesia with and without bilateral USG-TAPB, at rest 2, 6, 12 and 24 hours after the operation. In Table 2 mean values of VAS score are given in two examined groups on movement after 2, 6, 12 and 24 hours after the surgery. Analysis showed that VAS score is significantly higher in patients who received only general anesthesia at rest and on movement, as well as after 2, 6, 12 and 24 hours after operation, versus patients who received general anesthesia + bilateral USG-TAPB.

Table 1*: Mean values of VAS score in patients who received GA + bilateral TAPB and only GA at rest 2, 6, 12 and 24 hours after surgery.*

TIME	GA + BILATERAL USG-TAPB (N1)				GENERAL ANESTHESIA (GA) (N2-CG)			
	AVERAGE	SD	MIN	MAX	AVERAGE	SD	MIN	MAX
After 2 h	0,36	0,30	0	1	4,07	0,78	3	5
After 6 h	0,67	0,57	0	2	3,50	0,77	3	5
After12h	0,49	0,47	0	2	3,56	0,62	3	5
After24h	0,53	0,51	0	1	4,36	1,24	3	6

Table 2*: Mean values of TAP block in patients who received GA + bilateral TAPB and only GA on movement 2, 6, 12 and 24 hours after surgery.*

TIME	GA + BILATERAL USG-TAPB (N1)				GENERAL ANESTHESIA (GA) (N2-CG)			
	AVERAGE	SD	MIN	MAX	AVERAGE	SD	MIN	MAX
After 2h	0,67	0,60	0	2	4,03	0,85	3	6
After 6h	0,61	1,67	0	2	4,06	1,11	3	6
After12h	0,81	0,96	0	3	4,17	1,02	3	6
After24h	0,60	0,72	0	2	5,03	0,76	4	6

There is a significant difference between two examined groups (Mann-Whitney U Test: Z = -4,435 p = 0,00009) in the need for opioids postoperatively. The patients who received general anesthesia had more need for opioids (66.67%) versus patients who received general anesthesia+bilateral USG-TAPB (they had no need for opioids after surgery).

Table 3*: Distribution of examiners of two examined groups according to the need of opioids postoperatively.*

OPIOIDES POSTOPERATIVELY	GA+ BILATERAL USG-TAPB (N1)	GA (N2 – CG)	TOTAL
NO	30 (100,0%)	10 (33,33%)	40
YES	0 (0%)	20 (66,67%)	20
TOTAL	30 (100,0%)	30 (100,0%)	60

There is a significant difference between two examined groups (Mann-Whitney U Test: Z = -3,418 p = 0,0063) compared to the nausea postoperatively. The patients who received general anesthesia had significantly larger occurrence of nausea versus patients who received general anesthesia+bilateral USG-TAPB. Nausea was registered only in one patient in GA+bilateral USG-TAPB group.

There is a significant difference between two examined groups (Mann-Whitney U Test: Z = -3,226 p = 0,0012) compared to the vomiting postoperatively. Patients who received general anesthesia were more significant outbreak of vomiting versus patients who received GA+bilateral USG-TAPB. Vomiting was not registered in patients who received GA+bilateral USG-TAPB.

VAS pain scores at rest and on moving were significantly lower in the TAPB group. Postoperative ketonal and tramadol consumption was lower in patients who received bilateral USG-TAPB.

Discussion

The use of ultrasound-guided sensory block of the anterior abdominal wall with local anesthesia for postoperative pain relief is an attractive method because of its simplicity and safety. Effective analgesia has shown to reduce postoperative stress response, reduce postoperative morbidity

and accelerate recovery from surgery. Another benefit of effective regional analgesic technique (TAPB) is reducing the intensity of pain, reduces incidence of side effects of analgesics and patients feel comfortable. Pain that occurs after laparoscopic bilateral inguinal hernia repair is quite underestimated, and its untimely and inadequate treatment often leads to prolonged and chronic pain that limits daily activities. TAP block is a very promising technique and has a major role in the management of postoperative pain as part of a multimodal analgesic strategy. TAPB provides effective analgesia during the first 24 hours after surgery operation in the lower abdomen or pelvis (1).

In our study we examined the effect of bilateral USG-TAPB performed under laparoscopic bilateral inguinal hernia repair. We got a statistically significant reduction in the values of VAS scale at rest and in moving in the TAPB group compared to the control group. In the TAPB group (N1) patients had no need for opioids after surgery (0% of the patients), postoperative nausea is minimized (only 1 patient had nausea or 3.33% of the patients) and none of the patients had vomiting (0%) during the first 24 hours postoperative. In the control group (N2), 66.67% of patients had needs for opioids in the postoperative period, 40% of them had nausea and 30% had vomiting in the first 24 hours postoperatively. TAP block reduces the need for intravenous ketonal and tramadol in the postoperative period. This reduction in the need for opioids is resulting in reducing the number of side effects of opioids.

Arora et al., included 71 patients for unilateral/bilateral laparoscopic hernia repair and the result was TAP block reduced postoperative pain up to 24 hours after laparoscopic hernia repair (9).

In the study by Kim et al., 40 patients were scheduled for a totally extraperitoneal (TEP) hernia repair under general anesthesia with and without TAPB. The USG-TAPB in patients that had undergone TEP reduced postoperative pain scores and the fentanyl requirement in the recovery room. Also, pain scores on coughing were reduced until postoperative 8 hours (10).

Aveline et al., in their study included 273 patients for unilateral open inguinal hernia repair with mesh. They reported that USG-TAPB controls pain on the day of surgery much better than the blind ilioinguinal-iliohypogastric nerve block in open inguinal herniorraphy (11).

Barisin et al., described the display case of high risk cardiac patient, ASA 4 status, with severe CAD and prior LAD PTCA, AVR, severe MR and TR 3+, hypertension, diabetes mellitus and severe stenosis of both femoral arteries, to whom should be done unilateral inguinal hernia repair. General anesthesia in such patient is highly risky. The patient received TAP block and a block of n. ilioinguinalis and n.iliohypogastricus performed under ultrasound. As a local anesthetic was used 25 ml 0.5% levobupivacaine. The operation was successfully performed, the patient was pleased and happy and postoperative sensory block lasted for 18 hours (12).

Conclusion

TAPB is becoming quite popular because of its relative simplicity and efficiency. In this technique there is a single bolus injection of local anesthetic into the TAP space that provides very effective

postoperative analgesia in the first 24 hours. As a component of multimodal analgesia, the TAPB reduces the needs for intravenous given opioids and subsequently reduces the opioid-related side effects.

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АНАЛГЕТСКИ ЕФЕКТ НА TRANSVERSUS ABDOMINIS PLANE (TAP) БЛОК ИЗВЕДЕН ПОД УЛТРАЗВУК КАЈ ЛАПАРОСКОПСКА ОПЕРАЦИЈА НА ОБОСТРАНА ИНГВИНАЛНА КИЛА

АПСТРАКТ

Вовед: Transversus abdominis plane (TAP) блокот е (нова) регионална анестезиолошка техника којашто обезбедува аналгезија на париеталниот перитонеум, како и на кожата и мускулите на предниот абдоминален ѕид со аплицирање на локален анестетик во просторот помеѓу m.obliquous internus и m.transversus abdominis. Болката после лапароскопска операција на обострана ингвинална кила може да биде од средна до јака и може да доведе до продолжен престој во болница, непредвиден болнички прием и одложено враќање кон нормалните секојдневни активности. Ние го следевме аналгетскиот ефект на TAP блокот кај пациенти кои се предвидени за лапароскопска операција на обострана ингвинална кила во рандомизирана контролирана клиничка студија.

Материјал и методи: Шеесет пациенти кои беа предвидени за лапароскопска операција на обострана ингвинална кила беа рандомизирани да добијат стандардизирана општа анестезија (n=30) или да добијат општа анестезија и обостран TAP блок изведен под ултразвук со bupivacaine (n=30). Сите пациенти добија стандардизирна општа анестезија и после вовед во анестезија на TAP групата и беше аплициран обостран TAP блок изведен под ултразвук. После хируршката интервенција, секој пациент беше иследуван на 2, 6, 12 и 24 часа после операцијата.

Резултати: Обостраниот TAP блок изведен под ултразвук значително ја намалува визуелната аналогна скала (VAS) за болка во постоперативниот период при мирување и во движење, ја намалува потребата за кетонал и трамадол во постоперативниот период и ја намалува појавата на постоперативно гадење и повраќање кај TAP блок групата после операција во споредба со контролната група.

Заклучок: Обостраниот TAP блок изведен под ултразвук обезбедува ефективна постоперативна аналгезија во првите 24 часа после лапароскопска операција на обострана ингвинална кила.

Клучни зборови: болка, ингвинална кила, лапароскопија, TAP блок, ултразвук.

 ISSN 2545-4366 | UDC: 616.728.2-001.5-089.168.1-06:616.12

INFLUENCE OF CARDIAC RISK PREDICTORS ON SURGERY OUTCOME IN ELDERLY WITH HIP FRACTURE

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ABSTRACT

Introduction: Patients with hip fracture are usually older and stress of trauma and surgery may increase cardiac morbidity and mortality.

The aim of this study was to compare the influence of cardiac risk factors on surgical outcome in elderly patients with hip fracture.

Methods: 120 patients with hip fracture older than 70 years with previously defined high or low per operative cardiac risk according to ACC/AHA guidelines were included and were assigned to two groups of 60 patients: Risk group –patients with high cardiac risk; and NR (non risk) group without or with low cardiac risk. Recipients from the both groups were pain relief with intravenous analgesia: Niflam 2 x 100 mg/iv and Tramadol 50 mg/iv every 8 hours;

As an end point of the study were registered the incidence of cardiac events in both groups: cardiac death, myocardial infarction, congestive heart failure, unstable angina and new-onset atrial fibrillation. In all patients was determined pain intensity by using Verbal Descriptive Scale as well as the side effects.

Results: Recipients with high cardiac risk has higher incidence of postoperative cardiac events versus patients with low cardiac risk (Risk group 46.6% vs. 15% in NR group) and the same result is with mortality rate (10% in Risk group vs. 0% in NR group). The values of VDS were equal in recipients from both groups.

Conclusion: Patients with hip fracture are classified as a high risk patients according the presents of high risk cardiac predictors, and have significantly higher incidence of postoperative cardiac morbidity and mortality.

Key words: perioperative cardiac risk; elderly; hip fracture; ACC/AHA classification.

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Introduction

Hip fractures occur the most commonly in elderly individuals as a result of minimal trauma and vertical falls (1). People of those age groups often suffer from chronic illness and they usually use the huge number of medications (2, 3). After gaining a hip fracture as a result of fall of these patients, complications such as acute respiratory infections are very often (4,5). In the early 1970s[4], the reported causes of in-hospital death were bronchopneumonia (25–49%), pulmonary embolism (12–19%), and cardiac events (12–16%). Later studies (5, 6) reported a decline in death from bronchopneumonia, with cardiac events as the principal cause of death (35–63%) in an unselected group of patients presenting with fractured femur. However, a large prevalence of morbidity and mortality in elderly is expected, because this population which in huge number suffers from coronary artery disease (CAD) rapidly is growing and by that so the number of necessary surgical interventions is growing (7,8,9).

Hip fractures cause a significant pain in the preoperative and postoperative period, which increases in an attempt to move the injured or operated leg (8,9,10). Trauma and pain induce "a complex response to stress", which is characterized by hormonal and inflammatory changes that lead to immunosuppression (11,12,13). Appropriate assessment of cardiac risk of these adult patients is very important for their perioperative treatment and assessment of their short-term and long-term surgical outcome (14-17).

The aim of this study was to compare the influence of cardiac risk factors on surgical outcome in elderly patients with hip fracture.

Material and Methods

This study was conducted as a prospective, controlled clinical study, at the University clinic for Traumatology, Orthopedics, Anesthesia, Reanimation and Intensive Care and the Urgent Center in Skopje, in the period from January 2015 to Mart 2016. The Clinical Research Ethics Committee of the University Clinic for Traumatology, Orthopedics, Anesthesia, Reanimation and Intensive Care and Urgent Center – Skopje and the Ethics Committee of the Faculty of Medicine – Skopje, granted ethical approval. Informed consent was obtained from each patient.

Inclusion criteria for the study: the study included 120 patients older than 70 years and ASA III and IV, surgically treated due extra capsular hip fracture (pertrochanteric, subtrochanteric or basocervical femoral fracture – for a fixation with DHS or DCS plate or PFN);

Exclusion criteria for the study: contraindications for performing the spinal block (no informed consent from the patient, history of coagulopathies, anticoagulant therapy <12h for low molecular heparin and <6h for heparin, infection on the puncture site, neurological diseases, high intracranial pressure and hipovolemia), malignancy; dementia / confusion; local anesthetic allergy or allergy on tramadol or niflam.

Preoperatively, the following demographic characteristics were registered in all patients: age, gender, body weight (kg), ASA status (classification according to the American Society of

Anesthesiologists), duration of surgery, and diagnosis (fracture femoris pertrochanterica, fracture femoris subtrochanterica fracture basocervicalis femoris).

After the admission on traumatology clinic, patients were classified in two groups: **Risk group -** patients with previously diagnosed CAD (as indicated by previous myocardial infarction, typical angina, atypical angina with positive stress test results or angiographic), or were at high risk for CAD stratificated according to ACC/AHA - American College of Cardiology/American Heart Association criteria and **NR group** (non risk patients) with low cardiac risk according to ACC/AHA criteria.

Risk predictors according to ACC/AHA - American College of Cardiology/American Heart Association for per operative cardiac morbidity

A. Major predictors: unstable coronary syndromes (unstable or severe angina. recent MI), decompensate HF, significant arrhythmias, severe valvular disease.

The presence of one or more of these conditions mandates intensive management and may result in delay or cancellation of surgery unless the surgery is emergent.

B. Intermediate predictors: history of ischemic heart disease, history of compensated or prior HF, history of cerebrovascular disease, diabetes mellitus and renal insufficiency.

C. Minor predictors: advanced age (greater than 70 years), abnormal ECG (LV hypertrophy. left bundle-branch block. ST-T abnormalities), rhythm other than sinus and uncontrolled systemic hypertension.

Functional capacity. Estimated Energy Requirement for Various Activities is MET = metabolic equivalent, which is measure for heart metabolic demand during different daily activates, shown in Table 1.

Table 1. *Functional capacity.*

1 MET	Self care?
	Eating dressing, or using the toilet?
	Walking indoors and around the house?
	Walking one to two blocks on level ground at 2 to 3 mph?
4 METs	Light housework (e.g., dusting, washing dishes)?
	Climbing a flight of stairs or walking up a hill?
	Walking on level ground at 4 mph?
	Running a short distance?
	Heavy housework (e.g., scrubbing floors, moving heavy furniture)?
	Moderate recreational activities (e.g., golf, dancing, doubles tennis, throwing a baseball or football)?
>10 METs	Strenuous sports (e.g., swimming, singles tennis, football, basketball, skiing)?
MET - metabolic equivalent; mph = miles per hour	

Persons with major predictors and 1- 3 MET-s have high postoperative cardiac risk while these with minor predictors and MET ≥ 4 have low postoperative cardiac risk (in our study they are signed as non risk patients).

Surgery-Specific Issues. In this study, were included elderly patients for fixation of hip fracture, which is urgent, surgery intervention classified as an intermediate risk surgery with risk of 5%.

The surgery in all patients was performed up to 72 hours after the admission, under spinal anesthesia, with 12 mg Bupivacaine 0,5% and Fentanyl 0.02 μg at the L2–L3 or L3–L4 interspace. ECG, heart rate, peripheral oxygen saturation, non-invasive pressure and urine production were per operatively routinely monitored. All patients had pain relief by administrating 100 mg Niflam iv/twice per day and Tramadol 50 mg iv/twice per day. If any of the patients felt moderate pain, additional 100 mg Niflam was given.

