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CONTENT

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HERBAL SUPPLEMENTS AND ANAESTHESIA

For thousands of years herbal supplements have been used in medicine to maintain or improve the health. Nowadays natural medicine is very popular. The consumption of herbal products for self-treatment of any medical disorder is growing. The benefits of some of them are well known, but the variety of their side effects makes their use dangerous, especially when they are used in combination with other drugs. These plant products contain multiple compounds and have the same pharmacokinetics and pharmacodynamic principles as drug to drug interactions (1). Recent reports on anesthesia meeting (ARUD 2017) about uncontrolled bleeding during surgery and sudden death of victims consuming herbal supplements imposed the actualization of this problem (2).

In the anesthesia practice, the recognition of the use of herbal medicine is not routine and their adverse effects are unknown. Patients wrongly believe that the herbal supplements are always safe, thus avoiding to share prior to the operation this information with their family, doctors and the anesthesiologists. In the standard anesthetics protocols, the routine inquiries of the patient about their self medications are missing. The contemporary knowledge of the influence of herbal supplements to other drugs and any possible interactions with medications used during anesthesia, highpoints the crucial importance of asking patients about self-medication (3).

All herbal agents have potentially unexpected effects including sedation, toxicity or impairment of coagulation, that may be influenced by age, gender or current therapy (4, 5).

The goal of this short report is to remind my colleagues anesthesiologists that the herbal supplements are not placebo, and that they have many side effects. Most herbal drugs have good safety profiles, but they have unwanted influence on anesthetic and surgical practice, which must be taken into consideration. The list of the used herbal supplements is too long, but the presentation of several examples is sufficient to support these findings.

In 2003, Williamson EM reported about the hepatotoxic effects of **kava** or **Echinacea** when they were taken with other concurrent drugs (6). The popular herbs such as **aloe leaf**, **guar gum** and **senna**, are often used for slimming. Their main effect is laxative, producing many disorders in gastro intestinal tract such as: change of the intestinal pH, affection of the intestinal motility and reduction of the absorption of the drugs (7).

St. John's Wort (Cantarion herb) is an herb that is widely used in our country. Very few professionals know that this herb induces the production of the cytochrome P450 enzymes and intestinal P-glycoprotein. As a result of this, its use leads to decreased absorption and reduced efficacy of the oral contraceptive pill or blood levels of warfarin, digoxin, protease inhibitors, theophylline and carbamazepine (8). St. John's Wort used in combination with other serotonergic drugs may produce alteration in mental status, autonomic dysfunction and neuromuscular abnormalities (9).

Some herbal remedies produce an increased inhibition of the production of the enzymes which can increase/ inhibit the therapeutic effects of some drugs (10).

In 2011, Sarah Spiteri Staines in the Journal of the Malta College of Pharmacy Practice, referred that herbs might produce a concurrent effect of the drug and give an increase in the drug effect (without increasing the amount of the drug) (11).

The herbs that have sedative, anticoagulant or antihypertensive properties are able to increase the effect of the drugs used during anesthesia. It is very important to know that herbs such as: valerian, gingko, garlic and ginger can enhance the hypnotic activity and the anticoagulant action of conventionally used drugs as benzodiazepines and warfarin (12).

It can be concluded that herbal supplements have influence over the management of the surgery and anesthesia. In general their use should be stopped a week before the operation. Prior to surgery the patients must be interviewed about their self-medication. Even the use of green tea may increase the bleeding during surgery.

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HEMODYNAMIC PROFILE OF UNILATERAL SPINAL ANESTHESIA IN ELDERLY PATIENTS

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ABSTRACT

Background: Hemodynamic stability is desired outcome of any anesthetic technique. Tachycardia, hypotension and hypertension can lead to perioperative myocardial infarction, and hypotension can lead to stroke. Spinal anesthesia in elderly patients provides stable hemodynamic profile. Unilateral spinal anesthesia (USA) has proven hemodynamic stability. This study is aimed to explore the hemodynamic profile of USA in elderly patients with hyperbaric Bupivacaine and Levobupivacaine.

Methods and Material: Elderly patients (over 65 years old), who were randomized to unilateral spinal anesthesia with either low dose of hyperbaric bupivacaine or hyperbaric levo-bupivacaine, were analyzed for differences in block characteristics, safety hemodynamic profile and other common side effects.

Results: 26 patients, average age 76.77±7.207 18 female and 8 male, ASA 2 and 3, who underwent surgery for hip fracture (56%), other leg fracture (12%), limb amputation (16%) and hernia repair (16%) were randomized in two intervention groups - Group I: USA with hyperbaric 5-10 mg Bupivacaine in 7% dextrose+20mcg Fentanyl and Group II: hyperbaric 5-10 mg L-Bupivacaine in 7% dextrose+ 20mcg Fentanyl. The two groups with comparable demographic characteristics had satisfactory surgical conditions with maximal Th10 sensory level for both groups; with a consecutive stable blood pressure, low rate of significant hypotension (1 case group I and 3 in group II), stable heart rate and low incidence of nausea, pruritus and PDPH. No ST segment changes were observed in the perioperative period.

Conclusion: Unilateral spinal anesthesia with low dose of hyperbaric bupivacaine or levo-bupivacaine is safe and reliable technique for elderly patients.

Key words: elderly, hemodynamics, unilateral spinal anesthesia.

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Introduction

Hemodynamic stability is desired outcome of any anesthetic technique. Tachycardia, hypotension and hypertension can lead to perioperative myocardial infarction (1); furthermore hypotension can lead to stroke (2). Elderly patients have increased mortality associated with anesthesia and surgery (3). The decaying physiological functions lead to impaired compensatory mechanisms to fight the surgical stress. Therefore, it is important to adjust the anesthetic management in elderly to preserve the hemodynamic function and to prevent any perioperative conditions that can lead to major cardiovascular events. For that matter, neuroaxial anesthesia was proven to benefit the elderly reducing the overall mortality and the incidence of perioperative myocardial infarction (4).

Spinal anesthesia's the most feared side effect is hypotension, which in its own right is responsible for more than half of the cases of myocardial ischemia compared to normotensive patients (5). Since its first use, this feared side effect has led to endless quests for the Holy Grail to modify the technique that would deliver stable hemodynamic profile. Spinal anesthesia is simple, reliable, affordable, predictable, accessible technique for many surgical and gynecological procedures. It has more than century long successful clinical use. It is also proven in elderly patients with hip fracture, to deliver more stable hemodynamic profile then general anesthesia (6). Research shows that the two main risk factors associated with development of hypotension seem to be high sensory level and advanced age (7).

Selective spinal block on one side of the nerve roots has a fifty year old theoretical and practical research (8). For a successful case of selective spinal block it is necessary to use sufficiently low anesthetic dose, difference in baricity of the anesthetic solution and the cerebrospinal fluid during lateral decubital position and sufficient time for setting the block. Whether hypobaric or hyperbaric solutions were used, what is common for any research so far is the positive outcome of stable hemodynamic profile, less hypotension and major cardiovascular and cerebrovascular perioperative events (9). The proposed mechanism that explains the prevented hypotension is limited pooling of the blood in the dilated veins and the contralateral reflexive vasoconstriction on the non-anesthetized side.

Our study aimed to explore the hemodynamic profile of USA with two different local anesthetics: hyperbaric bupivacaine and hyperbaric levobupivacaine in elderly patients. The objective was to test the difference in efficacy to produce clinically relevant unilateral spinal anesthesia and safe hemodynamic profile between the different local anesthetics in elderly patients.

Material and Methods

This study was performed at the University surgery hospital St Naum Ohridski Skopje in 2016, as a part of a bigger project aimed to investigate three different anesthetic preparations in unilateral spinal anesthesia in all eligible patients for spinal anesthesia, and their block characteristics as well as side effects. The inclusion and exclusion criteria are corresponding with the indications and contraindication for any spinal anesthesia. A group of 60 patients meeting the inclusion criteria were randomized in three groups, per 20 patients in each group. The sample size was calculated to be sufficient to detect statistically significant difference in block height (two dermatome difference between the groups), with study power of 80 and alpha error of 0.05 using Epi Info. Group I placed in lateral decubital position received intrathecally 5-10 mg Bupivacaine 0.5% heavy (7% dextrose preparation) with Fentanyl 20μg; Group II received 5-10 mg Levo-Bupivacaine 0.5% heavy (7% dextrose preparation) with Fentanyl 20μg and group III received 5-10 mg Levo-Bupivacaine 0.5% heavy (3% dextrose preparation) with Fentanyl 20μg [see diagram 1].

Diagram 1. Group I Bupivacaine 0.5%, preparation

I group	Bupivacaine 0.5% heavy (7% Dextrose)	Dosage
Bupivacaine 0.5% heavy (commercial preparation)	2 ml	10 mg
fentanyl	0.4 ml	20mcg
Total volume	2.4 ml	
Bupivacaine 0.5% heavy	1.5 ml	7.5 mg
fentanyl	0.4 ml	20mcg
Total volume	1.9 ml	
Bupivacaine 0.5% heavy	1 ml	5 mg
fentanyl	0.4 ml	20mcg
Total volume	1.4 ml	
II group	**Levo-Bupivacain 0.5% heavy (7% Dextrose)**	**Dosage**
Levo-Bupivacaine 0.5%	2 ml	10 mg
Dextrose 35%	0.6 ml	210 mg
Fentanyl	0.4 ml	20 mcg
Total volume	3 ml	
Levo-Bupivacaine 0.5%	1.5 ml	7.5 mg
Dextrose 35%	0.5 ml	175 mg
Fentanyl	0.4 ml	20 mcg
Total volume	2.4 ml	
Levo-Bupivacaine 0.5%	1 ml	5 mg
Dextrose 35%	0.4 ml	140 mg
Fentanyl	0.4 ml	20 mcg
NaCl 0.9%	0.2 ml	
Total volume	2 ml	

All the patients were premedicated with diazepam according to body weight and pre-hydrated with Ringer lactate 10 ml/kg half an hour before spinal block according to their hydration status and cardiovascular tolerance. After standard monitoring (ECG, noninvasive blood pressure measurement, SaO2), patients were placed in lateral decubital position, the spinal puncture was performed with Quincke spinal needle, size 25-26G, at L3-4 level. Once free flow of cerebrospinal fluid was obtained and the needle bevel turned to the dependent leg, the rate of injection of the anesthetic preparation was kept at 1 ml per 30 seconds. Patients were held in the lateral decubital position until Th10 sensory level was reached, and then turned supine. In rare cases when Th10 was not reached, patients were turned supine after 20 minutes in lateral decubital position when the sensory level block was sufficient to perform the operation.

Patients were tested for motor and sensory level by anesthetist blinded for the intervention group. Patients were tested for sensory and motor block during lateral decubital position and after turning supine every minute. The sensory block after administration of USA was tested using discrimination of cold/warm sensation using 70% ethanol solution swap along the mid-clavicular line on both sides of the body and also pin-prick test for pain to determine the maximal sensory level reached. The time from puncture until Th10 sensory level reached was recorded on the anesthesia station timer and noted in the Patient Record Form. Also the maximal sensory level reached was recorded during lateral decubital position and after turning supine on both legs. Unilateralization of the sensory and motor block was also recorded. Patients were considered having unilateral spinal block only if they didn't have sensory nor motor block to any level throughout the operation time. Motor block was tested using the Modified Bromage scale, with four levels of motor block (Bromage 3 – Unable to move feet or knee; 2 - Able to move just the feet; 1 – Just able to move knees; 0 – Full flexion of knees and feet). The sensory block and motor block regression was tested after the surgery in the postoperative anesthesia care unit. And the time from spinal puncture to sacral dermatomes block regression was recorded.