On admission to the traumatology ward, a detailed history was obtained, a physical examination was performed, and all cardiovascular medications were recorded.

1. In patients from the both groups all **cardiovascular medications** were recorded.

2. The **degree of analgesia** was monitored: 2, 12, 24 and 48 hours after the surgery, by using Verbal Descriptive Scale (0 - without pain, 1 - moderate, 2 – moderate to severe, 3 – severe, and 4 - unbearable pain). The degree of analgesia was assessed at rest and during passive flexion of the hip.

3. **Study end points:** The primary end point of the study combined cardiac death, myocardial infarction (elevation of the troponin -T concentration, either new Q waves (duration ≥ 0.03 s) or persistent changes (4 days) in ST-T segment), unstable angina (defined as severe precordial chest pain that lasted 30 minutes or more and was unresponsive to standard therapeutic maneuvers, associated with ST-segment or T-wave changes without the development of Q waves or cardiac enzyme abnormalities), congestive heart failure (CHF) (defined by clinical - shortness of breath, rales, jugular venous distention, peripheral edema, third heart sound and radiologic - cardiomegaly, interstitial edema, alveolar edema, signs that required a change in medication involving at least treatment with diuretic drug) and new-onset atrial fibrillation in the post operative period (required 12-lead electrocardiographic confirmation). Cardiac death was defined as death due to myocardial infarct, CHF, or arrhythmia.

Statistical Analyses. Into series with numeric values and homogeneous distribution, the descriptive parameters were assessed, i.e. measures of central tendency (average, standard deviation, minimum and maximum values of the analyzed parameters). Into series with attribute marks, the structural percentages were calculated (relations, proportions). For determination of significant differences, the independent sample tests were utilized, depending on data distribution (Chi-square test, Yates corrected Chi-square test, Fisher exact test, Kolmogorov-Smirnov test, t-test for independent samples, Mann-Whitney U test and the difference between two proportions). Statistically significant and meaningful were values of $p < 0.05$, and highly significant values of $p < 0.01$.

Results

Basic demographic characteristics of patients are shown in Table 2.

Female respondents dominated in both groups, but distribution differences between the both analyzed groups didn't show statistical significant difference. There were no significant

differences in distribution of all other demographic characteristics between patients in both groups. Both analyzed groups were homogenous considering all demographic characteristics.

In Table 3 it is shown the distribution of the patients who were treated and those who were not treated with cardiologic medications.

Table 2. *Demographic characteristics.*

	SA	EDC	p level
Gender male/female	20 / 10	25 / 5	> 0.05
Age (years)	77.63±6.4	80.23±5.2	> 0.05
Body weight (kg)	67.97 ± 8.6	68 ± 9.1	> 0.05
ASA status III. IV	20/10	21/9	> 0.05
Type of fracture pertr/subtr/basocerv	25/2/3	23/4/3	> 0.05
Duration of surgery (min)	111.5 ± 11.1	105.67 ± 8.4	> 0.05

Table 3. *Distribution of the patients according the cardiologic therapy usage*

Cardiac therapy	Risk	NR
with therapy	42 (70 %)	41 (68,3 %)
without therapy	18 (30 %)	19 (31,6 %)
p	> 0.05	

There was no difference in distribution of the both groups, and the results show that 70% of the patients from the both groups received therapy, while, only 30% of both groups were untreated.

Figure 1 and figure 2 show the results of analgesia according to Verbal descriptive scale at rest and during passive hip flexion.

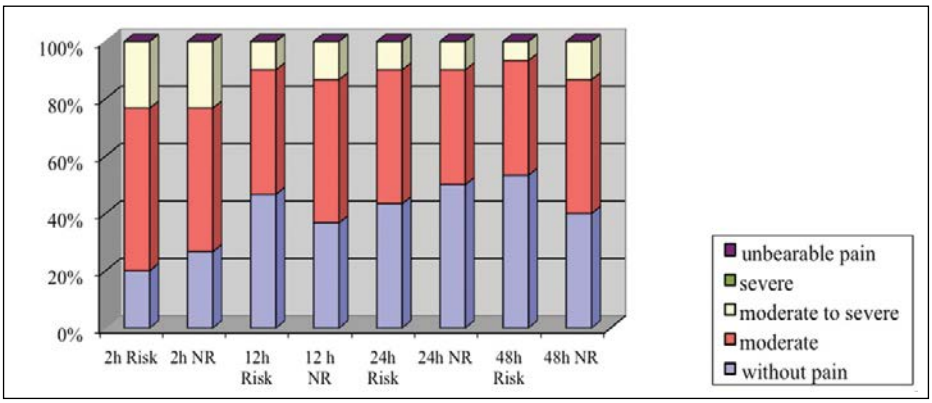

Figure 1. *Verbal descriptive scale during the rest – comparison of the groups*

2h	U=280	Z= -0,9	p=0,5
12h	U=308	Z= 0,0	p=1,0
24h	U=240	Z=- 1.2	p=0,3
48h	U=300	Z=- 0,02	p=0,9

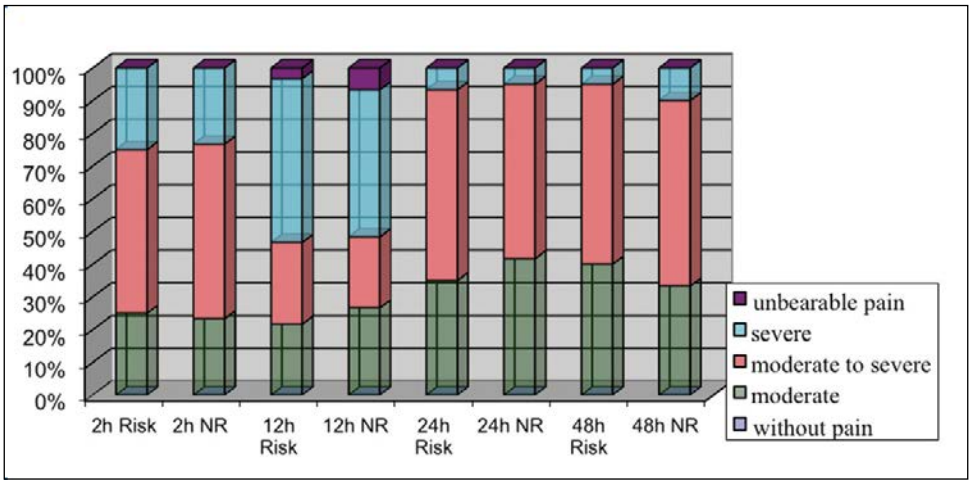

Figure 2. *Verbal descriptive scale during passive hip flexion – comparison of the groups*

2h	U=300	Z= 0,02	p=0,9
12h	U=312	Z= 0,0	p=1,0
24h	U=270	Z=-.8	p=0,4
48h	U=250	Z=- 1,1	p=0,2

There was no difference in distribution of the patients in the both groups, and they all had the same level of pain relief.

In Table 4 are shown cardiac complications, their comparison between the groups and their statistical analyses.

Table 4. *Cardiac complications*

Cardiac complications	Risk	NR
Cardiac death	6 (10%)	0
Total cardiac death	6 (5%)	
Myocardial infarction	4 (6.67%)	2 (3.33%)
Congestive heart failure	10 (15%)	4 (6.67%)
Unstable angina	6 (10%)	0
New-onset atrial fibrillation	8 (12%)	4 (6.67%)
Total complications	28 (46.6%)	10 (15%)
Statistical analyses	Risk vs. NR Chi-square 10.3 df=1 p=0.001** p<0.01	
Total complications (for both groups)	38 (31.6%)	

Discussion

The major finding of this study was that the incidence of postoperative cardiac complications and mortality were higher in high-risk patients with fractured hip versus those with low risk. The combined incidence of these cardiac events was 31.6% (38 from 120 patients) in both groups, actually 28 patients with cardiac complications were from high-risk group versus 10 patients with cardiac complications from non-risk group. In our study, in all examined patients, the surgery was performed in first 72 hours after the admission, under the same, spinal anesthesia and all of them

received general intravenous analgesics as a postoperative pain relief method. In this study, we examined only the influence of different cardiac predictors on surgery outcome, incidence of cardiac complications and mortality. The results of postoperative cardiac morbidity in this study is similar to the results of Matot et al.[15] and Auerbach et al.[14], who examined incidence of cardiac events in hip fracture patients who were pain relief by using general or continuous epidural analgesia. In both studies, the authors come to the conclusion that the incidence of cardiac complications was higher in patients with general versus continuous epidural analgesia (32.3% with general analgesia group versus 5.8% patients in group with continuous epidural analgesia). Per operative cardiac risk in this study was determined by using cardiac predictors according to ACC/AHA criteria (7). Matot et al.[15] also conduct their study on the selected group of patients with high cardiac risk, respectively respondents had either known CAD (as indicated by previous myocardial infarction, typical angina, atypical angina with positive stress test results, or angiographic or scintigraphic evidence of CAD), or were at high risk for CAD (the patient had at least two of the following cardiac risk factors: age $\geq$ 65, hypertension, current smoking and diabetes mellitus). Incidence of postoperative cardiac events in group of patients with general analgesia is similar with our results.

From the other side, Scheinin et al.[9] demonstrated that per operative analgesic management with continuous epidural analgesia, started preoperatively, reduced the amount of myocardial ischemia in elderly patients with hip fractures. In contrast to our study, however, an unselected group of patients was included in that study and the study end point did not include clinically relevant adverse cardiac events, such as CHF or unstable angina and dysrhythmias. The results from these previous studies[9, 14, 15] may not be relevant to the present study, because in these three studies, the respondents were divided in two groups with two different types of analgesia (intravenous and continuous epidural). However, these results show that effective analgesia affects the postoperative cardiac morbidity, probable, because it decreases stress reaction.

In our study, incidence of mortality as a result of cardiac complications was 5% in all 120 examined patients, but all six patients who died were only from high risk group, so mortality rate actually was 10%. However, this event rate is consistent with earlier studies that reported in-hospital mortality rates ranging from 1.4% to 12% in unselected groups of patients with hip fractures (2-6). In the early 1970s, Riske et al.[4] as most frequent reported causes of in-hospital death were bronchopneumonia (25–49%), pulmonary embolism (12–19%), and cardiac events (12–16%). Roche et al.[5] in their prospective cohort study, conducted over the nonselective group of patients with hip fracture, as a main reason for in-hospital death, reported: bronchopneumonia (46%), cardiac events (23%) and pulmonary embolism (14%). These authors noted that death from cardiac origin occurred early after fracture, peaking at 2 days after injury. Muhm et al.[6] in their study from 2013 reported a decline in death from bronchopneumonia, with cardiac events as the principal cause of death (35–63%) in an unselected group of patients presenting with fractured femur. Our results in the high-risk patients are therefore consistent with these observations in an unselected group of patients presenting with hip fracture.

Hip fracture surgery is emergency surgery and in our study it was performed up to 72 hours after the admission of the patients. Emergency surgery has been reported to correlate independently with development of life-threatening or fatal cardiac complications, according to ACC/AHA guidelines (7). Moreover, approximately half of the patients presenting with a hip fracture are older than 80 years (1), have a history of cardiovascular disease, and have ASA physical status III–V. These elderly patients might therefore have an especially poor tolerance for the complications that are likely to occur during the stressful period of an emergency hospitalization (13). Juelsgaard et al.[17] conducted a prospective study of cardiac mortality in patients with hip fracture, who had CAD. In these study, two patients (5%) who suffered from cardiac failure and myocardial infarction died. In our study, 31.6% from the patients had adverse cardiac outcomes during their in-hospital stay, and 5% from these patients died. It is expected that morbidity and mortality will increase because of the rapid aging of the surgical population and greater prevalence of more advanced CAD (7).

Arinzon et al.[13], Beattie et al.[16] and Juelsgaard et al.[17], in their studies, analyzed the postoperative cardiac morbidity and mortality depending time of the operation after the admission and they have demonstrated a clear advantage in early surgery. Nevertheless, the current recommendation is that the patients' age and their comorbidities are the greatest risk factors, which influence the short-term and long-term outcome. Current recommendations are that it should be given enough time for studying and preparing patients with comorbidities (10,11).

In all recipients in our research was recorded cardiologic therapy which was received before the injury and they continued with the same medication in the whole peri-operative period, unless necessary to be changed. In the both groups 70% of the patients were treated with cardiologic medications, while 30% of them, in the both groups did not have cardiologic therapy, although, according the clinical examinations, these patients had cardiologic comorbidities. In these patients, according the standard examinations (hematological analyses, ECG and chest x-ray), if there was need, new cardiologic therapy was admitted and the cardiologist was consulted. If there was need, also, additional diagnostic examinations were conducted, especially heart ultrasound. Most frequent recommendation from the cardiologist for these high-risk patients was "to continue with already recommended therapy" and "there is no contraindication for surgical treatment. Our approach to these adult patients with high and even low cardiac risk is in full compliance to the recommendations in the studies of Guryel et al.[10] and Katsanos et al.[11], who during the evaluation of the patients at high cardiac risk for non cardiac surgery recommended the inclusion of appropriate anti-edematous and cardiology therapy, depending on type of heart disease, while, from diagnostic methods, as well as in our study, they recommend echocardiography. Within the ACC/AHA recommendations for perioperative preparation of cardiac patients for non-cardiac surgery from 2007 (7), the results of cardiology consultations were investigated, which were again, conducted in order to set up common surgical, anesthetic and cardiac consent and recommendation for treatment of 55 patients older than 50 years. The

most common recommendations of 40% of cardiology consultations were "to proceed with the case", "no contraindication for surgery" and "to continue with existing drug therapy." Review of 146 medical consultations suggests that the most of these consultations do not give specific recommendations for patients' treatment. Only 5 (3.4%) of consultations identified new findings, while 62 (42.5%) do not contain any recommendation.

Our random election program did not fully succeed in creating two comparable groups, because in both groups there were significantly higher proportion of women than men and this is one additional limitation of our study. Gender difference is interpreted with the knowledge that hip fractures are more common in women due to frequent osteoporosis, the main risk factor for these fractures, as defined in the study by Parker and Johansen (1).

The present study shows that the overall incidence of preoperative adverse cardiac events was higher in high-risk group of patients. Despite the statistical significance of these findings, we believe that care should be taken in interpreting the difference in morbidity and mortality between the two groups. This is particularly important because the number of the observed complications was few and the study groups were relatively small.

Conclusion

Patients with hip fracture classified as a high risk patients according the presented of high risk cardiac predictors, have significantly higher incidence of postoperative cardiac morbidity and mortality. The purpose of preoperative evaluation and stratification of the patients is important to perform an evaluation of the patient's current medical status; make recommendations concerning the evaluation, management, and risk of cardiac problems over the entire perioperative period, and provide a clinical risk profile that the patient, anesthesiologist, and surgeon can use in making treatment decisions that may influence short- and long-term cardiac outcomes.

Conflict of interests. *Not declared.*

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ВЛИЈАНИЕ НА ПРЕДИКТОРИТЕ ЗА КАРДИЈАЛЕН РИЗИК ВРЗ ХИРУРШКИОТ ИСХОД КАЈ ПОСТАРИ ПАЦИЕНТИ СО СКРШЕНИЦА НА КОЛК

АПСТРАКТ

Вовед. Пациентите со скршеница на колк. се најчесто постари пациенти, и кај нив, стресот од траумата и операцијата, може во голема мера да ја зголеми инциденцијата на постоперативниот кардијален морбидитет и морталитет.

Цел на трудот е да се спореди какво е влијанието на предикторите за кардијален ризик врз исходот од хируршката интервенција кај постари пациенти со скршеница на колк.

Материјал и методи. Во оваа студија беа опфатени 120 пациенти со скршеница на колк на возраст над 70 години со претходно утврден висок или низок периоперативен кардијален ризик според ACC/AHA препораките и беа поделени во 2 групи од 60 пациенти зависно од типот на кардијалниот ризик: Риск група – пациенти кои се со висок кардијален ризик; и НР група – пациенти без или со низок кардијален ризик. Испитаниците од двете групи беа обезболувани со интравенска аналгезија, и тоа: Niflam 2 x 100 mg/iv и Tramadol 50 mg/iv на секои 8 часа. Крајни точки на студијата беа инциденцијата на срцеви компликации кај двете групи: инцидентна срцева смрт, инфаркт на миокардот, конгестивна срцева слабост, нестабилна ангина и новонастаната атријална фибрилација. Кај сите пациенти се одредуваше степенот на аналгезија со Вербалната Дескриптивна Скала.

Резултати. Испитаниците со висок кардијален ризик имаат повисока инциденција на срцеви компликации наспроти испитаниците со низок ризик (Риск група 46.6% наспроти 15% во НР групата), а воедно и намалена стапка на морталитет (10% во Риск групата наспроти 0% во НР групата). Вредностите на ВДС скалата беа еднакви кај испитаниците од двете групи.

Заклучок. Пациенти со скршеница на колк, класифицирани како пациенти со висок кардијален ризик, врз основа на присуство на предиктори на висок кардијален ризик, имаат сигнификантно повисока инциденција на постоперативен кардијален морбидитет и морталитет.

Клучни зборови: ACC/AHA класификација, кардијален периоперативен ризик, постари пациенти, фрактура на колк.

 ISSN 2545-4366 | UDC: 616.61-089.843:616.153.495.9

POSTOPERATIVE SERUM CREATININ LEVEL IN TWO DIFERENT HYDRATION REGIMES IN LIVING DONOR KYDNEY TRANSPLANATATION

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ABSTRACT

Introduction: Early graft function is very important and can be achieved with adequate intraopeartive perfusion characteristics of the graft and urine output. The goal of this study was to examine the influence of targeting central venous pressure (CVP) on early graft function.

Material and methods: After approval of Ethical committee of the Medical Faculty-Skopje, we obtained inform consent of 60 patients, ASA 2-3 undergoing renal transplantation of living-related person in the Clinic of Urology – Skopje. A prospective clinical study was performed in the period of 2 years. Patients were divided into 2 groups of thirty patients : group **A** receiving normal saline intraoperatively targeting for CVP to 15 mmHg until vascular clamps were off and group **B** receiving normal saline 10ml/kg/h.

We recorded lactate at the end of the surgery, onset of diuresis and total urine output from unclamping the renal vessels to the end of the surgery in both groups and postoperative serum creatinine in 3times (3, 12, 36 hours).

Results: The onset of diuresis in seconds was insignificantly longer in group B $p>0,05$ ($p=o,31$). The average value of postoperative levels of the lactate showed that in group B the levels of the lactate were significantly higher for $Z=-5,79$ and $p<0,001$ ($p=0,000$). We didn't find any statistical differences in postoperative serum creatinine in both groups.

Conclusion: Our study didn't show any benefit from targeting CVP to 15 mmHg. We couldn't find any significant difference on onset of diuresis and urine output after the unclamping the vessels. However, in the constant infusion group (group B) the level of the lactate was higher CVP. In postoperative biochemical parameters we had no statistical difference between the average values of serum cratinine.

Key words: onset of diuresis, serum creatinine, kidney transplantation.

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Introduction

For patients with end-stage renal disease (ESRD), transplantation provides better survival and quality of life than dialysis (1–5).

For transplantation, respectfully, early graft malfunction has been associated with decreased graft survival and increased complications. A specific task for the anesthesiologist is to maintain and optimize the volume status and the hemodynamic status of the patient before the kidney reperfusion and thereby to provide better graft functioning (6-9).

Central venous cannulation and monitoring is still recommended for all patients who are undergoing transplantation, because this is considered to be an adequate monitoring for intravascular volume status. A lot of studies have examined specific values of perioperative central venous pressure (CVP) that are correlated to reduced risk of postoperative graft failure (7-10). On the other hand, patients with end stage renal disease (ESRD) have a narrow margin of safety with intravenous hydration and may oscillate between hypo and hypervolemia.

Intra-operative volume expansion is associated with increased renal blood flow and immediate improvement of graft function (12.13). This immediate improved function is associated with increased graft survival and lower patient mortality (13-16). Central venous pressure should be usually maintained in the range from 10 to 15 mm Hg. Better graft functioning (due to better volume input) leads to early diuresis and sometimes to reduced usage of diuretics.

Diuretics (furosemide), osmoticagents (mannitol), and sometimes dopamineagonists (dopamine, fenoldopam) are administered to promote diuresis immediately after reperfusion, but only mannitol, when combined with volume expansion, has been shown to decrease the incidence of acute tubular necrosis after transplantation (15). Hypotension results in decreased graft perfusion, therefore maintaining an adequate intravascular volume and careful titration of medications are important targets for every patient.

To our knowledge, no published studies have validated the correlation between time course of the volume expansion and the period of renal ischemia and beside the recommendation for CVP values. Controversies for the exact recommended value of the CVP are still popular. However, the clearance of the creatinine is still considered to be the most important measurement for evaluation of recovery of the graft in new environment.

Methods

After approval of Ethical committee of the Medical Faculty-Skopje, we obtained inform consent of 60 patients, undergoing renal transplantation of living-related person in the Clinic of Urology – Skopje. A prospective clinical study was performed in the period of 2 years. Patients were divided into two groups: group **A** (n=30), receiving normal saline to intraoperatively targeting for CVP 15 mmHg until vascular clamps were off, and group **B** (n=30) receiving normal saline 10ml/kg/h.

The exclusion criteria were: severe left ventricular impairment, cardiomiopathy with ejection fraction bellow 50%, problem with coagulation, excessive bleeding during the operation, resistant graft arterial spasm or any other surgical difficulty.

All transplantations in this study were performed by the same surgical team. All patients underwent full medical and surgical history, and routine laboratory investigations (i.e., blood Hb, plasma proteins, coagulation status, serumel ectrolytes, blood glucose, lactate, arterial blood gases, chest radiograph and echocardiography). All patients underwent preoperative hemodialysis, 24 hours before the renal transplant surgery.

All patients underwent standard anesthesia protocol: standard monitoring, ECG in 5 leads, noninvasive blood pressure and pulse oximetry before the induction were recorded. Before the induction to anesthesia, epidural catheter was inserted (on level L2-L3 or L3-L4 and it was given a test dose of bupivacain of 10 mg). The epidural catheter was not used until the end of surgery in order to avoid any interference with intraoperative hemodynamics. At the end of the intervention all patients received epiduraly100mcg fentanyl and 20mg of bupivacain in volume to10ml. Induction anesthesia protocol was with remifentanyl in dose 0,5mcg/kg and propofol 2mg/kg and the intubation was facilitated with dose of atrcurium 0,5mg/kg. Anesthesia was maintained with remifentanyl of 0,25mcg/kg and propofol 0.5-1mg/kg depending on the depth of anesthesia which was recorded with entropy electrodes. Patients were ventilated with mixed oxygen/air 50-50% with tidal volume of 7-9ml/kg and end-tidal CO2 between 35-40mmHg (Datex-Ohmeda Avance S-5). After the induction, the central venous catheter aseptically was placed in the internal jugular vein and pressure was transdused and recorded. For measuring invasive arterial pressure an arterial catheter was placed in a. radialis and it was recorded.

Levels for total urine output (ml) and the level of plasma creatinine (mmol/L) were analyzed postoperatively in 3 times – on the 3rd, 12th and 36th hour after the surgery.

Results

The most of the patients underwent for hemodialysis 24 hours before surgery, except 4 patients in group A (in whom hemodialysis was not required) and 2 patients in group B. Preoperative blood Hb and serum creatinine were similar in both groups. Average Hb in group A was 116.73±19.07 and for group B was 112.93±17.19. Average creatinine for group A was 632.63±187.00 and for group B 556.52±164.14.

Table 1. *Demographic and operative data of both groups*

	Group A (n=30)	Group B (n=30)
Age (years)	37.87±9.32	41.47±10.25
Sex F/M	15/15	17/13
Body weight kg	74.17±10.92	70.83±11.83
Duration of surgery (min)	236.67±40.33	250.83±61.65

Cold ischemia (min)	210.10±33.98	221.43±35.62
Warm ischemia (sec)	170.30±39.34	184.20±38.13
Months on hemodialysis	12.17±13.32	17.95±31.71
Comorbidites		
None	11	16
Hypertension	16	11
Hypertension and diabetes melitus	3	3

Values are expressed in mean±sd; group A is CVP 15 target group, group B constant infusion group.

The onset of diuresis and urine output at the end of the surgery showed no statistical differences between the groups, but in 5 patients in control group we didn't achieve urine output at the end of the surgery. (Table 2)

Table 2. *The onset of dieresis and urine output at the end of the surgery*

Parameter	RankSum Gr.A	RankSum Gr.B	U	Z	p-level	Valid N Gr.A	Valid N Gr.B
Urine output	829.50	710.50	364.50	-0.18	0.86	30	25
Onset of diuresis (sec)	780.00	760.00	315.00	-1.01	0.31	30	25

The average value of postoperative levels of the lactate (mmol/L) showed that in group B, the level of the lactate was significantly higher for $Z=-5.79$ and $p<0.001$ ($p=0.000$). (Table 3)

Table 3. *Lactate at the end of the surgery*

Parameter	RankSum Gr.A	RankSum Gr.B	U	Z	p-level	Valid N Gr. A	Valid N Gr.B
Lactate	523.50	1306.50	58.50	-5.79	0.000	30	30

The creatinine levels in serum (mmol/L) in postoperative period for both groups in 3, 12 and 36 hours are shown in the Table 4. Between average values of serum creatinin in relation between 3, 12 and 36 hours for $p>0.05$, we didn't find any statistical differences.

Table 4. *Serum cretinin (mmol/L) in 3, 12 and 36 hours after the surgery*

T	Group	R1	{1}	{2}	{3}	{4}	{5}	[6}
1.	A	Creatinin/3h		0.000	0.000	0.97	0.009	0.000
2.	A	Creatinin /12h	0.000		0.000	0.008	0.99	0.004
3.	A	Creatin /36h	0.000	0.000		0.000	0.000	0.77
4.	B	Creatinin/3h	0.97	0.008	0.000		0.000	0.000
5.	B	Creatinin /12h	0.009	0.99	0.0009	0.000		0.000
6.	B	Creatin /36h	0.000	0.004	0.77	0.000	0.000	

Discussion

Many studies suggest that during kidney transplantation the systolic and diastolic should be higher than 120/85mmHg. They also suggest that the MAP should be higher than 95mmHg and CVP above 10 mmHg (10-16). These values are favorable to ensure maximal filling pressure of the graft and its fast recovery. Intraoperative volume expansion is associated with increased renal blood flow and better immediate graft function (15,16). Early graft malfunction has been associated with decreased graft survival and increased recipient complication (12). Carlier at al. showed that maximal hydration during anesthesia up to 100ml/kg and 30ml/kg/h and CVP 10-17 were associated with improved early graft function (8).

Many of the clinical trials showed that regimen targeting CVP before cross-clamp of the donor's kidney provides more favorable outcome (10,15,17). They showed that high hydration regime provides more turgid graft and faster onset of diuresis. Prolonged arterial hypotension can lead to graft hypo perfusion and after that to prolonged time for graft recovery and delay graft function (17-19). In both groups we didn't had any episode of hypotension and there was no need for vasopresors. The time of surgery, cold ischemia and warm ischemia were similar in both groups.

Our study didn't show any benefit from targeting CVP to 15 mmHg. We couldn't find any significant difference on onset of diuresis and urine output after the unclamping the vessels. However, in the constant infusion group (group B) and the level of the lactate was higher but this doesn't have any clinical implication because the level of serum lactate in both groups was in normal range. In 5 patients in the control group we didn't achieved a urine output at the end of the surgery. Decreased values of serum creatinine in the postoperative period are good sign of fast recovery of the graft (10,15-19). In our study 36 hours after the transplantation, 9 patients in group A had normal values of serum cratinine and 6 patients in group B. The average values of serum cratinine for time of 36 hours after the surgery in group A was 220.64±158.10 and 238.68±131.50 for group B. In postoperative biochemical parameters we had no statistical difference between the average values of serum cratinine.

Conclusion

This study shows that there isn't any statistical difference between the groups, but however in group B we had 5 patients with no diuresis at the end of the surgery. In the control group we had statistically higher values of serum lactate, but still they were in normal range. Our study didn't show any benefit of targeting CVP.

This study has limitations. We only evaluated onset of the diuresis and have not considered whether there are long–term benefits. There is need for larger study to confirm if there is true benefit (improved long-term outcomes).

In creation of this study we didn't have any conflict of interest.

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ПОСТОПЕАРТИВНО НИВО НА КРЕАТИНИНОТ ВО ПЛАЗМА ПРИ ДВА РАЗЛИЧНИ ВИДОВИ НА ХИДРАЦИСКИ РЕЖИМИ КАЈ БУБРЕЖНА ТРАНСПЛАНТАЦИЈА ОД ЖИВ СРОДЕН ДОНОР

АПСТРАКТ

Вовед: раната функција на графтот е многу важна и се постигнува со соодветни интраоперативни карактеристики на префузијата на органите, а со тоа и добра диуреза на крајот од интервенцијата. Улогата на користење на целен интраоперативен централен венски притисок (CVP) врза раната функција на графтот беше цел на оваа студија.

Матријал и методи: по обезбедената согласност од етичката комисија на Медицинскиот Факултет во Скопје добивме согласност од 60 пациенти АСА 2-3 кои беа закажани на Клиниката за урологија за бубрежна трансплантација од жив сроден донор. Проспективната клиничка студија беше изведена во период од 2 години. Пациентите беа поделени во две групи од по 30 пациенти: група А пациенти кај кои беше администриран физиолошки раствор до постигнување на целен CVP од 15 mmHg до крајот на анстомозите и група Б каде пациентите добиваа физиолошки раствор со брзина од 10ml/kg/h. Параметри кои беа следени во постоперативниот период: лактати (mmol/L), почеток на дуиреза изразена во секунди, вкупната количина на урина на крајот од интервенцијата и постоперативното ниво на креатининот во плазмата во 3 времиња (3, 12, 36 часа) по интервенцијата.

Резултати: почетокот на диуреза изразено во секунди за $p > 0,05$($p=0,31$) беше подолго во испитуваната група, но статистички незначајно. Средната вредност на постоперативните лактати за групата Б беше сигнификантно повисока за $Z=-5,79$ и $p<0,001$($p=0,000$). Не најдовме статистички значајна разлика во нивото на креатинин во трите времиња помеѓу двете групи.

Заклучок: Нашата студија не покажа корист од целно насочен CVP во однос на континуираната администрација на течности во интраоперативниот период кај бубрежна таранспланатација од жив донор. Нивото на лактати беше сигнификантно повисоко во контролната група, но без клиничко значење поради фактот дека во двете групи нивото на лактати беше во референтни вредности.

Клучни зборови: бубрежна трансплантција, креатинин, почеток на диуреза.

ORIGINAL ARTICLE ISSN 2545-4366 | UDC: 618.14-089.87-089.5-032:611.8]:616.24-002.2

COMBINED SPINAL-EPIDURAL ANESTHESIA FOR ABDOMINAL HYSTERECTOMY IN PATIENTS WITH COPD

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ABSTRACT

Introduction: All patients with chronic obstructive pulmonary disease (COPD) are with increased risk for intra and postoperative complications during abdominal surgery. In our study we present another approach in anesthetic management in these highly risk patients.