The hemodynamic profile was monitored through ECG heart rate, noninvasive blood pressure measurement on GE Datex Ohmeda S/5 Anesthesia work station. The ST analysis was also used to record possible ST change during the surgery and in the immediate postoperative period. The heart rate, the systolic, diastolic and mean arterial blood pressure were recorded on baseline, immediately after anesthetic administration (0 minutes) and every 5 minutes thereafter (0, 5, 10, 15, 20, 30 minutes, end of operation) for every individual patient. Absolute drop of blood pressure, defined as drop to less than 60 mmHg mean arterial pressure and relative hypotension, defined as drop to more than 30% of the baseline blood pressure value were recorded. Use of vasopressors and/or colloid to treat the hypotension was recorded.

Side effects as nausea, vomiting, postoperative post puncture headache and pruritus were recorded as variables throughout the perioperative period.

The data from the Individual Patient Form were transferred by the investigator into Excel table as numerical variables.

The secondary data analysis was made by sub-analysis of the group of elderly patients as defined as being over 65 years, regardless of the surgery. After the data selection, the group which received the 3% dextrose l-Bupivacaine 0.5% was excluded from the analysis due to low sample size.

The statistical analysis was made using statistical program SPSS Statistics 20 for Windows. Descriptive and analytical statistics were used to test the hypothesis and present the data obtained. Descriptive analysis (mean, standard deviation, median, range, proportions) was used to present the results for patients' demographics (age, sex, ASA status, baseline mean arterial pressure, hypertension at baseline, dose of the anesthetic used, total volume of the anesthetic solution, operation time, intraoperative fluid volume), block characteristics of each group (maximal sensory level reached, time from spinal puncture to reach Th10 sensory level, time from spinal puncture to regress to S2 sensory level, unilateralization at lateral decubital position, unilateralization after turning supine, Bromage 3 and 2 motor level at lateral decubital position, Bromage 3 and 2 motor level after turning supine), hemodynamic parameters (mean arterial pressure at baseline, 0, 5, 10, 15, 30 and end of surgery, relative hypotension, absolute hypotension, bradycardia, use of vassopressors, ST segment change from baseline), and side effects (nausea and vomitus, postpunctural dural headache and pruritus, stroke, myocardial infarction).

Analytical methods used were Chi-squared test to analyze difference between dichotomous data, ANOVA test between continuous data, Wilcox test for categorical data and Mann Whitney test for continuous non-normally distributed parameters.

P less than 5% percent was considered statistically significant.

Results

Twenty six patients were eligible for the secondary data analysis that met the inclusion criteria, with average age of 76.77±7.207 (range 65 to 90 years old), 18 female and 8 male, ASA 2 and 3 (26% and 74% respectively), who underwent surgery for hip fracture (56%), other leg fracture (12%), limb amputation (16%) and hernia repair (16%). The two intervention groups have comparable demographic characteristics, age, sex, ASA class, baseline MAP; also comparable anesthetic dose used, total intraoperative intravenous fluids, operation time (see Table 1). The only significant difference is the volume of the anesthetic used which can be explained by the difference in preparation of the anesthetic solution. Also it was deliberately chosen not to correct for the difference in volume used since it has been repeatedly proven that there is no difference in the spread of the anesthetic between different volumes while the total dose is kept the same (10). Therefore the difference in anesthetic volume between the two studied groups was expected outcome and one counted for. The profile of the type of surgery was also similar, with predominance of hip fracture fixation (Group I - 47%, and group II - 70%), other lower limb fracture (7% and 20%, respectively), limb amputation (Group I 27%), hernia repair (20 and 10%, respectively). (See Table 1 for detailed information).

Table 1. *Demographic characteristic and baseline data for the intervention groups*

Baseline data	Group I (n=16)	Group II (n=10)	p-value
Age (mean±SD,[range]), years	75.37±6.281, [65-88]	79.00±8.340, [66-90]	0.219
Sex (m:f), %	73:27	70:30	0.856
ASA class, I:II:III (%)	0:23:77	0:30:70	0.708
Baseline MAP, (mean±SD), mmHg	106.87±15.445	110.30±14.622	0.584
Hypertensive at baseline (MAP>107mmHg), %	47	60	0.513
Anesthetic dose, (mean±SD), mg	7.812±0.8539	8.500±1.2910	0.114
Anesthetic volume, (mean±SD), ml	1.963±0.1708	2.650±0.3028	<0.001*
Operation time (mean±SD), min	83.08±29.447	71.50±33.916	0.391
Intraoperative iv fluid volume, ml	1185.00±250.610	1220±238.281	0.753

Block Characteristics

All the patients had sufficient surgical condition to start the operation, and only one patient (out of 26), needed additional analgesia for closure. The maximal sensory level reached in both groups was Th10, with similar reach time of the Th10 sensory block in both groups (9.13±4.893 minutes [mean±SD] and 8.70±5.355 minutes, group I and II, respectively).

Table 2. *Block characteristics for the two intervention groups*

Results	Group I (n=16)	Group II (n=10)	p - value
Maximal sensory level (median)	Th10	Th10	1
Time to reach Th10, (mean±SD, [min-max]), min	9.13±4.893 [5-25]	8.70±5.355 [3-20]	0.836
Time to regress to S2, (mean±SD, [min-max]), min	140.22± 39.36 [75-195]	147.00±47.621 [80-219]	0.752
Unilateralization, lateral position (%)	67%	60%	0.739
Unilateralization, supine (%)	53%	30%	0.259
Bromage class-dependent leg, lateral 3:2, %	53:47	80:20	0.182
Bromage class-dependent leg, supine 3:2, %	67:27	80:20	0.436
Bromage class, nondependent leg lateral 3:2, %	0:7	0:10	0.424
Bromage class, nondependent leg supine 3:2:, %	7:13	0:30	0.343

As shown in Table 2, there is no statistically significant difference between the intervention groups in the peak sensory level, time to reach the Th10 sensory level, the regression to S2 level, and the motor block. Also unilateralization was comparable between the two groups.

Hemodynamic Data

Our results confirm the positive effect of unilateral spinal anesthesia on hemodynamic stability and predictable hemodynamics in elderly patients. Patients in group I who experienced relative hypotension were only 6.7%, i.e. only one patient, and 30% in group II, or 3 patients, and in both groups none of the patients experienced absolute drop of mean arterial pressure bellow 60 mmHg. In four cases the hypotension was easily treated with colloid bolus and one patient also received minimal dose of ethylephrine as vasopressor. There was no case of bradycardia.

Table 3. *Mean arterial pressure at baseline, 0, 5, 15 and 30 minutes after puncture for the two intervention groups*

	Group I	Group II	p
MAP, baseline [mean±SD], mmHg	106.87±15.445	110.30±14.622	0.470
MAP, 0 minutes [mean±SD], mmHg	108.13±16.643	110.30±14.622	0.523
MAP, 5 minutes [mean±SD], mmHg	99.00±21.67	101.50±16.147	0.803
MAP, 15 minutes [mean±SD], mmHg	88.27±16.752	90.20±20.741	0.846
MAP, 30 minutes [mean±SD], mmHg	84.47±16.703	84.90±17.375	0.846

Side effects

There were insignificant cases of the usual side effects of spinal anesthesia: one case of pruritus, one case of post dural puncture headache and one case of nausea.

Discussion

Elderly patients are vulnerable category of patients and it is prudent for many reasons to explore the specifics and create interventions and recommendations that apply for their age group. The mortality rate associated with surgery and anesthesia increases with the increasing age. Cardiac events have become leading cause of death in the last few decades in the elderly surgical population (11), contrary to the earlier reports when pneumonia and respiratory complications were predominant (12). The perioperative period for the elderly patients should include evaluation, optimization of any preexisting conditions, maintenance of stable perioperative hemodynamics, use of the least surgical invasive procedure, prevention of hypoxemia, hypothermia and delirium and effective postoperative pain control (3).

The use of regional anesthesia and neuroaxial anesthesia has protective value in the elderly patients and compared to general anesthesia (6); may lead to reduction of the perioperative mortality in patients undergoing surgery with intermediate to high cardiac risk.(13). Maintaining stable hemodynamic profile can be challenging with the standard spinal anesthesia (14, 15) and efforts have been made throughout the clinical and research history of the spinal anesthesia to modify the technique for more desirable hemodynamics. We choose to investigate the unilateral spinal anesthesia in our elderly patients, since it is easy to perform, patients can be easily placed in position, high success rate and acceptable for the surgeon, patient and anesthesiologist. We also included the newer, potentially less cardiotoxic anesthetic, levobupivacaine to compare already proven racemic bupivacaine. The less cardiac toxicity associated with levobupivacaine, make the same attractive for cardiovascular challenged elderly patients.

The low dose of anesthetic insures less sympathetic block, and keeping the block limited to the one side, potentially also induce contralateral vasoconstriction that prevent hypotension. Many studies have confirmed the benefit of selective spinal block on the hemodynamic stability (16). We found that unilateral spinal anesthesia provide stable hemodynamic profile that protects the elderly patients in the intraoperative period. These findings are also supported in other studies (17).

We did not find any difference between the studied local anesthetics in the block characteristics, which leaves the statements of the less potency of the levo-bupivacaine, being more isobaric than bupivacaine on body temperature, as theoretical, rather than clinically relevant (18, 19). It is not expected that we can confirm the safety profile of levobupivacaine over racemic bupivacaine in such a small dose that is used during USA.

The time to reach the peak sensory level was found to be similar in both groups and around 10 minutes and turning the patients supine after that to prepare for surgery, we found to be

adequately safe and effective and also compared to previous recommendations to keep the lateral position longer (15-20 minutes), unnecessary. Compared to studies with the 15-20 minutes of lateral position, we did not find difference in unilateralization after turning supine (18).

Supported by the findings of this study, we would recommend the unilateral spinal anesthesia with low dose of hyperbaric bupivacaine for elderly patients undergoing one-sided surgery bellow the umbilicus over levo-bupivacaine, more expensive option, without accompanying risk. Also hyperbaric bupivacaine is commercially available as 0.5% bupivacaine in 8% dextrose and mixed with opioid as adjuvant provides sufficient baricity to produce unilateral spinal anesthesia with limited peak sensory level. This study also supports turning the patient supine once the Th10 level reached without the unnecessary delay to 15-20 minutes as previously recommended. [18, 20].

What remains to be answered is the question whether the total dose of anesthetic used is the protective factor against hypotension or the limitation of the block on one side; or the combination of the two factors.

Conclusion

Unilateral spinal anesthesia provides stable, effective anesthesia for the elderly patients for the most common lower body surgeries.

Low dose of hyperbaric bupivacaine with fentanyl as adjuvant is safe and reliable anesthetic, commercially available, that is suitable for unilateral spinal anesthesia with no increased risk for cardiotoxicity due to low anesthetic dose used during unilateral spinal anesthesia.