Methods: We analyzed 20 patients, ASA III, scheduled for elective abdominal hysterectomy. After appropriate preoperative preparation in every patient epidural catheter was placed on Th_{12}-L_1 or L_1-L_2 level, while spinal punction with standard spinal anesthesia was performed on lower levels. We evaluate basic hemodynamic parameters, patients' satisfaction and postoperative pulmonary complications.

Results: All hemodynamic parameters showed decrease in the first 30 minutes and then constant flow until the end of surgery. 4 patients developed postoperative pulmonary infection, and ended well. All patients were very satisfied with anesthesia procedure.

Conclusion: Combined spinal-epidural anesthesia provides good hemodynamic stability, large patients' satisfaction with fewer postoperative pulmonary complications in patients with COPD. Encouraging this anesthesia technique might increase the safety margin of surgery in patients with severe pulmonary diseases.

Key words: COPD, abdominal hysterectomy, postoperative pulmonary complications.

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Introduction

Anesthesiologists are more and more facing with high risk patients with many morbidities admitted for elective surgery. Chronic pulmonary diseases are especially important for anesthesiologists and are constantly increasing. Based on the study of Murray (1) from 1996 chronic pulmonary disease was ranked 12th in 1990s, while it is predicted to be ranked 5th in 2020s to all diseases in the world.

Abdominal hysterectomy is usually performed in general anesthesia alone or in combination with epidural anesthesia, very rarely in regional anesthesia alone. Regional anesthesia has an advantage of retaining of conscious state; it is associated with decreased incidence of deep vein thrombosis and reduced postoperative risk of pulmonary, cardiovascular and gastrointestinal complications. But it requires additional performance time, technical skills and has its own contraindications, as well as side effects. In a COPD patient regional anesthesia alone is associated with lower incidences of composite morbidity, pneumonia, prolonged ventilator dependence and unplanned postoperative intubation (2).

All patients with chronic obstructive pulmonary disease (COPD) are with increased risk for intra and postoperative complications during abdominal surgery. Arozullah et al. (3) published the largest study investigating the risk index for postoperative respiratory failure and pneumonia in non thoracic surgery. COPD was found to be a major predictor for postoperative complications. In a smaller study from 2002 [4] besides COPD, asthma, age > 65, history of smoking > 40 years, productive cough and exercise intolerance were all found to significantly increased risk for postoperative pulmonary complications.

The definition of severe COPD (from the National Surgical Quality Improvement Program-NSQIP) is chronic obstructive pulmonary disease resulting in any one or more of the following: functional disability from COPD (e.g., dyspnea, inability to perform activities of daily living), hospitalization in the past for treatment of COPD, chronic bronchodilator therapy requirement with oral or inhaled agents or a forced expiratory volume in 1 second (FEV1) of <75% of predicted on pulmonary function testing (2).

We are presenting the management of 20 patients with COPD undergoing abdominal hysterectomy under combined spinal-epidural anesthesia (CSEA).

Methods

We performed a prospective study on 20 female patients, scheduled for elective abdominal hysterectomy, all of them belonging to American Society of Anesthesiologists physical status III in the period between January 2015 and January 2017.

Patients were included if they had a NSQIP preoperative diagnosis of severe COPD. Patients with coagulation abnormalities, vertebral deformities and refusal for regional anesthesia were excluded from the study.

All patients were previously well prepared, all routine investigations were carried out and detailed pulmology examination was performed although some studies (5) for preoperative

evaluation of lung function did not reveal specific parameters of lung function predictive for postoperative complications. Just the existence of COPD increases the risk.

No patient received oral premedication due to the fact that benzodiazepines reduce the respiratory strength, but all of them received intravenous premedication with 2 mg of Midazolam.

In the operating theatre all patients were monitored for noninvasive blood pressure, electrocardiography and pulse oximetry.

Epidural catheter was placed on T12-L1 or L1-L2 level, while spinal punction was performed on L2-L3 or L3-L4 level in sitting position with 26G or 27G spinal needles. For spinal anesthesia 14-16 mg Bupivacaine with 10 μg Fentanyl was used. Epidural catheter was activated only if desired sensory level was not achieved or the duration of operation prolonged more than 120 min. We used 0.5 % plain Bupivacain starting with 5 ml to maximum 15 ml.

All patients received supplemental oxygen through oxygen mask 2l/min. Intraoperatively heart rate (HR) and Mean arterial pressure (MAP) were monitored every 5 minutes and recorded at an interval of 5, 10, 15, 30, 60 minutes and at the end of surgery. Saturation with oxygen was monitored continuously, but recorded in every 10 minutes. Hypotension and bradycardia was defined as 20% reduction from base line values. Anesthesia time was calculated from start of anesthesia to the end of surgery.

Postoperatively the most important outcome for this study was postoperative pulmonary infection. We also observed postoperative intubation, ventilator dependence and 30-day mortality.

Patients' satisfaction with the anesthesia procedure in terms of pain relief, comfort, acceptance as a choice for future and overall satisfaction were recorded.

Results

Data of all 20 patients enrolled in the study were included in the analysis. The demographic and clinical characteristics of the group sample are given in table 1.

Table 1. *Demographic and clinical characteristics for the matched patients*

Clinical variable	Mean	SD
Age (years)	62	±10
Body mass index	26	±7.2
	Number	%
DM (insulin dependent)	5	25
DM type II	4	20
Smoker	8	40
Hypertension	15	75
Myocardiopathia chr	4	20

DM-diabetes mellitus

11 patients have excellent analgesia only with spinal anesthesia, while 9 patients received additional 0.5% Bupivacain on the epidural catheter. 7 patients needed epidural analgesia from the start of the operation due to the insufficient sensory block. Average Bupivacain consumption was 9.5 ± 3.5 ml. Another 2 patients needed Bupivacain on the epidural because the duration of the operation lasted more than 150 minutes. Each patient received 8 ml of 0.5% Bupivacain.

Hemodynamic parameters HR, MAP and saturation with oxygen are shown in table 2 and represented graphically in figure 1.

Table 2. *Hemodynamic parameters at various time intervals*

Time intervals (minutes after the start of anesthesia)	HR (beats/min)	MAP (mm Hg)	SpO_2 (%)
Before the start of anesthesia	72±10	112±18	96
5 min	68±9	110±18	96
10 min	64±8	106±16	95
15 min	62±8	98±12	94
30 min	58±7	88±10	94
60 min	62±6	90±11	95
120 min	64±6	92±10	96

HR-heart rate
MAP-mean arterial pressure
SpO_2-saturation with oxygen

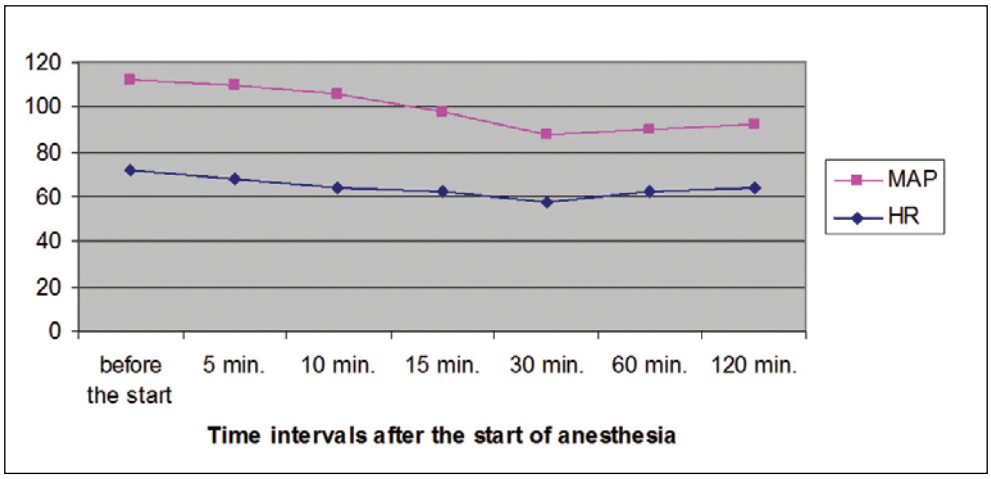

Figure 1. *Variations of heart rate (HR) and mean arterial pressure (MAP) in different time intervals*

Mean HR showed small decrease immediately after anesthesia. Only one patient (5%) needed 0.5 mg Atropine for treatment of bradycardia (table 2, figure 1).

Mean MAP showed slow decrease in the initial 30 minutes and after that blood pressure followed one constant flow. Hypotension was noticed in 3 patients, but only 2 needed 0.5 mg Phenylephrine for correction of hypotension (table 2, figure 1).

SpO_2 showed a small decline within 15 minutes of combined spinal-epidural anesthesia and then maintained constant till the end of the surgery (table 2). Oxygen was given to all patients continuously. None of the patients had SpO_2 less than 90%.

Mean anesthesia time in minutes was 95.5.

Postoperative pulmonary infection was one of the study outcomes. We followed the patients all the time during their stay in the hospital and contacted them till 30th day of the surgery. 4 patients developed postoperative pulmonary infection, but it was diagnosed and treated on time. No patient needed postoperative intubation or ventilator. The 30-day mortality was zero.

Patients' satisfaction with the anesthesia procedure was assessed on four parameters (pain relief, comfort, acceptance for future and overall satisfaction). Patients in our study were very satisfied with the anesthesia on all parameters (pain relief 85%; comfort 95%; acceptance for future 100%; overall satisfaction 100%).

Discussion

Abdominal hysterectomy is usually performed in general anesthesia, but general anesthesia in high risk surgical patients with significant pulmonary disease can trigger many adverse effects. A review of 141 prospective randomized trials (6) showed that regional anesthesia compared with general has an advantage of decreased incidence of deep vein thrombosis, renal failure and reduced postoperative risk of pulmonary, cardiovascular complications as well as decreased mortality. Retaining the conscious state and spontaneous breathing is also very important part of regional anesthesia. Among the various regional anesthesia techniques that can be used for total abdominal hysterectomy combined spinal epidural anesthesia has gained popularity over the years and has become a popular technique for various gynecological operations. Various advantages of CSE technique include fast and reliable segmental anesthesia with minimal risk for toxicity followed by excellent analgesia in the postoperative period (7).

Typical hemodynamic effects of spinal block include a reduction in blood pressure with only a mild reduction in heart rate, ejection fraction or cardiac output even in patients with poor left ventricular function. Hypotension develops due to a reduction in systemic vascular resistance and central venous pressure secondary to the sympathetic blockade, with vasodilation and redistribution of central blood volume (8). Hypotension was observed in 3 patients in our study and was treated with small doses of vazopresors, effectively. Bradycardia was observed in 1 patient, treated with Atropine. Oxygen saturation remained within normal limits during the procedure demonstrating that spinal block can be safe, even in the absence of tracheal intubation. On the other hand, epidural as a part of CSEA offers flexibility, when sensory block is insufficient or the duration of the anesthesia is extended. We needed injection of Bupivacaine on the epidural catheter in 7 patients due to insufficient sensory block and in 2 patients because of prolonged surgery time. Epidural is also ideal for postoperative pain control. One recent study (9) comparing combined spinal-epidural and general anesthesia for

abdominal hysterectomy in non COPD patients showed us very good hemodynamic stability in patients with CSEA.

Compared with general anesthesia, the use of regional anesthesia in patients with severe

COPD is associated with a lower incidence of postoperative pulmonary complications. 4 of the patients in our study developed postoperative pulmonary infection, but without need of intubation or ventilator support. One recent study from 2015 (2) that included more than 5000 surgical patients with COPD, half of them receiving general, other half regional anesthesia showed us that in a COPD patient regional anesthesia alone is associated with lower incidences of composite morbidity, pneumonia, prolonged ventilator dependence and unplanned postoperative intubation. This association is most notable in patients receiving spinal anesthesia. In this study all these advantages did not extend to mortality, which was similar between groups. A meta-analysis of older studies (6) that compared 9559 patients found a one-third reduction in mortality with regional anesthesia, but the study was not limited to COPD patients.

Patients' satisfaction with the anesthesia procedure assessed on four parameters showed us in our study very big satisfaction with the procedure. Patients were very satisfied with the anesthesia on all parameters. Tangpaitoon et al reported significantly better patients' satisfaction in CSEA group compared with general anesthesia group in patients undergoing percutaneous nephrolithotomy (10).

Conclusion

Constant advances in anesthesiology techniques especially the combined spinal-epidural technique led to much safer anesthesia and extension of operative indications. Combined spinal epidural anesthesia provides good hemodynamic stability, big patient satisfaction, less composite morbidity shown by fewer pulmonary complications in patients with COPD. Encouraging this anesthesia technique might increase the safety margin of surgery in patients with severe pulmonary diseases.

Using regional anesthesia with spontaneous breathing should be offered to high risk patients whenever it is possible.

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КОМБИНИРАНА СПИНАЛНА-ЕПИДУРАЛНА АНЕСТЕЗИЈА ЗА АБДОМИНАЛНА ХИСТЕРЕКТОМИЈА КАЈ ПАЦИЕНТКИ СО ХОББ

АБСТРАКТ

Вовед: Сите пациенти со хронична опструктивна белодробна болест (ХОББ) се со зголемен ризик од интра и постоперативни компликации при абдоминална хирургија. Во нашата студија ние покажуваме друг пристап во анестезијата кај овие високо-ризични пациентки.

Методи: Анализиравме 20 пациентки ASA III, закажани за елективна абдоминална хистеректомија. По соодветна предоперативна подготовка, кај сите пациентки беше поставен епидурален катетер на ниво Th_{12} - L_1 или L_1-L_2, а стандардна спиналната анестезија беше изведена на пониско ниво. Евалуиравме основни хемодинамски параметри, задоволство на пациентите и постоперативни белодробни компликации.

Резултати: Сите хемодинамски параметри покажаа намалување во првите 30 минути и последователен константен тек се до крајот на операцијата. 4 пациентки развија постоперативна белодробна инфекција, добро завршија. Сите пациентки беа задоволни со анестезиолошката техника.

Заклучок: Комбинирана спинална-епидурална анестезија обезбедува добра хемодинамска стабилност, големо задоволство кај пациентките со помалку постоперативни белодробни компликации кај пациентки со ХОББ. Поттикнувањето на оваа анестезиолошка техника може да ги зголеми безбедносните граници на хирургијата кај пациентки со тешки белодробни заболувања.

Клучни зборови: абдоминална хистеректомија, постоперативни белодробни заболувања, ХОББ.

ORIGINAL ARTICLE ISSN 2545-4366 | UDC: 616.831-001-073.7:543.422.3-74

NEAR INFRARED SPECTROSCOPY AS PROMISING NEUROMONITORING IN TRAUMATIC BRAIN INJURY – PILOT STUDY

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ABSTRACT

Introduction: Cerebral oxymetry with Near Infrared Spectroscopy (NIRS) method provide noninvasive monitoring of microvasculature in the brain and reflects the balance between oxygen delivery and oxygen consumption. Since this system provides direct measurement of oxygen saturation in cerebral cortex any disbalance is early warning sign for potential cerebral ischemia. The purpose of this study is to determine the usefulness of NIRS as method for prevention and early recognition of secondary brain changes in traumatic brain injury (TBI) and forehanded treating of these changes.

Materials and methods: NIRS monitoring was conducted in seven patients with TBI. We kept tracking following parameters: Glasgow Coma Scale (GCS) on admission to determine the severity of TBI, systolic blood pressure (SBP), mean blood pressure (MBP), Pulse oxymetry (SpO2), and regular laboratory. Regional cerebral oxygenation was measured using cerebral oxymetar INVOS 5100 Somanetics®.