The waiting time can be safely shortened to the time to reach the desired sensory level appropriate for the surgery to turn the patient to the operating position.

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ХЕМОДИНАМСКИ ПРОФИЛ НА УНИЛАТЕРАЛНА СПИНАЛНА АНЕСТЕЗИЈА КАЈ ПОВОЗРАСНИ ПАЦИЕНТИ

АПСТРАКТ

Вовед: Хемодинамска стабилност на пациентот е посакувана при секоја анестетичка техника. Промените како тахикардија, хипотензија и хипертензија, може да предизвикаат перипоративен миокарден инфаркт, а хипотензијата може да доведе до мозочен удар. Спиналната анестезија кај повозрасни пациенти резултира со стабилен хемодинамски профил. Исто така, унилатералната спинална анестезија е докажана техника со поволен хемодинамски профил. Нашето истражување има за цел да го прикаже хемодинамскиот профил на унилатералната спинална анестезија со употреба на хипербарен раствор на бупивакаин и левобупивакаин кај повозрасни пациенти.

Методи и материјал: Повозрасни пациенти (над 65-годишна возраст), закажани за оперативен зафат беа предмет на ова истражувањето, при што по случаен избор беа поделени во две истражувачки групи: унилатерална спинална анестезија со ниски дози на хипербарен бупивакаин или хипербарен левобупивакаин. Се испитуваа квалитетот на спиналниот блок, хемодинамскиот профил и други чести несакани ефекти.

Резултати: 26 пациенти, со просечна возраст од 76.77±7.207, 18 жени и 8 мажи, АСА 2 и 3, кои биле оперирани заради фрактура на колк (56%), други фрактури на нозе (12%), ампутација на нога (16%) и ингвинална хернија (16%); беа поделени во две испитувани групи: Група 1 доби унилатерална спинална анестезија со хипербарен бупивакаин во раствор од 7% декстроза во доза од 5-10 mg и додаток на фентанил 20mcg и Група 2: унилатерална спинална анестезија со хипербарен левобупивакаин во раствор од 7% декстроза и тоа 5-10 mg и додаток на фентанил 20mcg. И кај двете групи со споредливи демографски карактеристики, се постигнаа соодветни хируршки услови со највисоко постигнато сензорно ниво до висина на Th10, стабилен крвен притисок, ниска стапка на значајна хипотензија (1 случај од Група 1 и 3 случаи од Група 2), стабилна срцева фреквенција и ниска стапка на гадење, пруритус и пост-пункциона главоболка. Не се забележани промени на ST сегментот во тек на перипоративниот период.

Заклучок: Унилатералната спинална анестезија со ниски дози на хипербарен бупивакаин или левобупивакаин е сигурна анестезиолошка техника кај повозрасните пациенти.

Клучни зборови: повозрасни, хемодинамика, унилатерална спинална анестезија.

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ADDUCTOR POLLICIS MUSCLE THICKNESS MEASUREMENT – A RELIABLE METHOD FOR NUTRITIONAL STATUS ASSESSMENT IN CRITICALLY ILL PATIENTS

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ABSTRACT

Introduction: Malnutrition in hospital patients is a worldwide problem which leads to increased morbidity and mortality rate. Nutritional assessment carried out immediately after admission of the patient allows to make a plan to start nutritional therapy in order to improve nutritional status and minimize the risk of complications**.** Among the different methods for nutritional assessment a new technique that enables a measurement of the thickness of adductor pollicis muscle has become popular in the last years.

The objective of this study was to determine the validity of the measurement of the thickness of adductor pollicis muscle in correlation to other anthropometric measurements for nutritional status assessment in critically ill patients.

Material and Methods: The pilot study included 24 patients treated at the Clinic for Anesthesiology, Reanimation and Intensive Care in the period from April to June 2017. The inclusion criteria were age older than 18 years and hemodynamically stable patients. Exclusion criteria were: pregnancy, current injury or deteriorated mobility from a previous injury, upper limb fracture in the last six months, and degenerative disease. The nutritional status was followed by: Weight and height, Body Mass Index, Mid Arm circumference, Triceps skinfold thickness, Mid Arm Muscle Circumference, Calf circumference, the thickness of Adductor pollicis muscle (TAPM) and Subjective Global Assessment.

Results: The mean TAPM measured in mm was 16, 67±2,16 in male and 13,00±1,73 in female patients for dominant hand, and 15,24±2,11 in male and 11,70± 2,54 in female for non-dominant hand. The mean TAPM in patients younger than 45 years was the highest for both the dominant (17, 11±2,47) and the non-dominant hand (15,67 ±2,55). The smallest mean TAPM

was measured in patients over 65 years of age both for dominant (14,43 ±2,50) and non-dominant hand (14,47 ± 2,67). According to the subjective global assessment the mean TAPM was highest in well-nourished patients (16.93 ± 2.16) and smallest in patients with severe malnutrition (12.50 ± 2.56). The correlation between the TAPM and other anthropometric measures showed significance only with Mid Arm Muscle Circumference (p = 0.003) and Calf circumference (p = 0.046) for the dominant hand and with Mid Arm circumference (p = 0.017), Mid Arm Muscle Circumference (p = 0.002) and Calf circumference (p = 0.009) for the non-dominant hand.

Conclusion: The measurement of the thickness of adductor pollicis muscle presents a reliable method for nutritional status assessment and it correlates to the other anthropometric measurements used in clinical practice in critically ill patients.

Key words: critically ill patient, nutritional assessment, thickness of adductor pollicis muscle

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Introduction

Malnutrition in hospital patients is a worldwide problem. There are numerous reasons for its occurrence like the disease itself, hypermetabolism or reduced intake and absorption of nutrients. [1] The incidence of malnutrition in critically ill patients is from 40 to 100%, and leads to increased morbidity with prolonged hospital treatment, increased infection rates, hypoproteinemia, edema, postoperative complications and increased mortality rate. (1)

It is very important to assess the nutritional status of the patient at hospital admission, to determine the presence or absence of malnutrition with one single goal, which is to provide an early and individualized diet plan. (2)

Anthropometry is an important tool for assessing nutritional status, and also an indicator and predictor of survival. Anthropometric measurements are accepted in all life conditions and allow classification of individuals according to the nutritional status.

So far, the known screening devices and anthropometric measures are considered variables susceptible to the impact of the critical illness. Throughout the years, numerous attempts for identification and development of new possibilities for determination of malnutrition have been made concerning critically ill patients, but consensus has not yet been reached.

A new technique that enables an assessment of the muscle compartment and correlates with other anthropometric, biochemical and inflammatory parameters is the measurement of the thickness of adductor pollicis muscle (TAPM). This method identifies changes of the whole body, and can be useful in detection of early changes associated with malnutrition, as well as in estimation of nutritional recovery. (3)

The objective of the study was to determine the validity of the measurement of the TAPM correlating to the other anthropometric measurements for nutritional status assessment in critically ill patients.

Material and Methods

The pilot study included 24 patients treated at the Clinic for Anesthesiology, Reanimation and Intensive Care (CARIL) in the period from April to June 2017.

The study included all the patients from the unit who could be evaluated during the first 24 to 48 hours after admission to the hospital. The inclusion criteria were age older than 18 years, and patients who were stable hemodynamically. Exclusion criteria were: pregnancy, current injury or deteriorated mobility from a previous injury, upper limb fracture in the last six months, and degenerative disease.

The nutritional status was followed by:

Weight and height - data for their value were obtained from the escort. The ICU did not have an available bed scale or a stadiometer, and patients were not clinically able to walk.

The Body Mass Index (BMI) was calculated by dividing the weight (kg) by squared height (m^2) and the data obtained were analyzed according to the references suggested in the literature. The adults were classified as per the references of the World Health Organization, considering the following intervals: low weight (BMI < 18.5kg/m^2), eutrophic (BMI from 18.5 kg/m^2 to 24.9kg/m^2) overweight (BMI from 24.9kg/m^2 to 29.9kg/m^2). The elderly were classified according to the cutoff points of Lipschitz, in which low weight was BMI ≤ 22 kg/m^2; eutrophic if BMI was between 22 kg/m^2 and 27 kg/,m^2; and overweight, if BMI > 27kg/m^2. (4, 5)

Mid Arm circumference (MAC) was measured using inelastic and inextensible tape measure. The non-dominant hand was measured with the elbow bent in 90° of flexion and the position of the palm above. The lateral point of the acromion and the lowest point of the olecranon were marked and the measurement was carried out in the middle between them.

Triceps skinfold thickness (TST) measures the adipose tissue and it is carried out on the back of the arm at the spot where the MAC is measured. At 2 cm from the marked place the examiner, with the help of his/her thumb and forefinger, raises the skin of the patient. The adipometer is positioned at 1 cm depth of the skin, the pressure is 10g/mm^2, we wait for 3 to 4 seconds and then note the measured value.

Mid Arm Muscle Circumference (MAMC) is a muscle mass index and is computed by the equation:

MAMC = MAC - (3.1415 × TST)

Calf circumference was determined using an inelastic tape positioned horizontally around the maximum circumference of the calf. Values below 31cm were considered indicative of reduced muscle mass showing some nutritional risk.

The TAPM was measured on the dominant and non-dominant side, with the patient seated, the arm flexed to approximately 90º, the forearm and the ventral side of the hand resting on the ipsilateral lower limb, the hand relaxed and using the adipometer with a continuous pressure of 10 g mm-². The muscle was clamped at the vertex of the imaginary triangle formed by thumb extension and index finger (picture 1). The procedure was done on the dominant and non-dominant hand three times, and the mean value was used as measurement of the TAPM.

Picture 1. *Measurement of the TAPM with an adipometer on the right hand*

Subjective Global Assessment

For the evaluation of the **Subjective Global Assessment (**SGA), family members answered questions focused on disease history, changes in weight, changes in nutritional intake, the presence of gastrointestinal symptomatology and functional capacity alteration. Physical examination was also included in order to determine the loss of subcutaneous fat, muscle tissue, the presence of sacral edema, edema of the ankle, and the presence of ascites. According to the obtained results the patients belong to three categories: well-nourished patients (SGA "A"), suspected/moderate malnutrition (SGA "B"), or severe malnutrition (SGA "C"). For statistical analysis, these data were transformed into dichotomous variables: no nutritional risk (nourished) and at nutritional risk (moderately malnourished and severely malnourished).

Statistical Analysis

All data were expressed as mean ± standard deviation and analyzed by SPSS 12.0 software. Group comparison was performed with t test (*student*) and $P < 0.05$ was considered statistically significant. The one-way analysis of variance (ANOVA) was used to determine whether there are any statistically significant differences between the means of three or more independent (unrelated) groups.

Results

The mean value of TAPM in the male group of patients was significantly higher than the mean value in the female group, either for TAPM for the dominant hand or TAPM for the non-dominant hand (**Table 1**)

Group Statistics	Sex	N	Mean ± Std. Deviation	Significance (p)
TAPM_DOMINANT	MALE	18	16,67 ± 2,169	
	FEMALE	5	13,00 ±1,732	0.002
TAPM_NON-DOMINANT	MALE	18	15,24 ± 2,110	
	FEMALE	5	11,70 ± 2,540	0.004

In terms of age, in the study there were three age groups. In the first group the patients are up to 45 years old, in the second from 45 to 65 years, and in the third group the patients are over 65 years of age. Our results showed the highest mean values of TAPM in the group of patients younger than 45 years, and the smallest mean values in the group of patients over 65 years of age for both the dominant and the non-dominant hand. ANOVA test showed that although there is a difference, that difference is not a statistically significant one (**Table 2**).