Result: According to data obtained in several patients, we noticed that any change in hemodynamic profile directly influenced the regional cerebral oxygen saturation. Lower value 20 % and more from basal ones correlates with unfavorable outcome as neurologic sequels. Decreased values of rSO2 in our cases were rectified with several simple interventions. In our cases, parameter which was most prominent cause for disturbed rSO2 was decreased mean arterial pressure (MAP).

Conclusion: Through analysis of values obtained with Near Infrared Spectroscopy which varied in some pathologic conditions indicates to possible benefit using the regional oxygen saturation in traumatic brain injury and presents important monitoring system for forehanded detection of occurring adverse secondary brain injuries.

Key words: cerebral oxymetry, near infrared spectroscopy, neuromonitoring traumatic brain injury.

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Introduction

Traumatic brain injuries without any doubt present enormous health and socio economic issue accompanied with high percent of mortality and morbidity especially in young population (1). It is well known that traumatic brain injuries (TBI) initiated whole cascade of events leading to secondary brain injury. These secondary changes consist of ischemic, electrolytic, neurochemical and immunological processes which subsequently damaged already disturbed brain (1,2).

The causes for secondary brain injuries can be intracranial and extracranial. The intracranial are intracranial hypertension, cerebral edema, disturbances in regional cerebral blood flow, seizures, excitotoxicity, mitochondrial dysfunction and metabolic disturbances. The extracranial are systemic as hypoxemia, hypotension, anemia, disturbance in glucose metabolism and other metabolic abnormalities. Prevention and decreasing of these secondary brain injuries can present main therapeutic goal in TBI management (4,5).

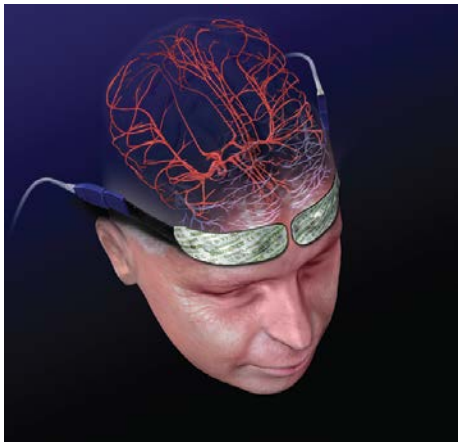
Neuromonitoring is more essential tool in intensive care unit and its primary goal is trauma brain injury management identification and prevention of secondary brain injuries and therapy guiding (2).

If secondary injury is recognized on time titrating and outcome will be much more beneficial. There are continuous achievements in quality of care for patients with TBI in operation room and in intensive care unit. Despite this progress, secondary brain injuries remain the biggest concern which can happen intraoperatively and in intensive care units (3). This concern initiates development of new technologies for monitoring and new strategies for early detection of brain dysfunction and appropriate neuroprotection. Still standard methods for monitoring do not provide direct measurements of brain processes. Nowadays we are talking about multimodal monitoring which provide monitoring of several parameters of brain physiology and function and consists of several invasive and noninvasive techniques.

In 1996, Samra et al. suggest that noninvasive monitoring technique with cerebral oxymetar using spectroscopy with electromagnetic waves near infrared light spectroscopy, can be clinically useful in time of management of patients with TBI, neurosurgical procedures and open heart surgery (4).

This method enables absolute measurement of oxygen cerebral saturation (rSO2). This parameter reflects the balance between oxygen delivery and oxygen consumption [5].

Cerebral oxymetry with NIRS (Near Infrared Spectroscopy) method provide noninvasive monitoring of microvasculature under the sensors measuring the oxyhemoglobin and deoxyhemoglobin in venous and arterial blood in ratio of 75:25 percent. This results with sensitive measurement in real time of venous oxygen reserve i.e. measuring the blood oxygen which remains after the extraction from the tissue. The method is based on transmission and absorption of electromagnetic rays in area near the infrared light spectrum (700 -100 nm) on different lengths passing the tissue. Since oxy and deoxyhemoglobin have different absorption spectrum, cerebral oxygenation is assessed according to their relative absorption of near the infrared radiation. Factors that can influence the absorption are scalp thickness, myelin sheets, liquor and changes in extracranial blood flow (6).



Pulse oxymetry use the spectroscopy of near the infrared radiation to estimate noninvasively and continuous the changes of blood oxygen saturation. The main difference is that cerebral oxymetry directly monitors the changes in regional oxygen saturation (rSO2) of predominately venous blood in the brain.

Since this system provides direct measurement of oxygen saturation in cerebral cortex any disbalance is early warning sign for potential cerebral ischemia.

Normal parameters for value of basal rSO2 are 60-78% with 10 % variation up and down (critical moment is value which is 20% lower from basal value). Threshold for it is much more individual and depends of accompanied disease, so it is necessary to establish the basal value of rSO2 in every patient. When changes in oxygen delivery and consumption occurred, it can be intervened with simple procedures before irreversible brain secondary injury might happen (7).

With this parameter it is enabled to indirectly monitor the perfusion and it represents sign for impairment of patient's condition much earlier from other systemic measurements and laboratory tests which can remain normal beside already occurred ischemia of the brain (8).

The purpose of this study is to determine the usefulness of NIRS as method for prevention and early recognition of secondary brain changes in TBI and forehanded treating of these changes.

Materials and Methods

NIRS monitoring was conducted in seven patients with TBI in period of November 2014 till February 2015 in Intensive Care unit of Clinic of Neurosurgery in Skopje.

In all patients were performed standard diagnostic and resuscitation methods for trauma patients and specific methods for treatment of traumatic brain injury according to novel guidelines for treatment of neurotrauma patients.

Beside standard therapy in patient, we performed therapy for stabilization of shock condition. We kept tracking following parameters: Glasgow Coma Scale (GCS) on admission to determine the severity of TBI, systolic blood pressure (SBP), mean blood pressure (MBP), Pulse oxymetry (SpO2), and regular laboratory. Regional cerebral oxygenation was measured using cerebral oxymetar INVOS 5100 Somanetics®. Noninvasive measuring was performed with two sensors i.e. Somasensors placed on frontal part of patient's head. Spectroscopic radiation near infrared

light passes through frontal part of the scalp entering the brain. The big letter R and L were used for determining the value of cerebral oxygenation in right and left hemisphere.

Results

In Table 1 we have parameters that were taken in patients at the moment of admission in intensive care unit: Glasgow Coma Scale (GCS), systolic arterial pressure (SAP), mean arterial pressure (MAP), Pulse oxymetry (SpO2), diagnosis, mortality on 24 day and age. The first parameter GCS in four patients show severe neurotrauma (GCS 3-8), 2 patients have moderate neurotrauma (9-13) and one patient with mild neurotrauma (GCS 14-15). One patient died in first 24 hour. Hemodynamic profile at the admission (SAP and MAP) in all patients has relatively moderate values.

Table 1 *Data on admission in ICU*

	GCS	SAP	MAP	SpO2	Diagnosis	Mortality On 24 day	Age
1	7	109	75	92	SAH traumatica Contusio cerebri	/	47
2	9	167	105	96	Contusio cerebri	/	63
3	12	174	113	99	Hematoma epidurale l.dex	/	24
4	7	146	98	93	Haemathoma subdurale l.dex	/	54
5	14	110	73	98	F-ra impressiva	/	33
6	4	98	63	87	Haemathoma subdurale bill Contusio cerebri	died	58
7	8	146	90	93	Contusio cerebri	/	39

GCS - Glasgow Coma Scale
SAP - systolic arterial pressure
MAP - mean arterial pressure
SpO2- Pulse oxymetry

In Table 2 values for regional cerebral oxygenation (rSO2) are noted in the first 24 hours. The basal values were determined and noted dramatic change i.e. decreasing was connected with algorithm for possible causes. The procedures for increasing the oxygenation were performed as soon as possible. After the intervention values returned to values near the basal ones i.e. cerebral oxygenation increased.

Table 2. *Values for rSO2*

	SpO2%	rSO2 basal %		rSO2 change %		rSO2 % difference		Cause
		right	left	right	left	right	left	
1	91	69	69	51	68	26	1,4	MAP<62mmHg,head position
2	96	74	73	66	67	0,8	8,2	MAP<79 mmHg
3	99	75	77	59	63	21,3	18,1	MAP <70 mmHg
4	93	59	67	52	58	11,8	13,4	Head position, SpO2
5	98	77	78	65	65	15,6	15,7	Hyperthermia
6	89	64	62	41	42	36	32,2	MAP <50 mmHg, SpO2=90, Hgb= 87 g/dl, Hct = 0.26
7	93	72	69	63	64	12,5	7,2	MAP <70 mmHg

Discussion

Monitoring of cerebral oxygen saturation presents a window for the processes running on cellular level at that moment. NIRS method monitors the changes of cerebral oxygen which is result of mechanic and hemodynamic processes.

According to data obtained in several patients, we noticed that any change in hemodynamic profile directly influenced the regional cerebral oxygen saturation. Lower value 20 % and more from basal ones correlates with unfavorable outcome as neurologic sequels.

Decreased values of rSO2 in our cases were rectified with several simple interventions (9). Examples of these interventions were: correct head position in neutral enabling permanent drainage of venous circulation from the brain; decreasing the cerebral metabolism with deeper anesthesia; decreasing the body temperature as protective measure. Specific type of intervention is when we have to increase the oxygen delivery as increasing the FiO2, increasing the cerebral blood flow, increasing the PaCO2 to normal values, increasing the blood pressure and increasing the hematocrit.

Decreasing of rSO2 under the critical value of 50 occurred in one patient, but much more warring was the moment of decreasing the values 20% more from basal values which occurred in three patients. With simple intervention we successfully returned the values of rSO2 to almost basal ones (10).

In our cases parameter which was most prominent cause for decreased rSO2, was decreased mean arterial pressure (MAP). This indicates that it is essential to maintain the stable hemodynamic in patients with TBI.

We suppose that with normalizing the cerebral oxygen saturation, the causes which can initiate severe secondary brain injuries, can be eliminated.

Conclusion

Through analysis of values obtained with NIRS which varied in some pathologic conditions indicates that is possible to benefit using the regional oxygen saturation in TBI and it presents important monitoring system for forehanded detection of occurring adverse secondary brain injuries. We used data from seven patients, but they were strong motive for expanding the investigation. Using this monitoring system has diagnostic values, but also enables right therapeutic decisions and consequently better prognosis in TBI.

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НЕВРОМОНИТОРИНГ СО СПЕКТРОСКОПИЈА БЛИЗУ ИНФРАЦРВЕНО ЗРАЧЕЊЕ КАЈ ТРАУМАТСКА МОЗОЧНА ПОВРЕДА – ПИЛОТ СТУДИЈА

АПСТРАКТ

Вовед: Неинвазивна техника на мониторинг со церебрален оксиметар кој користи спектроскопија на блиску до инфрацрвениот спектар на светлина може да биде клинички корисна за време на менаџирање на пациенти со мозочна траума. Овој систем бидејќи обезбедува директно мерење на кислородната сатурација во мозочниот кортекс, негов дисбаланс е ран предупредувачки знак за потенцијална церебрална исхемија. Целта на оваа студија е иницијално да се утврди корисноста од спектроскопијата блиску до инфрацрвената светлина како метода во превенцијата и рана детекција на секундарни мозочни повреди кај трауматските мозочни повреди и правовремено третирање на истите.

Материјал и методи: Невромониторинг со спектроскопија близу инфрацрвеното зрачење беше спроведен кај седум пациенти со присутна траума на мозокот. Се следеа следниве параметри: Глазгов Кома Скала при прием за одредување на клиничката тежина на трауматските мозочни повреди, систолен артериски притисок, среден артериски притисок, периферната кислородна сатурација и лабораториски наоди. Регионалната мозочна оксигенација се мереше користејќи го церебралниот оксиметар INVOS Somanetics® кој направи неинвазивното мерење со два сензора, т.н. сомасензори кои се поставија во фронталниот дел на главата од пациентот.

Резултати: Во Табела.1 се прикажани параметрите кои се бележеа кај пациентите при самиот прием во единицата за интензивно лекување: Глазгов кома скала, систолен артериски притисок, среден артериски притисок, вредностите на пулсната оксиметрија, дијагноза и морталитет мерен по 24 дена. Во Табела бр. 2 се прикажани вредностите на регионалната церебрална оксиметрија. Кај нотираната подрастична промена на регионалната церебрална оксиметрија (намалување) се употребија процедури за зголемување на мозочната кислородна сатурација. Со отстранување на причината се вратија вредностите на променетата регионалната церебрална оксиметрија на своите базални вредности, односно повторно се покачи мозочната кислородна сатурација.

Заклучок: При анализа на вредностите добиени со спектроскопијата на блиску до инфрацрвената светлина кои варираа при одредени патолошки состојби може слободно да се зборува за корисноста на употребата на регионалната церебрална сатурација во трауматските мозочни повреди и оди во прилог на фактот дека станува забор за важен дополнителен мониторинг систем за правовремена детекција на настанување на несаканите секундарни мозочни повреди. Користењето на овој мониторинг параметар има дијагностичка вредност, но истовремено и дозволува правовремена терапевтска одлука, а со самото тоа ќе влијае и на подобра прогноза на трауматските мозочни повреди што треба да биде поттик за понатамошни истражувања.

Клучни зборови: невромониторинг, спектроскопијата на блиску до инфрацрвената светлина, трауматска мозочна повреда, церебрална оксиметрија.

 ISSN 2545-4366 | UDC 616-089.819-06

INCIDENTS DURING LAPAROSCOPY - HEMODYNAMIC DESTABILISATION - COINCIDENCE OR FACT?

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ABSTRACT

In the recent years, laparoscopic surgery has gained popularity in everyday surgical practice. The effect of the artificial pneumoperitoneum with carbon dioxide (as standard gas for insufflations during laparoscopy) on the hemodynamic and respiratory stability, has been widely studied and known. On the other hand, many studies suggest that different gasses can be used for pneumoperitoneum, even though their effect on cardiovascular system is not well established. Controversial data from case reports, where accidentally different gasses were insufflated, open new debate for patient stability and safety. We present a case of patient scheduled for elective laparoscopic cholecystectomy where accidental intraabdominal insufflations of oxygen 100% lead to marked hemodynamic destabilization. Our case, endured with scientific facts, give us the right to suspect that when oxygen (O_2) is insufflated with same pressure and flow as CO_2 could correlate with hypotension and bradycardia more quickly than carbon dioxide. This leads to a question"can anesthesiology intraoperative parameters serve as an important indicator for preventing any serious complication during pneumoperitoneum?". Another opened question is "Should we always blindly believe in the declarations of the facilities and agents that we are working with?".

Key words: destabilization, fire, incident, indicator, insufflation with oxygen(O_2), laparoscopic surgery.

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Introduction

In recent years, laparoscopic surgery has gained popularity in everyday surgical practice and has become a routinely used method in the abdominal surgery. Pneumoperitoneum (during laparoscopy) can be achieved by insufflation of carbon dioxide (CO_2) or as novel literature suggests many other gasses (1). However, so far the effect of the artificial pneumoperitoneum with CO_2 has been widely studied and therefore this gas is still considered to be"golden standard" for laparoscopy (1,2).

Peritoneal distention and increased intra-abdominal during artificial pneumoperitoneum have well-known effects on hemodynamics and respiratory stability. The rise in intra-abdominal pressure has effects on the venous return and together with the pressure effects and hypercarbia effects, can be the cause of hemodynamic destabilization manifested as hypotension, bradyarrhythmia or tachyarrhythmia (2).