		N	Mean ± Std. Deviation	Significance (p)
TAPM_DOMINANT	<45	9	17,11 ± 2,472	0.111
	45-65	7	15,71 ± 2,215	
	>65	7	14,43 ± 2,507	
TAPM_NON-DOMINANT	<=45	9	15,67 ± 2,550	0.156.
	46-65	7	14,26 ± 2,220	
	>66	7	13,14 ± 2,688	

According to the subjective global assessment, in our study there were 15 well-nourished patients (SGA "A"), 6 patients with suspect/moderate malnutrition (SGA "B"), and 2 patients with severe malnutrition (SGA "C"). The mean values of TAPM were the highest in the group A and the smallest in the group C for both dominant and non-dominant hand. With ANOVA test we found that the difference between the groups is statistically significant (**Table 3**).

		N	Mean ± Std. Deviation	Significance (p)
TAPM_ DOMINANT	A	15	16,93 ± 2,154	0.009
	B	6	14,33 ± 2,251	
	C	2	12,50 ±,707	
	Total	23	15,87 ± 2,564	
TAPM_NON-DOMINANT	A	15	15,69 ± 2,064	0.001
	B	6	12,92 ± 1,686	
	C	2	10,00 ±,000	
	Total	23	14,47 ± 2,615	

Table 4 shows the correlation of the thickness of adductor pollicis muscle in relation to the other anthropometric measures. The correlation between TAPM in the dominant hand and TAPM in the non-dominant hand is very large 0.914 (p <0.000). TAPM in the dominant hand is correlated to MAMS 0.588 (p = 0.003) and CALF, 0.421 (p = 0.046), while data show that there is no correlation to MAC, 0.384 (p = 0.070), and TST, -0.049 (p = 0.825). TAPM in the non-dominant arm is correlated to MAC, 0.493 (p = 0.017), MAMS 0.602 (p = 0.002) and CALF, 0.533 (p = 0.009), while the data show no correlation to TST, 0.127 (p = 0).

		MAC	TST	MAMC	CALF	TMAP_ DOMINANT	TMAP_NON-DOMINANT
MAC	Pearson Correlation	1	,709**	,838**	,737**	,384	,493*
	Sig. (2-tailed)		,000	,000	,000	,070	,017
	N	23	23	23	23	23	23
TST	Pearson Correlation	,709**	1	,214	,618**	-,049)	,127
	Sig. (2-tailed)	,000		,327	,002	,825	,565
	N	23	23	23	23	23	23
MAMC	Pearson Correlation	,838**	,214	1	,545**	,588**	,602**
	Sig. (2-tailed)	,000	,327		,007	,003	,002
	N	23	23	23	23	23	23
CALF	Pearson Correlation	,737**	,618**	,545**	1	,421*	,533**
	Sig. (2-tailed)	,000	,002	,007		,046	,009
	N	23	23	23	23	23	23
TMAP_ DOMINANT	Pearson Correlation	,384	-,049)	,588**	,421*	1	,914**
	Sig. (2-tailed)	,070	,825	,003	,046		,000
	N	23	23	23	23	23	23
TMAP_NON-DOMINANT	Pearson Correlation	,493*	,127	,602**	,533**	,914**	1
	Sig. (2-tailed)	,017	,565	,002	,009	,000	
	N	23	23	23	23	23	23

*. Correlation is significant at 0.05 level (2-tailed).
**. Correlation is significant at 0.01 level (2-tailed).

Discussion

The majority of critically ill patients, globally, do not receive proper nutrition during hospitalization in intensive care units. Nutritional assessment carried out immediately after admission of the patient allows to make a plan to start nutritional therapy in order to improve nutritional status and minimize the risk of complications. Evaluation of the nutritional status in hospital conditions comprises the history of the disease with habits and changes in respect to nutrition, evaluation of biochemical values and body composition with physical examination. (6)

Shakir and Waterlow are the pioneers in the use of anthropometry and thanks to their hard work, measuring of the body compartment is a part of a routine physical examination. (7, 8) The protein compartment is represented by muscle mass, subjected to the influence of malnutrition, which can lead to its reduction. Changes in muscle mass are a good indicator of the patient's diet and the outcome of the current disease. (9)

For the evaluation of the body compartment, several methods have been developed, adapted for use in different scenarios. The results obtained with dual energy X-ray absorptiometry (DXA) and air-displacement plethysmography proved to be realistic in the epidemiological scenario. The high cost, technical compatibility, and low availability, are limiting their use in clinical practice. (10)

Technique used in a clinical environment, especially in surgical and renal patients, patients with chronical illness or critical illness, and at the same time an indicator of malnutrition, length of stay and mortality, is the thickness of adductor pollicis muscle. (11)

Assessment of the thickness of the adductor pollicis muscle (APM) has been reported for evaluating the muscle compartments of the body. It is a muscle of the hand with two heads that adducts the thumb by bringing it toward the palm. It is a fleshy, flat, triangular, and fan-shaped muscle deep in the thenar compartment beneath the long flexor tendons and the lumbrical muscles at the centre of the palm. It overlies the metacarpal bones and the muscles. Anatomically, the APM is the only muscle in the body that could be directly measured. Measurement of the thickness of APM is fast, easy, low cost and non-invasive.(12)

Measurement of the thickness of adductor pollicis muscle on the dominant hand is superior to the non-dominant one and the values are always higher. There is evidence that the muscle of the dominant hand starts to weaken first with reduced daily activity and shows more expressed atrophy in malnutrition. In order to avoid misrepresentation of the nutritional status it is recommended to measure the adductor pollicis muscle on the non-dominant hand.

The first published study from Lameu et al. included 421 healthy patients and the mean muscle thickness of adductor pollicis muscle for the both sexes of the dominant hand was 11.5 ± 2.76 mm. (13) Different methodological approaches resulted in different values of muscle thickness. The second study of Lameu et al. performed with patients in the wards of the Medical Clinic from the Hospital of the University of Rio de Janeiro, found out an average of TAPM for a total sample of 14.2 ± 3.7 mm in the dominant hand and 13.8 ± 3.7 mm in the non-dominant hand. (14) However, Freitas et al. in their study that included 82 cancer patients observed minor variations of TAPM on the dominant hand for both sexes and amounted to (13 ± 3.2 mm). (15)

In our study the mean value of TAPM was higher compared to the other studies which means that our patients arrived at a hospital with a lower nutritional risk compared to patients in the other studies who have poorer nutritional status at admission.

Regarding the gender, a significant difference has been identified in the studies carried out so far. In our study, the mean value of TAPM of the dominant hand in men was 16.67 ± 2.14

mm, and in the non-dominant hand was 13.00 ± 1.73 mm, while in women, the mean value of the dominant hand was 15, 24 ± 2.11 mm, and in the non-dominant hand the value was 11.70 ± 2.54 mm. Statistical significance is p = 0.002, for the dominant hand, and p = 0.004 for the non-dominant hand. According the results for the values of TAPM in different age groups, the most of the studies show different values in different age groups. Gonzalez et al. found that the age group from 30 to 60 years old shows significantly higher muscle-thickness values than other age groups. In the background, there is no biological explanation, but a technical point. (16) The results from our study correspond to the results from the others studies showing that the mean value of TMAP in the group of patients younger than 45 years was the highest and that the smallest mean value was in the group of patients over 65 years.

The SGA is the gold standard for subjective evaluation of malnutrition. Rezende et al., examined 168 surgical patients and established a reasoned correlation between subjective and objective methods of nutritional assessment in the perioperative period. (17) In their study, in which the thickness of adductor pollicis muscle was used as a predictor of the outcome of a critical illness, it has been determined that 25% of patients are severely undernourished. The value of TAPM in the left (12.3 ± 5.5 mm) and in the right hand (12.9 ± 5.3 mm) is significantly lower (p <0.001) in severe malnourished patients (SGA-C) compared to patients scored as patients with mild malnutrition (SGA-B) (right hand = 16.8 ± 5.7 mm and left hand = 15.9 ± 5.9 mm) or being nourished (SGA-A) (right hand = 17.2 ± 5.4 mm and left hand = 15.8 ± 4.6 mm). From this it follows that a significant correlation between SGA and TAPM exists only in patients who are undernourished. (18) According to the subjective global assessment, in our study there were 15 well-nourished patients (SGA "A"), 6 patients with suspect/moderate malnutrition (SGA "B"), and 2 patients with severe malnutrition (SGA "C"). The mean value of TMAP in group A is the highest or 16.93 ± 2.16 for the dominant hand and 15.69 ± 2.064 for the non-dominant hand, and the lowest in the group C, 12.50 ± 2.56 in the dominant hand and 10.00 in the non-dominant hand.

Caporossi, examining the patients on intensive care, found that there is significant positive correlation between the values of TAPM and AC, AMA and TSF measurements. (19) Similar results were obtained in the study by Rosalie et al. [35], with included 124 patients who underwent large digestive surgery where the values of TAPM on both hands correlated positively with all anthropometric variables. (20) Opposite to him, Lameu et al [30], in his study found a significant positive correlation between the values of TAPM and anthropometric parameters, but only in those patients that showed muscle mass and not in those who calculated fat. (21) It is important to note that this study does not investigate critically ill or surgically ill, but only healthy persons. In our study in critically ill patients TMAP in the dominant hand was in correlation to MAMS 0.588 (p = 0.003) and CALF, 0.421 (p = 0.046), while the data show no correlation to MAC, 0.384 (p = 0.070), and TST, -0.049 (p = 0.825). The obtained statistical results indicated that TMAP in the non-dominant hand is correlated to MAC, 0.493 (p = 0.017), MAMS 0.602 (p = 0.002) and CALF, 0.533 (p = 0.009), and there is no correlation to TST, 0.127 (p = 0.565).

The determination of TAPM has its limitations. It is considered that it does not represent only the muscle body mass, but can be influenced by other factors. Lameu et al. emphasized the body frame as a variable that influenced TAPM and determined a progressive increase in TAPM in individuals with a small, medium or large body frame, evaluated by the wrist circumference. The previous muscle activity and water body compartment are other moments of great importance.

Conclusion

Proper nutritional assessment is a challenge. All methods for nutritional assessment show differences in results, but one is common that they are effective and positively correlate to the setting of diagnosis for nutritional risk. The measurement of the thickness of adductor pollicis muscle presents a reliable method for nutritional status assessment and it correlates to other anthropometric measurements used in clinical practice in critically ill patients.

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МЕРЕЊЕ НА ДЕБЕЛИНАТА НА АДУКТОРНИОТ МУСКУЛ НА ПАЛЕЦОТ - АДЕКВАТЕН МЕТОД ЗА НУТРИЦИСКА ПРОЦЕНА КАЈ КРИТИЧНО БОЛНИ

АПСТРАКТ

Вовед: Малнутрицијата кај болничките пациенти е светски проблем кој води до зголемување на морбидитетот и морталитетот. Нутрицискатa процена извршена веднаш по приемот на пациентот во болничката институција, овозможува да се направи план за започнување на нутриционска терапија со цел да се подобри нутрициониот статус и да се минимизира ризикот од компликации. Меѓу различните методи за процена на нутрицискиот статус припаѓа и новата техника на мерење на дебелината на адукторниот мускул на палецот, која стана популарна последните години.

Целта на студијата беше да се утврди валидноста на мерењето на дебелината на адукторниот мускул на палецот и неговата корелацијата со други антропометриски мерења за процена на нутритивниот статус кај критично болните пациенти.

Материјал и методи: Во пилот-студијата беа вклучени 24 пациенти третирани на Клиниката за анестезиологија, реанимација и интензивна нега во периодот од април до јуни 2017 година. Критериумите за вклучување беа возраст над 18 години и хемодинамска стабилност на пациентите. Критериумите за исклучување беа: бременост, тековна повреда или влошена подвижност од претходна повреда, фрактура на горните екстремитети во последните шест месеци и дегенеративна болест. Нутрицискиот статус кај пациентите се следеше преку мерките на: тежина и висина, индекс на телесна маса, обем на ниво на средина на надлактица, дебелина на кожен набор на трицепс, обем на мускулите на средина на надлактица, обем на подколеница, дебелина на адукторниот мускул на палецот и субјективната глобална процена.

Резултати: Средната вредност на дебелината на адукторниот мускул на палецот мерена во mm беше 16, 67 ± 2,16 кај мажи 13,00 ± 1,73 кај жени за доминантната рака, и 15,24 ± 2,11 кај мажи и 11,70 ± 2,54 кај жени за не-доминантната рака. Средната вредност на дебелината на адукторниот мускул на палецот кај пациенти помлади од 45 години беше највисока и за доминантната (17, 11 ± 2,47) и за не-доминантната рака (15,67 ± 2,55). Најмалата средна вредност на дебелината на адукторниот мускул на палецот беше измерена кај пациентите над 65 години како за доминантна (14,43 ± 2,50), така и за не-доминантна рака (14,47 ±2,67). Според субјективната глобална процена, средната вредност на дебелината на адукторниот мускул на палецот беше највисока кај добро хранетите пациенти (16,93 ± 2,16) и најмала кај пациентите со тешка малнутриција (12,50±2,56). Корелацијата помеѓу дебелината на адукторниот мускул на палецот и другите

антропометриски мерки покажа сигнификантност со обемот на мускулите на средината на надлактицата (p = 0.003) и обемот на подколеницата (p = 0.046) за доминантната рака и со обемот на средината на надлактицата (p = 0.017), обемот на мускулите на средината на надлактицата (p = 0,002) и обемот на подколеницата (p = 0,009) за не-доминантната рака.

Заклучок: Мерењето на дебелината на адукторниот мускул на палецот претставува сигурен метод за процена на нутрицискиот статус и е во корелација со другите антропометриски мерења кои се користат во клиничката пракса кај критично болните пациенти.

Клучни зборови: дебелина на адукторен мускул на палецот, критично болен пациент, нутриционска процена.

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INCIDENCE OF CLINICAL SIGNS OF RESIDUAL NEUROMUSCULAR BLOCK AT THE POSTANESTHESIA CARE UNIT IN PATIENTS AFTER GENERAL ANESTHESIA WITH LONG ACTING NEUROMUSCULAR DRUGS – OUR EXPERIENCE

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ABSTRACT

Introduction: Ever since curare was introduced into the practice of anesthesiology in 1942, it became a valuable addition to the anesthesiologists' armamentarium. Neuromuscular blocking drugs (NMBD) have since become an important adjunctive in the most cases of general anesthesia. Recent studies suggest that use of intermediate acting NMBD, neuromuscular monitoring and reversal of neuromuscular block, may affect early postoperative outcomes and reduce the incidence of residual neuromuscular block (RNMB). The aim of this study is to compare the incidence of clinical signs of RNMB in the PACU in two groups of patients receiving long acting NMBD.

Material and Method: Prospective descriptive study conducted at the University Surgical Clinic St. Naum Ohridski – Skopje in 78 patients receiving general anesthesia with long acting NMBD. Patients are divided into two groups depending if neuromuscular function was monitored or not intraoperatively.

Results: The incidence of clinical signs of RNMB at the PACU was 20.51% in the unmonitored and 15.38% in the monitored group. There was higher incidence in mild hypoxemia and airway muscle weakness in the unmonitored group.

Conclusion: Residual neuromuscular block continues to be a common clinical occurrence in PACU. In the early recovery period after anesthesia it is difficult to differentiate the signs of RNMB of the effects of the drugs used during anesthesia. Although there are strong recommendations for use of neuromuscular monitoring, still many anesthesiologists base their neuromuscular management on clinical signs.

Key words: neuromuscular blocking drug, postanesthesia care unit, residual neuromuscular block

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Introduction

Tens of millions of people worldwide are subjected to general anesthesia every day. Anesthesiologist's armamentarium consists of drugs which purpose is to produce hypnosis, amnesia, analgesia, hemodynamic stability and immobility. Generally, neuromuscular blocking drugs (NMBD) are used in order to facilitate intubation and to achieve immobility and optimal surgical field. The most common and serious complication of use of NMBD is the residual neuromuscular block (RNMB), that has a tendency to have a relatively undetected occurrence in the postanesthesia care unit (PACU).

What is residual neuromuscular block? When quantitative monitoring of the neuromuscular function was introduced into the practice of anesthesia, RNMB was defined as inadequate reversal of neuromuscular function, as train-of-four (TOF) ratio of below 0.7. More recent data suggest that a TOF ratio of <0.9 is "the golden rule" for RNMB instead (1, 2). Probably the most accurate definition of RNMB would be presence of signs and symptoms of muscle weakness in the early postoperative period after administration of NMBD (3).

Residual paralysis in PACU can affect morbidity in patients recovering from general anesthesia and is a risk factor that can affect early postoperative outcomes. The adverse effects of RNMB, such as impairment of pharyngeal coordination, delayed initiation of the swallowing reflex and reductions in the upper esophageal sphincter tone dramatically increase the risk of aspiration (3). As addition to these, the impairment of dilatation function of the upper airway muscles, the decrease in inspiratory flow and the impaired hypoxic ventilatory drive, dramatically increase the need of emergency reintubation that greatly increases the risk of postoperative pulmonary complications.

RNMB is a preventable safety problem. Recent outcome studies suggest that use of intermediate acting NMBD, perioperative neuromuscular monitoring and reversal of neuromuscular block may reduce the incidence of RNMB (4). Intermediate acting NMBDs reduce the incidence of RNMB in comparison to the long acting NMBDs (5).

Monitoring of the neuromuscular function is the factor that recently is the most commonly stressed in reducing the incidence of RNMB. There are two methods for neuromuscular monitoring. Qualitative (subjective) method is where visual or tactile assessment of response to peripheral nerve stimulation is performed. It is one of the most common methods used for monitoring of the neuromuscular function in the operating room, PACU and ICU. Available data provide that tactile assessment could be slightly more sensitive in detecting fade during neuromuscular stimulation compared to visual assessment. The quantitative method, on the other hand, provides more objective data on neuromuscular monitoring. It provides accurate, numerical value of the train-of-four (TOF) ratios. The quantitative monitoring is more reliable method in excluding RNMB because fade is difficult to detect subjectively when train-of-four ratio is between 0.4 and 0.9 (3).

In our study we compared the incidence of clinical signs of RNMB in PACU in two groups of patients, group A (not monitored) and group B (monitored).

Material and Method

This prospective descriptive study was conducted in the University Surgical Clinic St. Naum Ohridski – Skopje, in a period of two weeks in January 2015. The ethical approval for this study was provided by the Ethical Committee of the University Surgical Clinic St. Naum Ohridski – Skopje.

The individual informed consent was waived by the Ethical committee because the study did not change routine care of patients or routine practice of the anesthesiologists. This study included patients within the two weeks period who were subjected to general anesthesia with long acting NMBD. Exclusion criteria were patients younger than 18 years old; patients scheduled for local, regional anesthesia or general anesthesia without long acting NMBD; patients intubated preoperatively outside the operation room and patients that were not extubated at the operation room.

During this timeframe 78 patients were enrolled in the study. Two groups were created; group A (n=39) where neuromuscular function was not monitored during anesthesia and group B (n=39) where neuromuscular function was monitored. Routine care for the patients was not changed and modifications of the custom practice of each anesthesiologist were not performed. The choice of drugs used for premedication and anesthesia as well as neuromuscular management were left to the discretion of the anesthesiologist in charge.

In the monitored group B, qualitative neuromuscular monitoring was performed during the surgical procedure with train-of-four-count (TOFcount) with Organon TOF-Watch® S.

The clinical signs of RNMB were registered at PACU as mild hypoxemia, SpO_2 between 90-93% with oxygen support via facemask of 4L/min; severe hypoxemia, SpO_2 below 90% with oxygen support via facemask of 4L/min; signs of respiratory distress, with respiratory rates higher than 20 breaths per minute and activation of accessory respiratory musculature; inability to take a deep breath on command; airway muscle weakness, with difficulty in breathing or swallowing; need for airway management, use of Guedel airway, laryngeal mask or intubation; need for additional reversal of neuromuscular block.

Data were statistically analyzed. Fisher's exact test was used for comparison of variables between the non monitored and monitored group. Categorical variables are expressed as percentages and continuous variables as mean and standard deviation. Statistical significance was set at P below 0.05.

Results

Demographic data of the patients of both groups are presented in Table 1 as mean ± standard deviation (M±SD).

Table 1. *Demographic data of patients*

	Group A	Group B	p
Gender m/f	23/16	18/21	/
Age	48,53±15,09	53,35±14,36	0.076
Hight (cm)	170,41±8,11	167,56±5,43	0.9639
Weight (kg)	72,13±15,38	71±14,65	0.6297

There were no statistical differences between the data in the two groups. In group A there were 39,5% ASA category 1, 51,28% ASA category 2 and 12,82% ASA category 3 patients. In group B there were 23,08% ASA category 1, 53,85% ASA category 2 and 23,08% ASA category 3 patients.

The most common comorbidities in each group of patients are shown in Table 2.

Table 2. *Comorbidities of patients*

	Group A	Group B
Cardiovascular	15,38%	17,95%
Respiratory	5,13%	7,69%
Diabetes Melitus	5,13%	7,69%
Smokers	38,46%	35,90%

In cardiovascular comorbidities were enlisted patients with heart failure, according to the NYHA classification and patients with known coronary artery disease. In respiratory comorbidities were enlisted patients with history of COPD, history of asthma, history of sleep apnea and recent respiratory infection within 2 weeks of surgery.

Table 3. *Surgical data*

	Group A	Group B	p
Elective	84,62%	94,87%	/
Abdominal / Other procedure	79,49%	56,41%	/
Duration of surgery (min)	73,02±58,62	67,38±39,75	0.6898

The duration of surgical procedure was longer in the unmonitored group.

Table 4. *Anesthesia management and LOS at PACU*

	Group A	Group B	p
Volatile / TIVA	2/37	9/30	/
T.d. of Pancuronium*	6,18±2,79	6,67±2,04	0.1894
Time to arrival at PACU (min)	67,20±23,36	59,18±19,49	0.9482
LOS at PACU (min)	76,89±26,38	79,46±22,31	0.3218

*t.d. total dose

There were differences in the management of anesthesia between the groups, but this is due to routine practice of the anesthesiologist in charge. Reversal of NMB was administered in every patient as part of the routine practice in our hospital. Time from last administration of NMBD and arrival at PACU was shorter in the monitored group.