Anyway, studies report different degree of complications and incidents when accidental CO_2 or other unwanted gas has been insufflated during pneumoperitoneum. Besides this, novel studies have suggested that different gasses can be used isolated or as an additive to pneumoperitoneum during laparoscopy (1,2). However, some questions arouse with these novel suggestions. Are there enough studies elaborating the safety issues when working with other gasses? Are the different gas pneumoperitoneum effects identical or different considering cardio respiratory stability? At the end, is there a parameter that can be a predictor or indicator if something unexpected and undesirable is about to happen?

We present a patient scheduled for elective laparoscopic cholecystectomy where accidental intraabdominal insufflation of oxygen 100% lead to marked cardio circulatory and hemodynamic destabilization.

Case report

We present a 68-year-old female patient scheduled for elective laparoscopic cholecystectomy in general endotracheal anesthesia. Patient was 60 kg body weight, smoker with medical history of previous hypertension (chronically treated with Tbl. Amlodipin a 10mg and Tbl. Metoprolol a 100mg). The patient underwent a standard preoperative diagnostic procedure and tests (ECG, RTG and Laboratory tests) and the results were within the normal ranges.

On the day of the surgery patient was premedicated with oral Apaurin 5 mg and was presented for surgery. Upon the entry in the operating theatre and after routine monitoring patient's vital signs were as follows NIBP:170\80mmHg, HR:60 bpm and Spo2:97%.

Induction in anesthesia was uneventful with midazolam 1mg, fentanyl 0,1mg, lidocaine 50mg and propofol 100mg. Intubation was facilitated with rocuronium bromide 0.6 mg/kg and after intubation patient was mechanically ventilated with RR-12, TV-450ml, on O_2- Air mix (50:50%) to achieve $EtCO_2$ from 31- 33 mmHg (Datex Omeda). Anesthesia was maintained with isoflurane (1-3%) and additional doses of fentanyl and rocuronium bromide.

Surgery started and after the trocars insertion CO_2 was insufflated with a flow of 1l/min and up to abdominal pressure of 14 mmHg. Surgery and anesthesia were uneventful except for small rice of the $EtCO_2$ (from 33 to 36 mmHg) that was noticed, all other parameters were stable and not very different from the baseline ones. As the surgery went on, gas supply cylinder was changed and after the change, reinsuflation of the gas was started with the above mentioned conditions. As soon as the reinsuflation started, decline in the EtCo2 was noticed (from 36 to 32mmHg) which was followed by onset of bradycardia (HR dropped to 40bpm) and extreme hypotension (NIBP :70/40 mmHg). At that time, Atropine 1mg and plasma expander Hydroxyl ether starch (HES) were given as a treatment for the cardio-circulatory destabilization. Surgical team was informed for the circulatory destabilization and within the seconds from the destabilization we faced an unusual and dramatic condition of intraabdominal smoke in the surgical field that was visualized trough the laparoscopic camera.

All the action with the cautery was stopped, cold saline was inserted through the trocars and the smoke went down. Cylinder which was started, was immediately changed and 5 minutes after the precaution matters were taken, patient stabilized hemodynamically. The rest of the surgery and anesthesia went normally; patient was extubated in operating theatre and sent to the recovery room for postoperative monitoring. Postoperative course for the patient was normal and after 4 days, patient was discharged fully recovered.

The cylinder which was a gas source during the surgical procedure was sent on further examination at the authorized distributor. The presence of 100% oxygen instead of carbon dioxide was proven.

Discussion

Practicing laparoscopic surgical methods in abdominal surgery means causing artificial pneumoperitoneum. Besides all the surgical benefits from the laparoscopic surgery, still risks like hemodynamic instability, cardio-circulatory unwanted events, ventilation associated disorders are part of the unwanted effects of gas induced pneumoperitoneum.

Artificial pneumoperitoneum, when CO_2 is insufflated, theoretically due to increased intra-abdominal pressure and CO_2 retention may lead to bradycardia or even cardiac arrest (3). Myles P et al. reported that 47% of all patients who undergo pneumoperitoneum experience some kind of arrhythmias, while 30 % of them develop severe bradycardia (4). These unwanted events have several explanations why they occur.

Firstly, possible mechanism for these cardiac rhythm alterations is vagus mediated cardiovascular reflex that is a result of extreme and rapid (rapid gas insufflation with high flow) distension of the peritoneum, secondly, possibility of gas embolism should be considered (4). Many authors confirm that slow gas insufflation and maintenance of the intraabdominal pressure between 12-15 mmHg are essential for hemodynamic stability in all patients (5,6). Dhoste debated that intraabdominal pressure of 12 mmHg and flow rate of 1 l are the only patterns that are needed for hemodynamic stability during laparoscopy (7).

As far as we can say for this case is that the insufflation of the CO_2 was slow with 1l flow and the intraabdominal pressure was maintained between 12-14 mmHg. Additionally, during the first 40 minutes our patient was stabile and no hemodynamic incidents were recorded. After the pneumoperitoneum was started, a rise in the $EtCO_2$ from 33 - 36 mmHg was noticed, but this is totally expected when CO_2 pneumoperitoneum is created. What is worth mentioning in this context is that present hypercarbia was not the cause for any hemodynamic incident. Also $EtCO_2$ didn't drop to concerning levels when bradycardia occurred so possible air embolism was not matter of question.

When we eliminate all the possible causes for hemodynamic instability and when we consider that hypotension and bradycardia occurred after the gas from the new cylinder was insufflated and right before smoke in the abdominal cavity was noticed, we can reliably confirm that there was something wrong with the new cylinder. From this point of view when we know that the cylinder was filled with O_2 instead of CO_2 we might assume or theoretically debate why hemodynamic instability occurred.

Some data reveal that when adding 3% of oxygen to the CO_2 for pneumoperitoneum higher insufflation pressures and longer duration of the pneumoperitoneum are noticed. However, authors confirmed that the addition of more than 3% of oxygen for pneumoperitoneum may be deleterious for the patients (8). What happened in our case is that probably from the new cylinder nearly 100% of O_2 was insufflated in the abdominal cavity and the insufflation resort of O_2 was extremely high, so extreme distension and vagal conducted bradycardia occurred. Additionally, the current surgical practice is to use 100% carbon dioxide, because it is not combustible and thus will not create an explosion even if the electrocautery generates a spark. Contrary to this when sparks, electrocautery and high percentage of O_2 are present, combustion is invincible. What basic physics reveals is that every gas when burnt with or without explosion, increase the gas volume to maximum (9). Therefore, for our patient we have noticed smoke and fire, so these features are complementary for deeper cardiovascular collapse.

To our knowledge besides these few studies and our study that theoretically confirm etiological link of abdominal insufflation with oxygen and consequent hypotension and bradycardia, we couldn't find any relevant data in the literature. All these give us the right to suspect that the oxygen as an insufflation gas could correlate with consequent hypotension and bradycardia and that the awake following of the anesthesiology intraoperative parameters may serve as an important indicator for preventing any serious complication.

From this point of view, the question remains wide open whether abdominal insufflation with normal oxygen flow and intra-abdominal pressure could be the etiologic agent for intraoperative hemodynamic instability manifested by hypotension and bradycardia, so further research in future should be done. Another question that should be left open is "Should we always blindly believe in the declarations of the facilities and agents that we are working with?".

Communication of the surgical and anesthetic teams in the OR during the surgery is also a very important factor in preventing and early treatment in any intraoperative complications.

Conclusion

A gas insufflation during laparoscopic surgery has its own effects on the cardio-circulatory system. Even after practicing surgery and anesthesia under the principles of good clinical practice, we should be prepared to expect even the unexpected. Hence, the preoperative assessment and preparing of the patient, careful practicing laparoscopic techniques, awake intraoperative monitoring are essential for practicing safe surgery and guiding safe anesthesia. Besides the oxygen flammability as a negative capacity due to a gas of choice for laparoscopy, the question remains wide open whether abdominal insufflation with oxygen, with normal flow and intra-abdominal pressure, could be the etiologic agent for intraoperative hemodynamic instability.

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ИНЦИДЕНТИ ВО ТЕК НА ЛАПАРОСКОПИЈА – ХЕМОДИНАМСКА ДЕСТАБИЛИЗАЦИЈА – ФАКТ ИЛИ КОИНЦИДЕНИЈА?

АПСТРАКТ

Последните години лапароскопската хирургија се стекнува со се поголема популарност во клиничката пракса. Влијанието на артефициелно предизвиканиот пнеумоперитонеум со јаглероден диоксид (како стандарден гас за инсуфлација при лапароскопија) врз хемодинамската и респираторна стабилност се добро проучени и познати. Од друга страна, многу студии сугерираат дека и други гасови може да се користат за предизвикување на пнеумоперитонеум, но нивните ефекти врз кардиоциркулаторната стабилност не се добро утврдени. Контраверзните репорти од акцидентална инсуфлација на различни гасови отвораат многу прашања во однос на различни аспекти на стабилноста и сигурноста на пациентите. Овде презентираме случај на пациент за елективна лапароскопска холецистектомија, каде ненамерна инсуфлација со 100% кислород доведе до значителна хемодинамска дестабилизација. Овој случај, поткрепен со научни факти, ни дава за право да се посомневаме дека кислородот (O_2), инсуфлиран под истиот притисок и со ист проток како и CO_2, може да корелира со хипотензија и брадикардија многу побргу споредено со пнеумоперитонеум со јаглеродниот диоксид. Ова води до прашањето: "дали анестезиолошките интраоперативни параметри можат да ни бидат индикатор за превенирање на посериозни компликации при пнеумоперитонеум?" Друго прашање кое сакаме да го отвориме е и "Дали секогаш слепо треба да им веруваме на декларациите на средствата и агенсите со кои работиме?"

Клучни зборови: дестабилизација, индикатор, инцидент, инсуфлација со кислород (O_2), лапароскопската хирургија.

 ISSN 2545-4366 | UDC : 616.65-089.7-032:611.623]:616.152.11

EVALUATION OF THE CHANGES OF ACID-BASE STATUS AND THE SERUM SODIUM CONCENTRATION IN TRANSURETRAL RESECTION OF PROSTATE

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ABSTRACT

Objective*:* Transurethral resection of the prostate (TURP) is endoscopic urological intervention used in the treatment of BPH. A possible complication in TURP procedure is systemic absorption of the hypotonic irrigation fluid known as TURP syndrome. Here we evaluate changes in the level of electrolyte and acid-base status during TURP, correlation of hyponatremia and acidosis in the appearance of TURP syndrome and the impact of the duration of the procedure on the level of hyponatremia and acidosis.

Methods and results*:* 20 male patients were divided into 2 groups according to the length of intervention: Group 1 (n = 9) less than 60 minutes and Group 2 (n = 11) more than 60 minutes. All TURP procedures were performed under general anesthesia and sterile water was used as irrigant. The level of Na +, K + and Cl-, pH, bicarbonate, lactate, base excess and Hb were determined through arterial blood pre-, intra- and postoperatively. **Conclusions***:* Postoperative values of the second group indicated significant hyponatremia and hypochloraemia compared to the preoperative values and acidosis with fall in pH of 7.41 to 7.37 compared to the first group of patients. Changes in both groups of patients are directly proportional to the volume of irrigation fluid, the duration of the procedure and the weight of the recessed prostatic tissue. In all of the cases there were changes in the examined variables, indicating a need for monitoring of electrolytes and acid-base parameters peri- and postoperatively as an opportunity for early detection and treatment of TURP syndrome.
Key words: acid-base status, irrigation fluid, TURP syndrome.

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Introduction

Benign prostatic hyperplasia BPH is enlarged prostatic gland, common disease in men over 40 years old. The symptoms include: urinary frequency, urgency, incontinence, night urination, a weak urine flow, dribbling, intermittency (1). The cause is unknown, but most experts agree that it's linked to hormonal changes that occur as a man gets older and some authors are compliant to hereditary hypothesis (2).

Transurethral resection of the prostate (TURP) is generally considered an option for men with moderate to severe urinary problems that haven't responded to medication (4). TURP has been considered as the most effective treatment for an enlarged prostate and effective replacement for open prostatectomy in most cases. (6,7) It can be carried under general anaesthesia, but spinal anaesthesia is considered to be optimal technique for TURP.

A triple lumen catheter is used for drainage and irrigation of the bladder after the intervention (8). The most common irrigation fluids used during the procedure are solutions of glycine, sorbitol, glucose, distilled water and mannitol (9). TURP syndrome is actually a clinical diagnosis based on symptoms and signs associated with excessive absorption of irrigation fluid into the systemic circulation (10,11). It consists of acute changes in the intravascular volume, changes in plasma concentrations and osmolarity.

Mild to moderate TURP syndrome may occur in 0.5-8% of patients (59, 60, 61), with mortality rate of 0.2-0.8%. (62.63) Severe TURP syndrome is a rare, but however it brings death to 25%. (28)TURP syndrome can occur in the first 15 minutes of resection (TURP syndrome early) up to 24 hours postoperatively (14). The clinical picture varies and is influenced by the type of the used irrigation fluid, the patient and surgical factors. The symptoms are vague, nonspecific and vary from sensations on the face and neck, lethargy, anxiety, fatigue, headache, dizziness, nausea, vomiting, dyspnea, arrhythmias, hypertension, bradycardia, restlessness, confusion. If not treated timely, the clinical manifestation can emerge into cyanosis, hypotension, cardiac arrest and death (15).

A certain quantity of irrigation fluid is absorbed in every TURP procedure (from 20ml/min to several L). 1L irrigant diffusion in the circulation for a period of 1 hour parallels to an acute decrease in serum sodium 5-8mmol/L (16). Acute hyponatremia with serum concentrations of sodium 115-120 mEq/L is a potentially serious condition (17). This kind of state may result in intravascular hemolysis and increase in serum potassium (18).

Hyperkalemic cardio toxicity upsurges with hyponatremia and acidosis (19). Moderate absorption of irrigation fluid during TURP leads to specific metabolic acidosis typical for TURP, so it can be referred to as "TURP acidosis" (21,22,23). Following the changes in acid-base status in TURP was almost ignored. There are some studies that examined changes in different serum variables, but there are not enough studies to observe the changes in acid-base balance during TURP. In evaluating and interpreting changes in acid-base status in TURP the Stewart-Conn's model can be applied, which is more focused on the impact of serum electrolyte concentrations on acid-base changes, compared to the conventional Henderson-Hasellbalch approach (20).

The responsibility for TURP syndrome should be shared by the anesthesiologist and urologist. The best prevention is choosing a correct surgical technique and preoperative evaluation, preparation of the patients and appropriate therapeutic measures.

This study analyzed changes in acid-base and electrolyte status in TURP, which indirectly reveals the absorption of the irrigation fluid into the systemic circulation, and hence early development and diagnosis of TURP syndrome and acidosis characteristics "TURP-acidosis".

Objectives

To evaluate changes in acid-base and electrolyte status in TURP. To evaluate the degree of correlation between acidosis and hyponatremia factors affecting the appearance of TURP syndrome (duration of the procedure, the weight of the recessed prostatic tissue, the amount of used irrigation fluid). To determine which of the factors that leads to TURP syndrome can have the greatest impact on the degree of hyponatremia and the emergence of "TURP acidosis".

Motive

The motivation for this study stems from the need to evaluate the impact of the duration of the procedure of TURP on changes in acid-base status and degree of hyponatremia, and therefore timely to recognize the absorption of larger quantities of irrigation fluid into the systemic circulation. Timely recognition and treatment of changes in acid-base status and electrolyte imbalance, particularly prevention, is essential to reduce the possible occurrence of TURP syndrome, and thus morbidity and mortality in patients treated with TURP procedure.