Table 5. *Clinical signs of RNMB*

	Group A	Group B
Mild hypoxemia	15,38%	10,26%
Inab. for deep breath	5,13%	5,13%
Airway muscle weakness	5,13%	2,56%

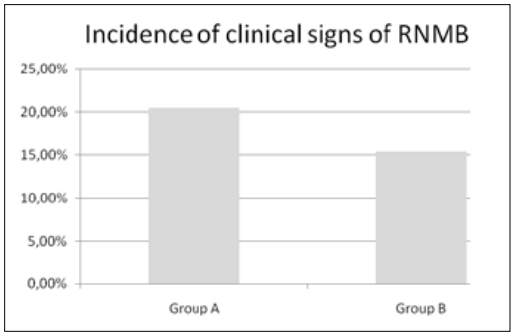

Figure 1. *Incidence of clinical signs of RNMB*

There was insignificant statistical difference in incidence of clinical signs of RNMB registered in both groups p=0.572835. In both groups there was no incidence of severe hypoxemia, signs of respiratory distress, nor need for additional airway management or need for additional reversal of NMB.

Discussion

Residual neuromuscular block can be a factor that can potentially affect recovery after anesthesia and can produce postoperative complications. The introduction of intermediate acting NMBD has reduced, but not eliminated the incidence of RNMB. Perioperative monitoring of the neuromuscular function is also stated as a factor in reducing the incidence of RNMB. In our study the incidence of clinical signs of RNMB is 20.51% in the unmonitored and 15.38% for the monitored group of patients. This incidence is within the reported range of RNMB assessed by quantitative monitoring which is from 2% to 64%, defined as TOF<0.9 (3).

Mild hypoxemia was reported in 15.38% and 10.26% in the not monitored and monitored group respectively. There was similar incidence in the inability to take a deep breath on command in both groups 5.13%. The incidence in airway muscle weakness was 5.13% and 2.56% in the not monitored and monitored groups respectively.

Residual neuromuscular block can be manifested as unpleasant symptoms of generalized muscle weakness in patients. In the early postoperative period in PACU there may be difficulties in differentiating the signs of RNMB from the lingering effects of other drugs used during anesthesia. The different states of alertness, depression of the ventilatory drive and airway obstruction can be due to the effects of a number of drugs commonly used such as opioids, benzodiazepines and volatile anesthetics.

There is different sensitivity of different muscle groups to the effects of NMBDs. Recent investigations have demonstrated that muscle groups of the upper airway, predominantly the muscles used for airway protection and patency are more sensitive to small degrees of RNMB. The effects on the pharyngeal function have been demonstrated even in TOF ratios <0.8. Swallowing was dramatically impaired and even aspiration was reported in cases of TOF ratio <0.9 (2, 6). The cause of this effect was attributed to the delayed initiation of the swallowing reflex, delayed pharyngeal coordination, reduced force of pharyngeal contraction and reduced upper esophageal sphincter tone (7). The effect of RNMB on airway muscle function was partial airway obstruction, manifested as reduced forced inspiratory volume in 1s (8). This was attributed to weakness of the upper airway dilatatory muscles (9). RNMB can have an effect on the respiratory function as wall. Minimal effects have been demonstrated on tidal volume, respiratory rate in patients with RNMB, but the reduction of hypoxic ventilatory response can be significantly impaired (10,11). The adverse effect on the hypoxic ventilatory response seems to be due to inhibition of neuronal nicotinic receptors in the carotid body (12, 13).

Conclusion

Residual neuromuscular block continues to be a common clinical occurrence in PACU. There is a well established association between RNMB and increased perioperative morbidity and mortality. In the early recovery period after anesthesia it is difficult to differentiate the signs of RNMB of the effects of the drugs used during anesthesia. “Most patients seem to tolerate residual block of modest extent without untoward result” (14). Although there are strong recommendations for use of neuromuscular monitoring, still many anesthesiologists base their neuromuscular management on clinical signs. Increased awareness of the dangers of unrecognized RNMB may lead to improved neuromuscular management.

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ИНЦИДЕНЦА НА КЛИНИЧКИ ЗНАЦИ НА РЕЗИДУАЛЕН НЕВРОМУСКУЛЕН БЛОК ВО ЕДИНИЦАТА ЗА ПОСТАНЕСТЕЗИОЛОШКА НЕГА КАЈ ПАЦИЕНТИ ВОДЕНИ ВО ОПШТА АНЕСТЕЗИЈА СО МУСКУЛНИ РЕЛАКСАНТИ СО ДОЛГО ВРЕМЕТРАЕЊЕ – НАШЕ ИСКУСТВО

АПСТРАКТ

Вовед: Уште од воведувањето на курарето во анестезиолошката пракса во 1942 година, тоа стана вредно дополнување на анестезиолошкиот арсенал. Од тогаш наваму мускулните релаксанти (МР) станаа важен дел кај повеќето случаи на општа анестезија. Новите студии укажуваат дека употребата на МР со средно времетраење, невромускулен мониторинг и декураризацијата на невромускулниот блок можат да влијаат на раниот постоперативен исход и да ја намалат инциденцата на резидуалниот невромускулен блок (РНМБ). Целта на оваа студија е да се спореди инциденцата на клинички знаци на РНМБ во единицата за постанестезиолошка нега (ЕПАН) кај две групи на пациенти кои се водени со МР со долго времетраење.

Материјал и методи: Проспективна дескриптивна студија изведена во Универзитетската клиника за хируршки болести Свети Наум Охридски – Скопје кај 78 пациенти водени во општа анестезија со МР со долго времетраење. Пациентите се поделени во две групи во зависност од тоа дали невромускулната функција е мониторирана или не интраоперативно.

Резултати: Инциденцата на клиничките знаци на РНМБ во ЕПАН изнесуваше 20.51% кај немониторираната и 15.38% кај мониторираната група на пациенти. Забележана е повисока инциденца на лесна хипоксемија и слабост на мускулатурата на дишните патишта кај немониторираната група.

Заклучок: Резидуалниот невромускулен блок сè уште претставува чест наод во ЕПАН. Во раниот постоперативен период тешко можат да се диференцираат знаците на РНМБ од ефектите на лековите коишто се користат за време на анестезијата. Повеќето анестезиолози сè уште се потпираат на клиничките знаци за водење на невромускулниот блок и покрај постоењето на силни препораки за употреба на невромускулен мониторинг.

Клучни зборови: единица за постанестезиолошка нега, мускулен релаксант, резидуален невромускулен блок.

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IMPLEMENTING LOW FLOW ANESHTESIA A LOGICAL APPROCH AND A PERSONAL EXPERIENCE

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Key words: low flow anesthesia (LFA), Volatile Anesthetic Agents (VAA), closed circuit anesthesia (CCA), General Anesthesia (GA), Total Intra Venous Anesthesia (TIVA).

Low Flow Anesthesia – an introduction and invitation

This text is an invitation and an introduction to LFA.

The low flow technique is just one example of a simple and logical process, but yet apparently cumbersome to apply.

It is *simple and logical* because it is the way the most GAs in the world are provided: volatile. TIVA is another other way of GA.

The LFA technique learning starts by understanding that the anesthetic gases follow **exactly the same pathway and physical rules as the oxygen!** And, in fact, of any other gases: that is from **high** pressure to **low** pressure. The only difference, and this element is **capital to understand**, is that **oxygen is consumed** in the metabolic process while the volatile anesthetics are **not**. The rest is pure physics.

Let's go back in school when we learned about the laws of gases and everything becomes simple.

If we imagine the body as a house with multiple rooms, and each room with a different volume and different things inside, the anesthetic gas will fill in gradually all of them until the partial pressure equilibrates all throughout the house.

The human body is built differently; there are no empty spaces, but the rooms are filled with different tissues with different capacities to absorb the anesthetic gases.

However, when the partial pressure of the gas in all the body "rooms" is equilibrated there is no more absorption. The body is equilibrated with the anesthesia circuit in terms of partial pressures. If theoretically the anesthesia machines were perfectly hermetic, once the body has equilibrated throughout all its compartments and with the anesthesia machine, there will be **no more absorption of gas.**

It becomes logical that at this point the vaporizers could be closed. Everything is inside the body.

But the reality is different:

1. The anesthesia machines and breathing circuits have leaks.
2. Once the surgeon has made the incision the body **stops being completely closed.** The loss is minimal, but for the sake of theoretical correctness it is not zero.
3. There is a very little, metabolism of the anesthetic gases.

At this point let's follow a step by step approach: the brain (the central point where the VAA acts) has equilibrated, ok. The only leaks are now represented by: the anesthesia machine and circuit and the losses through the surgical wound. This is the only volume of gas that we need to feed to the circuit and patient from this moment on. Anything above that is lost to the scavenger because it is not absorbed anymore. As simple as that!

But … wait a minute … haven't we forgot something? Of course, the sampling line! That tiny little tubing that takes gas from the patient and brings it to the gas analyzer and helps us see what happens in the whole system. If the gas analyzer is diverting the gas to the scavenger through its exhaust port, we need to compensate for that too. If it is returned to the circuit, then, theoretically, nothing is lost over there.

As you saw up to now all is plain clear. But the paradox starts exactly here: we work with volatile anesthetic almost on a daily basis. It is our "bread and butter". And yet, for different reasons, many practitioners are reluctant to reduce the flows.

As in many other fields of the human activity, an idea came across someone's mind many years before the technical development keeps pace with the thinking. That method was slowly

forgotten. Generation after another doesn't teach that method and, when the machinery comes to reality, there are almost no teachers to apply the theory.

It happened with the regional anesthesia. The idea was there long ago (August Bier), but the spinal needles were not the same needles we know today. Think of the LMA: in the beginning the anesthesia community was reluctant to use it. Would you start an OR today without an LMA at hand? And the examples can go on.

The LFA, however, is very easy to understand. It is the anesthesia we are performing every day … but at a much more logical level.

At this point I need to warn every early enthusiast that as any high quality method, **it must be understood and applied at slow and progressive paces.**

The theory is ok, but it must be applied in small aliquots, otherwise, instead of enjoying an excellent academic and clinical tool, we invite disaster through the main gate. It takes time and continuity, but at the end every clinician would wonder how he/she was ever able to work with higher flows before.

When starting learning LFA a few requirements must be met:

1. Solid reading and understanding of the theory,
2. Know your anesthesia machine: do you return the sampled gas to the circuit? Yes (CCA)? No?,
3. Do you use pure oxygen as the carrier gas? Yes? No? If you use another gas what do you use: Air? N2O?,
4. Do you have a gas analyzer?

All these elements are extremely important. At very low flows the gas composition is easily influenced by adding or not another gas to oxygen. Using N2O limits usually the lower limit of the total flow and precludes the use of CCA as N2O quickly accumulates and dilutes oxygen. And the examples can go on.