Materials and Methods

This study included 20 male patients, age 50-80 and ASA classification I-II, scheduled for elective TURP. The patients were divided into two groups according to the length of the intervention. Group 1 (n = 9) in less than 60 minutes and Group 2 (n=11) over 60 minutes. The study excluded patients with heart, lung, kidney disease, patients undergoing transurethral emergency procedures, patients with severe electrolyte disturbances, patients treated with diuretics, diarrhea, vomiting, patients with diabetic or other metabolic acidosis. The patients that had some signs of TURP syndrome at the time of the intervention, and thus needed to be applied diuretics or hypertonic sodium, were also excluded from the study. All TURP procedures were performed in general endotracheal anesthesia and all patients underwent pre-anesthetic assessment and preoperative routine examinations. Before induction of general endotracheal anesthesia in each patient was inserted an intravenous cannula and was applied solution Ringer Lactate of 15-20 ml/kg/h (130 mmol/L Na +; 5,4 mmol/L K +; 1,8 mmol/L Ca ++; 112 mmol/L Cl-, and 27 mmol/L Lactate). In none of the patients were applied colloid solutions, plasma, blood transfusions and blood derivates. General anesthesia was conducted with propofol (1,5 mg/kg), fentanyl (0,3 mg/kg) and rokuroniumbromid (0,6 mg/kg). After endotracheal intubation,

anesthesia was maintained with adequate doses of propofol and additional doses of rokuronium. The mechanical ventilation was performed, so that PaO2 was maintained at 140-200 mm Hg and PaCO2 of 40 mm Hg. In all patients was set cannula of a.radialis, and samples of arterial blood were taken before, during and after the intervention. Using a gas analyzer, the samples were assessed for pH, pCO2, bicarbonate base excess, serum concentrations of Na +, K +, Cl-, lactates and hemoglobin. The strong ion difference (SID) can be calculated based on the equation:

$$SID = (Na + + K +) - (Cl- + Lac-)$$

During the intervention in each patient was conducted basic monitoring: ECG, SpO2, noninvasive blood pressure, pulse in minta and PetCO2. The results of the analysis were compared between the two groups. All the data are normally distributed and presented as mean values with standard deviation. T-test for statistical analysis and the value of $p < 0,05$ was considered statistically significant.

Results

The examined parameters gave the following results: There is a statistically significant difference between the two groups of patients in the size of the recessed prostatic tissue, the total amount of the used irrigation fluid and the total amount of Ringer's lactate with TURP. In the second group of patients, where the duration of the intervention is more than 60 minutes, there was used a greater volume of irrigation fluid, more infusion of Ringer lactate and the recessed prostatic tissue was bigger. The concentration of hemoglobin that represents dilution and loss of blood, showed a significant reduction in both groups of patients, but in the second group of patients, this reduction was significantly more pronounced in relation to the first group.

Table 1.

	Group II (n=11)	Group I (n=9)
Infusion of ringer lactate (ml/m^2)	789±294	524±290
Volume of irrigation fluid (L)	17±9	11±6
Hb (preoperative) Hb (postoperative) (gr/dl)	12.89±1.46 11.53±1.58	13.71±1.21* 13.09±1.46
Resected prostatic tissue (gr)	28.6±16.5	20.0±8.9
Length of intervention (min)	103±39	73.3±17*

**p<0.05, intergroup difference, t-test*

The changes in pH during TURP were of metabolic origin. pH value decreased significantly in both groups. The second group had mild development of metabolic acidosis, declination of the value of HCO3- and base excess (bE) and the first group had significantly, but less declination in the pH value. Again, small but still significant reductions in HCO3- and bE were observed

in the first group of patients. The concentration of sodium and chlorine in the serum was significantly reduced in both groups of patients, and the concentration of potassium in the serum was unchanged. The lactate was increased in the second and in the first group and the strong ion difference (SID) had presented a significant reduction in both groups. All these changes in the parameters were particularly pronounced in the second group of patients where the duration of the intervention was greater than 60 minutes.

Table 2.

	Group II (n=11)		Group I (n=9)	
	t0	t1	t0	t1
pH	7.414±0.0049	7.369±0.041*	7.438±0.051	7.416±0.0047*†
pCO_2	38.5±3.7	39.3±3.0	36.3±4.4	36.3±3.7
HCO_3^-	24.3±2.3	21.9±2.1	24.7±1.5	23.7±1.9
BE	-0.4±2.5	-0.3±2.6*	0.6±1.9	-0.9±2.2*
Na^+	139.4±2.0	132.6±4.8*	138.6±1.7	135.4±2.7*
Cl^-	105.4±2.7	101.6±4.5*	105.1±3.2	102.8±2.8*
K^+	3.6±0.3	3.8±0.3	3.5±0.4	3.6±0.3
Lactate	1.2±0.3	2.3±0.7	1.1±0.2	1.6±0.5†
SID	36.5±2.8	32.5±2.0*	37.2±2.3	34.6±2.4*

**p<0.05, intergroup difference, t-test †p<0.05, intergroup difference, t-test*

Discussion

TURP is endoscopic intervention with possible complications due to absorption of irrigation fluid (> 1000 ml) and possibility of occurrence of hypervolemia, electrolyte imbalances, neurological and circulatory disorders (24). The study of Miyao et al. presented hyponatremia in patients undergoing TURP [25]. Moskovitz et al. in their study did not reveal significant electrolyte changes in the use of distilled water for irrigation (26). Safety using distilled water for irrigation has been described by Shih et al. (27). Norlen and his associates in their study proved changes in serum sodium at absorbing larger quantities of irrigation fluid (28). For determining the absorption intensity of irrigation during TURP, more methods can be used. The method of determination of the standard concentration in expired gas was first postulated by Hahn. It can detect small absorption of irrigation fluid (100-150 ml) in every 10 minutes period (29). Hahn RG in its hypothesis presents that the levels of absorption of irrigation fluid in TURP are associated with the diffusion of sodium ions from the interstitial fluid into the plasma. Part of this sodium is "captured" and disposed through bleeding and urinary excretion. The level of trapped sodium increases with the amount of bleeding and two thirds is bound to plasma loss, and a third with osmotic diuresis. This mechanism contributes to the absolute loss of sodium from the body (30). Shariat et al. in their study have a different presentation about

changes in serum electrolytes. In their study other variables are identified: hypotension (8.3%), hypertension (7.8%), nausea (6.4%) and vomiting (2.8%) (31). Monitoring changes in serum electrolyte in TURP, is simple and economical method for indirectly determining the irrigation absorption (32). This study found slight change in electrolyte and acid-base status because the patients in who appeared early signs of suspected TURP syndrome were excluded from it. This was done very carefully because the TURP syndrome is missing stereotypical representation. This study proved a mild metabolic acidosis in the second group of patients and very discreet metabolic acidosis in the first group.

We found an increase in serum lactate in the second group of patients compared to the first group. There are not any accurate data of linear correlation between the increased lactate concentration and the applying of Ringer lactate. In this study we have eliminated the possibility of lactic acidosis as a cause of metabolic acidosis and evaluated the changes in acid-base and electrolyte status caused of irrigation absorption. According to the Stuart's model, changes in acid-base status and the development of metabolic acidosis can be explained by changes in serum electrolyte concentration. The Strong ion difference (SID) is calculated from the serum concentration of sodium, potassium, chloride and lactate. Basically, metabolic acidosis is present in both groups (higher for the second patients group) as a result in reduction of the strong ion difference (SID). The reasons for the reduction in serum sodium concentration observed in both groups of patients may be due to infusion of Ringer lactate or absorption of irrigation fluid. In the study of Scheingraber S. and his associates is described an occurrence of hyperchloremic acidosis with a decrease in serum sodium (140-138 mmol/L) and increased chlorine serum (104-106 mmol/L), for a period of 2 hours and a rapid infusion of Ringer lactate in patients susceptible to lower gynecological and abdominal surgery (33). In our study, in both groups was reported a significant decrease in serum concentrations of chlorine, thus proving that changes in the concentrations of sodium and chlorine are caused by irrigation absorption predominantly than infusion therapy. Pronounced metabolic acidosis would be expected in a greater degree of hyponatremia. Metabolic acidosis present in TURP would be gravely defined as dilutional acidosis (22). Otherwise the hyperchloraemic acidosis, acidosis described in TURP could be termed as "TURP- acidosis."

Conclusion

Due to moderate absorption of irrigation fluid in TURP discrete metabolic acidosis occurs without clinical manifestations. None of the patients in this study manifested clinical signs of TURP syndrome. However, more irrigation absorption can lead to pronounced clinical metabolic acidosis and electrolyte imbalance, and evaluation of electrolyte and acid-base status is of great importance in patients undergoing TURP in order to reduce the possibility of TURP syndrome.

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ЕВАЛУАЦИЈА НА ПРОМЕНИТЕ НА АЦИДО-БАЗНИОТ СТАТУС И СЕРУМСКАТА КОНЦЕНТРАЦИЈА НА НАТРИУМ ПРИ ТРАНСУРЕТРАЛНА РЕСЕКЦИЈА НА ПРОСТАТА

АПСТРАКТ

Вовед*:* Трансуретрална ресекција на простатата (TURP) е ендоскопска уролошка интервенција која се користи во третманот на БПХ. Можна компликација во постапката TURP е системска апсорпција на хипотонична иригациска течност позната како TURP синдром. Ние направивме евалуација во промените на ниво на електролити и ацидо-базниот статус за време TURP, корелација на хипонатремијата и ацидозата со појавата на TURP синдромот и влијанието на времетраењето на постапката на нивото на хипонатремија и ацидоза.

Методи и резултати: 20 машки пациенти беа поделени во 2 групи во зависност од должината на интервенција: Група 1 (n = 9) пациенти кај кои интервенцијата траеше помалку од 60 мин. и група 2 (n = 11) повеќе од 60 мин. Сите TURP процедури беа изведени под општа анестезија, а како иригант се користеше стерилна вода. Нивото на Na +, K + и Cl, pH, бикарбонати, лактати, базен ексцес и Hb се утврдуваше преку артериска крв пред-, интра-и постоперативно.

Заклучоци: Постоперативните вредности кај втората група укажаа значајна хипонатремија и хипохлоремија во споредба со предоперативните вредности и ацидоза со пад на pH вредноста од 7.41 на 7.37 во споредба со првата група на пациенти. Промените во двете групи на пациенти се директно пропорционални со волуменот на иригационата течност, времетраењето на постапката и тежината на ресецираното простатично ткиво. Во сите случаи имаше промени во испитуваните варијабли, што укажува на потребата за следење на електролитите и ацидо-базните параметри пери- и постоперативно, како можност за рано откривање и лекување на TURP синдромот.

Клучни зборови: ацидо-базен статус, иригациона течност, TURP синдром.

 ISSN 2545-4366 | UDC: 616.6-089:616.155.16

PERIOPERATIVE CHANGES IN CARBOXYHEMOGLOBIN AND METHEMOGLOBIN

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ABSTRACT

Introduction: The inhalation of tobacco smoke can substantially raise the level of carboxyhemoglobin in the blood. The carboxyhemoglobin level can thus identify those people at risk from any of the diseases associated with the inhalation of tobacco smoke even if carbon monoxide is not directly implicated in the pathogenesis of those diseases.

Aim: The aim of the study was to investigate the range of carboxyhemoglobin and methemoglobin in the smoking and non-smoking patients and the effect of pre-oxygenation with 100% of oxygen on their level. Furthermore, we evaluated the perioperative changes in carboxyhemoglobin and methemoglobin during surgery.

Material and methods: The study included 20 patients scheduled for urological surgery under general endotracheal anesthesia, aged 18–60 years without any history of respiratory disease, divided into two groups. In the study group (n=10) were included patients who were smoking cigarettes or tobacco pipe, while the control group (n=10) included nonsmokers. In groups carboxyhemoglobin and methemoglobin levels were determinate pre-operatively (T_0), after pre-oxygenation with 100% oxygen before induction in anesthesia (T_1) and postoperatively (T_2). The influence of smoking was disregarded in the analysis, because smoking was shown to increase exogenous and endogenous carbon monoxyde, respectively.

Results: Postoperative carboxyhemoglobin levels were lower than the preoperative, (from 2.2 ± 1.32SD vs. 2.02 ± 0.65SD) for smoking group and (from 0.56 ± 0.29SD vs. 0.44 ± 0.21SD) for nonsmoking group. Postoperative values of carboxyhemoglobin (2.02 ± 0.656 vs 0.44 ± 0.211, p=0.000) were higher in the smoking group compared to nonsmoking group. On the other hand

values of methemoglobin postoperatively (0.25 ± 0.108 vs. 0.29 ± 0.070, p=0.33) were lower in smoking compared with nonsmoking group, but no significant difference was found. In both groups, methemoglobin increased after pre-oxygenation and postoperative, and there was no effect of smoking on the changes in methemoglobin.

Conclusion: Changes in carboxyhemoglobin and methemoglobin concentrations in arterial blood occur during urological surgery, although these amplitudes are small when compared with carbon monoxide intoxication and methemoglobinemia. It is likely that organ perfusion and functions are affected by these monoxide gas mediators during urological surgery.

Key words: carboxyhemoglobin, methemoglobin, perioperative, urological surgery.

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Introduction

The inhalation of tobacco smoke containing up to 5% carbon monoxide can substantially raise the level of carboxyhemoglobin (COHb) in the blood (1,2). Levels of up to 16% have been recorded in cigarette smokers (3), and the COHb level of inhaling smokers is significantly higher than that of nonsmokers (4). The COHb level can thus identify those people at risk from any of the diseases associated with the inhalation of tobacco smoke even if carbon monoxide is not directly implicated in the pathogenesis of those diseases (5).

On the other hand, carbon monoxide (CO) is produced by heme oxygenase (HO) which catalyzes the cleavage of the porphyry ring of heme. Heme oxygenase activity is high in the brain, spleen, liver and testis. Heme oxygenase-2 is dominant in the brain and testis, while HO-1 is dominant in the spleen. Heme oxygenase-1 is induced by heme, hemoglobin, hypoxia, oxy-radicals, cyclic adenosine monophosphate (AMP), heat shock, and cytokines via activation of the transcriptional process (6,7). However, it still remains unknown whether: surgically induced stress, sepsis, orchidectomy, splenectomy or hepatic resection in the clinical situation increases the concentration of HO-1 by induction of the enzyme or decreases it by reduction of the enzyme.

Hemoglobin with ferrous heme is converted to methemoglobin (MetHb) with ferric heme in the presence of NO or other oxidizing agents, while MetHb is converted to hemoglobin enzymatically by MetHb reductase (8). Therefore, MetHb is maintained at a constant level. However, excessive production of MetHb relative to total MetHb reductase activity results in an increase in MetHb.

The physiological and pharmacological roles of NO have been elucidated extensively in experimental and clinical models for several decades (9-11). By contrast, CO which is homologous to NO as a monoxide has only recently been studied as a novel gaseous mediator for maintenance of circulatory homeostasis and regulation of organ function (12-14). Because is difficult to metabolize CO in vivo, and CO binds with high affinity to hemoglobin, it is easy to measure the endogenous production of CO as COHb using spectrophotometry (5).

Therefore, the aim of the study was to investigate the range of COHb and MetHb in the smoking and non-smoking patients and the effect of pre-oxygenation with 100% of oxygen on the level of COHb and MetHb. Furthermore, we have evaluated the perioperative changes in COHb and MetHb during surgery.

Material and Methods

This prospective clinical study was performed at the Clinic for Traumatology, Orthopedic Diseases, Anesthesia, Reanimation and Intensive Care Skopje. After obtaining written information consent from patients, we enrolled all consecutive patients scheduled for elective urologic surgery under general endotracheal anesthesia, aged 18–60 years, under physiological score for preoperative assessment of health – ASA (American Society of Anesthesiologists) 1 and 2. The study excluded all patients having surgery under local or regional anesthesia, patients with any history of respiratory disease, pregnant patients, and transplant patients. The patients were assigned into two groups - smokers (smoking ≥10 cigars or 30 grams of pipe tobacco per week) (15) and never-smokers (those who had never smoked cigarettes or pipe tobacco) (15).