I describe here my own technique. There are many other techniques described in literature and all are good, as long as the clinician know what he/she is doing:

1. After i.v. induction and the insertion of the LMA/ETT, I open the oxygen tap to 10 times the theoretical basal oxygen consumption. The vaporizer (I use SEV) is opened to 8%.
2. It doesn't matter if you decide to ventilate or let the patient breathe, it will be noticed that the ETSEV and the MAC reach 1.5 MAC in roughly 1 minute, but this is only an approximation. At this point the total flow can be reduced at the theoretical oxygen consumption plus the leaks, but the SEV vaporizer must be left open to 8%. Usually, a small decrease in the MAC can be noticed but soon after the MAC will start rising again (signaling the vessel rich tissues are almost saturated).
3. Now the SEV vaporizer dial can be slowly reduced as guided by the gas analyzer.

With SEV this process usually takes 10-15 minutes. Higher flows can speed even further this phase (uptake), but this is usually not necessary in an elective surgery. This is the phase where the patient is scrubbed, covered etc. This allows for a smooth uptake and quietness for the anesthesiologist that can also complete other specific tasks.

It is highly recommended that whoever wants to start practicing LFA to do it with someone experienced in the technique. My own experience taught me that letting the clinician accommodate alone to small and progressive reductions in the total flow is the best way. In many places I've noticed clinicians commonly use flows of 1.5-2 liters/minute, oxygen + air or oxygen + N2O. I would suggest reducing both gases in 50 ml steps each (total 100 ml/min) and just follow what happens on the monitor (gas analyzer) and bellows or balloon (if the patient breathes). I recommend staying at this phase for a week. Once a comfort zone and understanding are reached another 100 ml can be reduced.

The more the flow is reduced the more important is the configuration of the circuit and the gas composition. Using only oxygen as the carrier gas makes the whole process very simple as there is no danger of hypoxia. Using N2O is more problematic as it accumulates very quickly in the circuit and a hypoxic mixture can develop.

Throughout the years I've noticed some very interesting things:

1. The more the clinician gets experience with the technique, the speed in the steps gets faster, that is - the flows are reduced every 3 days or so, not one week.
2. Most clinicians are still reluctant to reduce flow to less than 500 ml/min. It is normal to be a bit fearful after so many years of using flows 3-4 times bigger than this. But it's a progress anyway.

At the human side of the story I wish to share with you several questions or answers that seem to repeat themselves in almost every place I presented the LFA. They only show that the most important and sometimes difficult element in changing things is the human factor.

Once I asked a younger colleague why is he using in the maintenance phase 1 LPM of O2 and 2 of N2O. He replied: I am not sure, but this is how we all do here because this is how we were told to do.

While addressing the economical aspect of LFA (cost reduction can reach as much as 80%) the general answer was: as long as I don't pay for them why should I bother. Is it so?

Atmospheric pollution was another irrelevant element in our discussion. ALL the colleagues I talked about it had absolutely NO idea where the scavenged gases go beyond the OR wall. Even when I told them they just go into the atmosphere they didn't even blink. Imagine the VAA would leave a trace as the exhaust of a car; then we would see them! Could that change our practice? Possible.

"But our anesthesia machines have leaks; we cannot reduce the flows as much". This is another mantra that comes again and again showing the unfamiliarity of many clinicians with the concept that all the calculations must be done only after these leaks are measured and compensated for. Of course, using higher flows usually compensates for everything, but also contributes to high losses of VAA.

In our days we are usually very interested in regional blocks, sepsis, trauma etc. These are important things, no doubt. But little or even no concern is given occasionally to the most used GA technique and the whole theory of LFA that can transform completely the way we work on a daily basis.

At times I am asked: "What is the best way to apply LFA?" This is a normal question but the answer is less simple. Imagine someone would ask which is the best way to drive a car from point A to B! Of course all cars have the same main commands. But the way we drive depends on the type of the car, the engine power, traffic, weather etc.

The same is valid for LFA: what patient are we having, what is the length of the surgery, what conformation has the breathing circuit, what are the comorbidities, if at all? In fact any clinician can choose his/her way of reducing the flow, the most important thing is knowing what you are doing. The rest is only technique.

How can we convince the nowadays clinician to adopt this technique? There is no definite or best answer. As long as there is no consensus in the Department the LFA is cumbersome and even potentially dangerous to apply. A local policy implemented by the hospital and the Chief of Department could be a start. Financially or otherwise rewarding the department or even individuals could be an idea as well.

For the ones that want to get a very interesting and interactive approach to LFA I would warmly recommend the GasMan computer program by Dr. James Philip. www.gasmanweb.com

It is also important to mention that the modern anesthesia workstations (Drager Perseus, iFlow Maquet, GE Aysis, Mindray A7 to mention only a few) have features that help "see" what the level of economy/waste we are at and some eventually reach alone the desired level of flow for optimum gas delivery and maintenance.

Suggested literature and sites

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2. "Low Flow Anaesthesia with Drager Machines".
3. The Virtual Anesthesia Machine: https://vam.anest.ufl.edu/
4. www.navat.org

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OBSTETRIC ANESTHESIA: PRESENT ASPECTS

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ABSTRACT

The study reviews the well-established ways to apply labor analgesia which are practiced widely, with a simultaneous analytical overview of current and influential aspects in the field of obstetric anesthesia. In the introduction, attention is paid to the global morbidity and the morbidity trend in the field of obstetric anesthesia, which shows positive changes, primarily as a result of more frequent application of regional obstetric anesthesia in general. The current procedures and methods with their specifics have been analyzed, as well as up-to-date data regarding side effects, which have been duly addressed. Special emphasis on the respiratory depression risk caused by intrathecal opioid route is considered, whose usability is very common today. From that aspect, the study is conceived as an opportunity for better information and understanding of the current aspects of obstetric anesthesia, with the ultimate goal of improving the final outcome of the process of labor, thus implicating better well-being for both mother and newborn.

Key words: obstetrics, labor analgesia, procedures, aspects.

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Obstetric Anesthesia Risk

Today, the inclusion of general anesthesia in obstetrics is represented in much smaller percentage than decades before. The increasing popularity of regional as opposed to general anesthesia was due not only to its practical and simple application, but also came as a result of a reduced risk of serious or fatal complications, as observed with general anesthesia. Historically, anesthesia and the complications it caused was in sixth place out of the total of maternal death causes in the USA (3.3%). In the next 5 years (1985-1990), as a result of general anesthesia, there were observed 32 deaths (per 1 million births) while with parturient receiving regional anesthesia there were a reported 1.9 total deaths per 1 million. According to recent data, in the period until the 21st century (the year 2000), total mortality rate was further decreased and a total of 1,6 deaths was registered. The conclusion is that the percentage was mostly a result of the replacement of general with regional analgesia ([1]).

Postpartum respiratory compromise, especially in obese patients, remains a significant factor in the obstetric mortality rate. To determine the possible causes, a revival retrospective study of 5.036 parturient delivered with CS reports that postpartum pain treatment with a multimodal approach of neuroaxial opioids (morphine or fentanyl), combined with oral analgesics (NSAIDs or morphine agents), neither led to an increased risk of respiratory complications, nor to serious respiratory desaturation, so the causes of postoperative respiratory compromise should be sought elsewhere([2 3 4]). Some other conditions, such as: early pre-eclampsia (≤34 weeks) ([5 6]), sepsis ,which shows a continuously increase to 10% per year during the last decade ([7]) and postpartum hemorrhage (PPH), are the most common and the most important factors for perinatal mortality. An interesting fact is that the retrospective of National Wide Inpatient Sample from 2013 shows a double increase in serious non-atonic PPH (1.9 / 1,000 in 1999 to 4.2 / 1000 in 2008) which necessitated the need for development of an urgent strategic and multidisciplinary approach to PPH protocols, especially in low-cost countries ([8]).

Moreover, recent experience reports that the application of classical laryngeal mask (LM) in parturient with impossible or difficult intubation leads to successful resolution in the most of the cases (68%), so LM is considered as a valuable alternative for obstetrics airway management ([9],[10]).

Epidural Analgesia for Vaginal Delivery

Epidural analgesia (EDA) became particularly popular in the field of obstetrics ever since the '80s of the last century. It has provided superior analgesia over other methods and is still the most exploited way for labor pain relief. Epidural continuous infusion of low concentrated anesthetics combined with lipophilic opioid, has proved to be very effective for maternity pain relief, with an excellent control of the intensity and duration of labor pain with minimal motor blockade ([11]).

For adequate pain relief of the birth process in the first stage of labor, what is required is epidural sensory block to T10 level, while T 4 level is required for eventual CS. In the second labor stage, where somatic labor pain is predominant, analgesia at the sacral S2-S4 level is required.

There are two ways of initiating the epidural analgesia in labor. C*lassical* or *traditional approach* means that epidurals initiate when labor have moved to its active phase, meaning a 3-5 cm minimal cervical dilatation with regular uterine contractions. *Liberal* access allows earlier epidural administration, alongside with the beginning of the first labor pains without taking account of the beginning of regular uterine contractions, when the membranes are ruptured and an oxytocin infusion is started. Comparing the early (cervical dilation <4-5 cm) with the delayed (classical) initiating of epidural (cervical dilation> 4-5 cm), the multicenter Cohrane analytical study conducted in 15.752 parturient receiving early or late epidural (Cochrane, MEDLINE and Embase data base analysis until 2014), reports that there was no difference both in terms of increased percentage of instrumental / operational completion of labor (CS) or among the second stage duration of these two regimes of epidurals. It was also reported that the neonatal parameters (Apgar <7 at the 1st and 5th min an pH) were not significantly different between the groups, so it is benefitial for the parturient to administer and start the epidural analgesia with the appearance of the *first labor pains* regardless of the labor progress, or in cases of risky pregnancy when the presence of a functional catheter enables avoiding general anesthesia that would pose a risk for her ([12]).

The question about whether epidural may lead to an increased rate of operative or instrumental delivery or second stage prolongation and the factors that contribute to this phenomenon has still remained a present topic of the controversy. The usage of a mixture of low concentrations of local anesthetic (0.125 -0.0625% bipivacaine) with lipophilic opioids (mostly fentanyl 1-5 μgr / ml or sufentanil 0.2-0.5 μgr / ml), reduces these negative influences over labor, as well as the prolongation of the second stage or instrumental labor procedures, thus forcing such a manner of application. Application of 1% lidocaine or chloroprocaine 2% in the first labor stage leads to faster action compared to bupivacaine enabled, but they have shorter-action and can cause intense motor blockade. Among all of the used anesthetics *bupivacaine* is still the most commonly used anesthetic for epidural analgesia during labor.

When comparing the two most exploited EDA regimes - *intermittent bolus dosage* versus *continuous epidural labor infusion*, revival systematic studies report that the intermittent bolus dosage at regular interval periods improves both the painless quality and maternal satisfaction compared to the continuous infusion; additionally it comes that this regime moderately reduces the total anesthetic amount compared to continuous infusion.

Nowadays, using the infusion pumps and perfusors in the form of *PCEA (patient-controlled labor epidural analgesia)* is an available option in many maternity hospitals.The delivery of the analgesic mixture controls the parturient itself - when pressing a button on the pump with the onset of the first labor pains. Total volume, speed of delivery and safe period of locking (lock-out period) is programed from the manufacturer, anesthesiologist or partly from the parturient. Most often, analgesia activation at the second labor stage (S2-S4) is carried out with an additional

dosage of the mixture in a semi-upright position, when the monitoring of blood pressure is necessary and a possibility of additional IV crystalloids is expected ([13]).