All patients underwent standard pre-operative protocol for nothing per mouth (for 6 hours) and premedication with oral Diazepam 5 mg. The standardized anesthesia protocol was commenced for both groups. After pre-oxygenation with 100% O_2 for 3 minutes, the induction has started with midazolam 1-2 mg fentanil (2-10 μg/kg) and propofol (1-2 mg/kg). The intubation was facilitated with rocuronium bromide 0.6 mg/kg. After two minutes the patients were intubated and mechanically ventilated with in-haled fraction with a mixture of O2 (50%) and air (50%). The anesthesia was maintained with continuous infusion of propofol 0,1 - 0,2 mg/kg/min, fentanil 1-2 mcg/kg and rocuronium bromide 0,3 mg/kg.

Arterial blood gas analysis was performed at three time points: T_{0} - before operation under respiration with room air; T_1 - after pre-oxygenation with 100% O_2 for 3 minutes with 6L/min flow, and T_2 - one hour after the operation in post-anesthesia recovery room under respiration with room air or oxygen inhalation with or without endotracheal intubation.

Carboxyhemoglobin, methemoglobin, total hemoglobin, and partial pressure of carbon dioxide (PCO_2 mmHg) and oxygen (PO_2 mmHg) in arterial blood were measured by blood gas analyzer (SIEMENS RAPID Point 500 Systems). COHb, and MetHb were analyzed spectrophotometrically using their specific absorption and reference wavelengths.

Statistical analysis was performed by analysis of variance and differences test. P -value less than 0.05 was considered as significant.

Results

In accordance with the including criteria, the study enrolled 20 patients in both groups. Between both groups of patients, the baseline demographic characteristics were similar with respect to gender, age, weight, height BMI and ASA.

The baseline demographics and the clinical characteristics of the patients are shown in Table 1.

Table 1. *Demographic and clinical characteristics (Mean ± SD).*

Parameters	Group Smokers n=10	Group Non-smokers n= 10	P
Sex M/F	7/3	6/4	NS
Age	43.35 ± 16.8	49.96 ± 11.3	NS
ASA I/II	0/10	1/9	NS
BMI (m^2)	25.1 ± 3.4	25.4 ± 2.5	NS

Abbreviations: F - female; M – male; ASA- American Society of Anesthesiologist, BMI-Body Mass Index; NS-Not significant (p > 0.05).

There was a variety of diagnosis and the mostly represented clinical diagnosis at the I and II group was kidney cancer with 30% in both groups. In table 2 are presented the characteristics of the surgery. In nonsmoking group 40% of the interventions were laparoscopic and in group II were only 30% laparoscopic.

Table 2. *Characteristics of the surgery (Mean ± SD).*

Groups	Surgery Open/Laparoscopic	Anesthesia time (min)	Operation time (min)	Blood transfusion (no/yes)	Transfusion unit
Smokers n=10	7/3	159 ± 52.9	129 ± 47.8	5/5	1
Non-smokers n=10	6/4	179.5 ± 61.4	146.5 ± 59.3	6/4	1.2

Table 3 shows the effect of smoking on the perioperative changes in arterial blood gas analysis for the control nonsmoking group. In the smoking group, COHb was significantly higher at all three time points than in the non-smoking group, and decreased significantly postoperatively from the preoperative value due to mechanical ventilation. In both groups, MetHb increased after preoxygenation and postoperative, and there was no effect of smoking on the changes in MetHb.

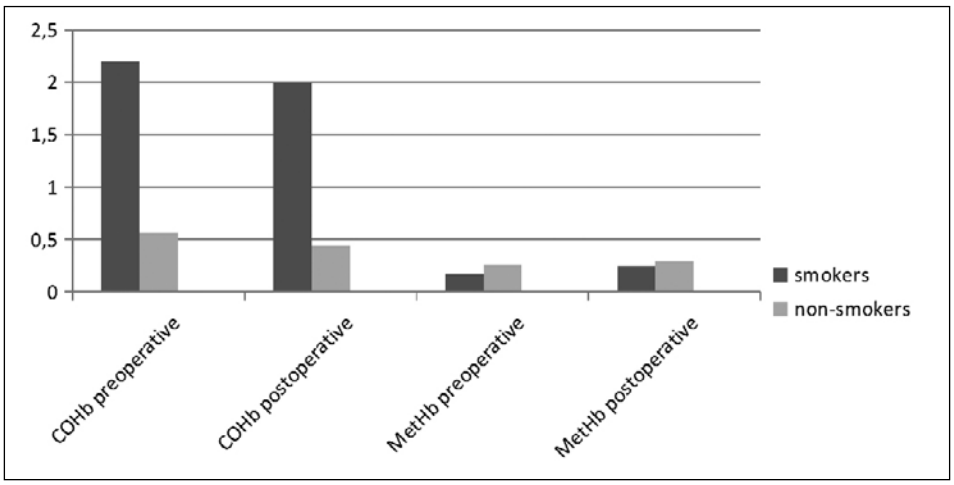
Table 3.*Perioperative changes in carboxyhemoglobin and methemoglobin in the Smoking and Non-smoking Group.*

	T_0	T_1	T_2
Group Smokers n=10			
COHb	2.2 ± 1.32	2.21 ± 1.43	2.02 ± 0.65
MetHB	0.17 ± 0.11	0.25 ± 0.15	0.25 ± 0.18
Total HB	143.4 ± 22.1	118.9 ± 31.53	115.4 ± 19.86
PCO_2	40.3 ± 5.14	50.48 ± 8.54	47.6 ± 6.2
PO_2	78.6 ± 11.7	105.6 ± 25.40	77 ± 8.04

Group Non-smokers n=10			
COHb	0.56 ± 0.29	0.53 ± 0.37	0.44 ± 0.21
MetHB	0.26 ± 0.15	0.34 ± 0.24	0.29 ± 0.07
Total HB	135 ± 24.87	126.8 ± 24.49	111.9 ± 19.85
PCO_2	40.3 ± 5.14	43.3 ± 6.09	41.6 ± 6.81
PO_2	85.64 ± 9.74	128.13 ± 30.67	90.7 ± 10.05

Values are expressed as mean ± standard error of the mean.
T_0 - preoperative; T_1 - after preoxygenation; T_2 - one hour after surgery;
COHb - carboxyhemoglobin; Hb - hemoglobin; MetHb - methemoglobin;
PCO_2 - partial pressure of carbon dioxide; PO_2 - partial pressure of oxygen.

The values of the COHb showed a decrease postoperatively (from 2.2 ± 1.32SD vs. 2.02 ± 0.65SD) for smoking group and (from 0.56 ± 0.29SD vs. 0.44 ± 0.21SD) for nonsmoking group. The average values of COHb between the two groups were statistically significantly different. At baseline preoperative value (T_0), p=0.0019, at the second time point (T_1) after preoxygenation the value was p=0.0021 and at the postoperative time point (T_2), p=0.000. As for the values of the MetHb, showed an increase postoperatively (from 0.17 ± 0.11SD vs. 0.23 ± 0.18SD) for smoking group and (from 0.26 ± 0.15SD vs. 0.29 ± 0.07SD) for nonsmoking group. The average postoperative values of MetHb between the two groups were statistically not significantly different. In the baseline preoperative time point T_0, p=0.21, at the second time point after preoxygenation T_1, p=0.32 and at the last postoperative time point T_2, p=0.33.



Graph 1. *Change of the average values of CoHb and MetHb in the groups.*

Discussion

The presented study was conducted as pilot study and showed how in clinical practice smoking has influenced on the levels of COHb and MetHb perioperative. The present analysis clearly indicated that smoking increases exogenous COHb and that the effect of smoking remains even

after mechanical ventilation. Although it has been reported that reaction of sevoflurane with soda lime which has not been used for more than 2 weeks generates CO (16), the possibility was ruled out due to the intravenous anesthesia used in our study and due to high frequent use of the anesthetic circuit at our hospital.

A significant increase of CO was routinely observed by Levy et al. (17) during general anesthesia in infants and children when low flow anesthesia was used. In our study we used normal flow anesthesia in all patients.

The presented study indicated that intubation anesthesia increases MetHb. Although nitroglycerin and sodium nitroprusside have been reported to cause methemoglobinemia, which is recognized by cyanosis (18), nitroglycerin and sodium nitroprusside were never used for hypotensive anesthesia in the present series.

Different from the study of Takeda, were nitrous oxide (N_2O) has been used in all cases (19), but contamination of NO in N_2O gas was completely negligible. In our study N_2O was not used, therefore, the increase of MetHb postoperatively was ascribed to endogenous NO or some other autoxidizing mechanism which converts ferrous heme (Fe+2) to ferric heme (Fe+3).

The laparoscopic operation creates a pneumoperitoneum with carbon dioxide (CO_2), but blood gas analysis did not indicate retention of CO_2 at several hours after extubation, or a pathway which converts carbon dioxide to carbon monoxide. It has also been proposed that laparoscopic surgery with electric cautery is likely to generate CO due to incomplete combustion of the tissue, but comparison between laparoscopic (n=4) and open surgery (n=6) in the nonsmoking group did not show any significant differences in COHb and MetHb. It has also been reported that the use of electric cautery in the laparoscopic surgery did not increase COHb (20).

Half-life of carboxyhemoglobin is 250 minutes, for the people breathing room air. This is reduced to 40 to 60 minutes with inhalation of 100% oxygen according to the review article of Dries (21). In our study preoxygenation with 100% oxygen for 3 minutes before anesthesia and surgery decreased the level of carboxyhemoglobin.

Locally generated CO is eliminated by Hb in circulating erythrocytes and is gradually released into the alveolar space of the lungs, where molecular oxygen is alternatively bound to the heme. Most endogenous generated CO is thus exhaled into the airway, and the alveolar oxygen tension determines the exchange rate between oxygen and CO (5). For these reasons, COHb in blood samples collected from patients could be altered by multiple factors such as surgical insults, hemoglobin concentrations, tissue oxygenation and pulmonary function (22). In this study, we chose patients who did not suffer from obvious respiratory or inflammatory disease, and we fixed the inspired oxygen fraction at 0.5 during the study except for the period of preoxigenation. We tried to maintain Hb concentrations > 100 mg/Dl, so that Hb concentration at sampling time did not differ between groups and were not correlated with COHb concentrations.

Carbon monoxide binds to hemoglobin to form COHb without oxygen-carrying capacity because of its 200 times stronger affinity, compared to oxygen. When COHb reaches to 10% of

total hemoglobin, namely around 10 mg/mL, CO intoxication appears as working disability and headache. When the concentration exceeds 30%, consciousness is lost. Thus, CO is known as a toxic gas [3]. Nevertheless, inducible and constitutive heme oxygenizes that produce CO from heme proteins are inherent in the human body, and the physiological role of CO as a toxic gas has yet to be elucidated completely. In the present study, the amplitude of COHb changes was not so large as compared to CO intoxication.

Because MetHb lacks oxygen carrying capability, methemoglobinemia is regarded as a causative factor of hypoxia. The body is equipped with methemoglobin reductase to eliminate MetHb from the blood (23). The amplitude of changes in MetHb during urological surgery is also rather small compared to methemoglobinemia, which causes cyanosis. However, since the generation velocities of these two monoxides fluctuate during urological surgery, these gas mediators are likely to affect organ function, although the present study does not investigate the effects.

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ПЕРИОПЕРАТИВНИ ПРОМЕНИ НА КАРБОКСИХЕМОГЛОБИН И МЕТХЕМОГЛОБИН

АБСТРАКТ

Вовед: Пушењето цигари го зголемува нивото на карбоксихемоглобин во крвта. Одредувањето на нивото на карбоксихемоглобин во популацијата, може да ги идентификува луѓето со зголемен ризик за развој на болест поврзана со пушењето, дури и во случаи кога карбон моноксидот не е директно имплициран во истата.

Цел: Целта на овој труд беше да се определи нивото на карбоксихемоглобин и метхемоглобин како и да се евалуираат нивните периоперативни промени кај пациенти пушачи и пациенти непушачи. Воедно, се анализираше и ефектот на преоксигенацијата со 100% кислород на нивото на карбоксихемоглобин и метхемоглобин.

Материјал и метод: Студијата вклучува 20 пациенти на кои им е закажана елективна уролошка интервенција со општа ендотрахеална анестезија, на возраст од 18–60 години, без лична анамнеза за респираторно заболување, поделени во две групи. Испитувана група пушачи (n=10) и контролна група не-пушачи (n=10). Карбоксихемоглобинот и метхемоглобинот беа одредувани во три времиња: предоперативно (T_0), после преоксигенација со 100% кислород (T_1) и постоперативно (T_2).

Резултати: Постоперативните вредности на карбоксихемоглобин во испитуваната група пушачи беа повисоки од вредностите на контролната група непушачи (2.02 ± 0.656 vs 0.44 ± 0.211, p=0.000). Постоперативните вредности на карбоксихемоглобин споредено со предоперативните беа пониски во двете испитувани групи: (2.2 ± 1.32SD vs. 2.02 ± 0.65SD) пушачи и (0.56 ± 0.29SD vs. 0.44 ± 0.21SD) непушачи. Вредностите на метхемоглобинот од друга страна пак беа пониски во контролната група непушачи споредено со вредностите на испитуваната група пушачи. Но, вредностите не беа статистички сигнификантни (0.25 ± 0.108 vs. 0.29 ± 0.070, p=0.33). Во двете групи вредностите на метхемоглобин беа покачени како после предоксигенацијата, така и постоперативно, без статистички сигнификантна разлика на вредностите помеѓу групите.

Заклучок: Иако се случуваат несигнификантни промени во вредностите на карбоксихемоглобин и метхемоглобин во тек на уролошки интервенции, сепак се смета дека овие промени се многу мали за да можат да влијаат на органската перфузија и функција.

Клучни зборови: карбоксихемоглобин, метхемоглобин, периоперативни, уролошки операции.

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The Journal is published twice a year (April and November), but additional supplements might be published when needed. MJA publishes original (professional and scientific) articles, review articles, case reports, therapeutic and technological innovation, discussions, critics, impressions from meetings, information for international conferences and reviews of new books or variate.

Manuscripts that are published should have not been published previously. Manuscripts that have been previously published only in form of abstracts are eligible for publishing in the journal but should be followed by additional letter send to the Editor, where the abstract details are noted (abstract number, which book of proceeding or doi, date and place).

The authors are responsible for respecting the ethical guidelines for medical researches, as well as for all that is explained, attitudes, analyses and shown results.

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The manuscript has to be written in **English**, followed by an abstract in Macedonia (after the references section).

Manuscripts should be written in **Microsoft Word** (*.doc format) with **Times New Roman** font and **size 12**. Margins on left, up and bottom should be 3cm and right margin should be 2,5cm.

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Material and method sections includes detailed description of the performances in the research as well as the statistical analyses used. This section should include: time during what the research was conducted, type of the study, place of where the research was undertaken, randomization or stratification used (clear description of the examined groups), exclusion and inclusion criteria, method, analysis types, apparatus and instruments used and referent values of the examined features (in SI-International System units).

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Discussion section emphasize the key finding of the actual research and compares these result to other relevant literature data.

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3. Books

Brown, D.L. Spinal, epidural, and caudal anesthesia. In R.D. Miller Miller's Anesthesia, 6th edition. Philadelphia: Elsevier Churchill Livingstone; 2005.p 98-198

4. Doctoral or master thesis

1. Jelisavac Cosic S.Urokinazni I tkivni aktivator plazminogena i njihov inhibitor u raku dojke (Master thesis).Zagreb: Farmaceutsko-biohemijski fakultet 2004, p.50

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Dag Stat. Mackinnon A. Available from :http//www.mhri.cdu.au/biostats.Accessed May 5th 2006.

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