Quality of labor analgesia: unfortunately, epidurals do not always guarantee complete lack of labor pains and mother satisfaction. Thangamuthu A. et al. in a study which included 1.521 mothers with a high 23% failure rate, have constructed a standard definition of a failed EDA that is widely accepted as a guide for success in obstetric anesthesia ([14]). The greatest failure rate of EDA occurs for the following reasons:

1. inadequate analgesia in the first 45 minutes of the start of the epidural procedure,
2. re-insertion of the epidural catheter or other epidural problems when placing the catheter (cancellation of the procedure),
3. accidental dural puncture,
4. general dissatisfaction among parturient of both EDA or obstetric service.

On the other hand, giving the epidural analgesia by experienced anesthesiologists (≥5 years of experience), insertion of epidural catheter between 5-6 cm in the epidural space compared to <5 cm or > 6 cm and good quality of labor analgesia in the first 45 minutes, leads to high percentage of success and satisfaction among the parturients. The timing of the day, duration of the labor, cervical dilation or the position of the parturient during insertion of the epidural catheter are factors that do not affect the quality of labor analgesia([15]).

The most common complications during analgesia still remain to be following: 1. the motor weakness of the legs with difficulty of standing or walking, 2. difficulty to urinate, 3. pruritus, 4. nausea and vomiting when using higher opioid doses, 5. hypotension as the common early effect of regional anesthesia and 6. fever independent of infection (6-23%). Dural membrane perforation with postdural puncture headache (PDPG) still remains one of the most frequent complications of neuraxial labor anesthesia. The treatment of PDPG, according to the latest Cohrane's Revue study from 2013, indicates that *cosyntropin* at a dose of 1 mg IV administered after delivery, enables most effective PDPG treatment and is shown to be significantly more effective than morphine, caffeine, indomethacin, IV aminophylline or dexamethasone ([16]).

Spinal Single-shot Analgesia for Vaginal Delivery

Single-shot analgesia for painless delivery is an alternative method of epidural analgesia and is mainly chosen where there is no service of labor epidural analgesia. The limited duration of the analgesic effect and the inability for additional analgesia particularly in the second stage of labor are limiting factors for its more spired usage. Spinal block with local anesthetic can affect both ambulation of the mother and pushing efforts of parturient more than epidurals. Because of that, spinal analgesia should be applied only with advanced labors with appropriate cervical dilatation or when there is an obstetric decision for surgical completion of delivery, when spinal anesthetic dosage has to provide adequate conditions for operative delivery (CS).

Spinal analgesia with *intraspinal opioids* (intrathecal narcosis, ITN) is based on the application of spinal opioids without local anesthetic. Spinal opioids (unlike local anesthetics) act on the so-called opioid receptors on the posterior roots of the medulla with no blockage of the sympathetic nervous system, so no major hypotension or motor affection, or influence over pushing efforts appears. Such manner of ITN is useful for high-risk mothers where functional sympathectomy caused by regional anesthesia present a high risk (hypovolemia, various heart diseases e.g. aortic stenosis, tetralogy of Fallot, pulmonary hypertension, etc.). Furthermore, ITN compared to intravenous analgesia probably causes less emetic symptoms and leads to better neonatal outcome ([17],[18],[19],[20]).

ITN is used in small doses of lipophilic opioids: 10-25 mcg fentanyl, 5-10 mcg sufentanyl, 10-12 mg of meperidine (pethidine, dolantin) or hydrophilic morphine. The optimal 'single-shot' intrathecal dose of morphine appears to be 0.075-0.15 mg and the ideal 'single-shot' epidural morphine dose is 2.5-3.75 mg([21]). IV administration of morphine does not provide fast analgesia onset (over 20 minutes), but owns prolonged action for nearly 4 hours of labor analgesia, with somewhat higher incidence of side effects, primarily nausea and vomiting, pruritus or late respiratory depression ([22]). Analgesic efficacy studies have not been adequately powered to show differences in the incidence of clinically significant respiratory depression, though the risk of serious depression is low, less than associated with the systemic opioid administration (9). Respiratory depression was previously thought to result from the interaction of opioid in the cerebrospinal fluid with ventral medullary opioid receptors. More recently, the pre-Bötzinger complex located in the medulla has been identified as the site responsible for the decrease in respiratory rate following systemic administration of opioids. Neurons in the pre-Bötzinger complex expressing neurokinin-1 receptors are selectively inhibited by opioids, and therefore the same are the mediators of opioid-induced respiratory depression. From that point of view, researchers have recently focused on non-opioid drugs such as serotonin receptor agonists. Early evidence suggests that ampakine (AMPA) receptor modulators and sodium/proton exchanger type 3 inhibitors, may be effective at reducing opioid-induced respiratory depression while maintaining analgesia, but further warrant studies are needed. Caution should be exercised when prescribing systemic opioids (intravenous or oral) in addition to neuraxial morphine as this can compound the potential for early or delayed respiratory depression. Opioid antagonists such as naloxone used to prevent or treat opioid-induced respiratory depression have number of limitations(25).

Spinal anesthesia with a mixture of local anesthetics with opioid has combined synergistic effect, which deepens and prolongs analgesic effect, thus reducing the total anesthetic amount and the risk of possible complications. In practice there are more possible combinations: 2.5 mg 0.5% bupivacaine plus 25 mcg fentanyl that acts synergistically and provide an excellent analgesic effect lasting longer than 2 hours. Adding the mixture of hydrophilic opioid (morphine 0.15mg) provides prolonged analgesic effect for nearly 4 hours.

Adequate safety studies for intrathecal tramadol have not yet been published, but Subedi et al reported on improving spinal analgesia for CS in a trial of 80 patients receiving tramadol. These researches reported that adding 10 mg intrathecal tramadol versus 10 μg intrathecal fentanyl to hyperbaric bupivacaine (10 mg) increased the median duration of postoperative analgesia (300 vs. 260 min, $p< 0.05$). The intrathecal tramadol group also had less shivering (5% vs. 43% incidence; $p< 0.05$), and there was no negative impact on neonatal Apgar scores, fetal pH status or other neonatal scoring ([23]).

Combined Spinal-epidural analgesia (CSE)

CSE combines the advantages of both methods: a rapid onset of spinal analgesia which continues epidural application. It is useful for mothers with intense labor pain early in the labor stages or before delivery. It is believed that CSE analgesia was introduced for reduction of some undesirable side effects of EDA: the risk of prolongation of the second delivery stage, increased use of oxytocin stimulation or because of the greater incidence of instrumental vaginal delivery seen with EDA. CSE can increase mobility during labor and can provide faster analgesic effect compared to EDA, which in total contributes to greater maternal satisfaction.

If an intrathecal opioid given, analgesia is prolonged within 1-2 hours; when the pain recurs, analgesia is established by giving a local anesthetic (with or without opioid) by the epidural route. Many combinations are possible for use, but the most exploited one used a mixture of 1-2.5 mg bupivacaine + fentanyl 20-25 mcg(5 mcg sufentanil) in 1.5 ml volume and added epidural: 0.08-0.125% bupivacaine + fentanyl 2 mcg / ml 10 -15 ml fractionated or continuous infusion 8-20 ml / hour.

The Cochrane-revival study, which included 27 other studies in the relevant matters with 3274 parturient, shows that CSE compared to EDA, owns higher efficiency in relation to the beginning of the analgesic effect (mean difference 2.87 minutes). The need for additional analgesia and the rate of instrumental delivery, as well as the urinary retention, also increased in some studies when CSE was applied ([24]). When comparing both methods, there are no significant differences in terms of motor weakness or mobilization of mothers during labor, the rate of CS, frequency of PDPG, hypotension or neonatal Apgar scores and umbilical pH values. However, one can conclude that there are no compelling reasons for favoring CSE over EDA in terms of better maternal satisfaction, apart from faster onset of action and a somewhat lesser degree of pruritus. But significantly more frequent occurrence of urinary retention, need for additional analgesia and common instrumental procedures, leads to the conclusion that CSE offers no clear advantages over epidural that would justify the reasons for replacing traditional epidural analgesia([25]).

Regarding postoperative analgesia with adding bilateral transverses abdominis plane (TAP) block to the multimodal post–cesarean delivery pain medication regimen (intrathecal morphine, NSAIDS or acetaminophen plus opioids) for breakthrough pain, the opinion of long-lasting postoperative analgesic benefits was not supported ([26],[27]).

Conclusion

This study primarily evaluates the established ways in labor analgesia, as well as the range of actual influential work regarding obstetric labor analgesia. It pays attention to the anesthesia risks and factors that affect obstetric morbidity and mortality rate, also comparing different anesthetic regimes for labor analgesia and accentuated factors that contribute to the quality of labor analgesia. It also emphasizes the most recent findings about side effects of regional analgesia mostly with references to opioid respiratory depression.

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АПСТРАКТ

Студијата прави пресек на етаблираните начини на родилното обезболување што се практикуваат нашироко, со истовремен осврт на актуелните и влијателни сознанија од акушерската анестезија. Во воведниот дел, се обрнува внимание на општата стапка на актуелниот морбидитет и морталитет во акушерската анестезија, кој доживува позитивни промени, пред сè како резултат на зачестената примена на регионалната анестезија во акушерството. Анализирани се одредени методи и специфики за родилното обезболување, како и современи сознанија за етиологијата на несаканите ефекти, со посебен осврт на ризикот од респираторната депресија предизвикана од интратекалната примена на опиоиди која денес многу често се применува. Од тој аспект, изнесените ставови се можност за подобро информирање и разбирање на современите аспекти на акушерската анестезија, а се со крајна цел да го подобрат крајниот исход од родилниот процес кај двете битија: мајката и плодот.

Клучни зборови: акушерство, аспекти, процедури, родилна аналгезија.

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PRESENCE OF THE SKIP METASTASIS IN THE AXILLARY PIT IN PATIENTS UNDERGOING SURGERY OF PRIMARY BREAST CARCINOMA WITH LYMPHADENECTOMY

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ABSTRACT

Introduction: Axillary status is an important prognostic factor for the breast carcinoma. The introduction of a minimally invasive procedure for determining the axillary status, detection and biopsy of the sentinel lymph node (SLND), gives us the possibility to remove only one node. This can predict condition of the other nodes. Possibility of occurrence of the skip metastasis in axillary pit, can give wrong result for the occupancy at the axillary pit.

Aim: Analysis of the 144 patients surgically treated for breast cancer by one surgeon in 2015 in order to assess percentage of skip metastasis.

Materials and methods: We analyzed the histopathological results of 144 patients surgically treated by one surgeon, where level (1-3) of the lymph nodes in axillary pit intraoperatively were determined and marked.

Results: There were analyzed 144 patients, with mean age of 57.3 years, with an average size of the tumor of 29,54mm + 18.89, with an average removed of 15.45 lymph nodes, and from the third floor 2.61. Thus positive for metastatic deposits were 3.76, and positive from the third level were 0.37. Only at two patients (1.38%) there were detected skip metastasis (affected 1-2 nodes in first level and positive nodes in the third level, but there was no patient's positivity in the third level if there was no positive nodes in the first and second level).

Conclusion: The percentage of skip metastasis in our study was 1.38%, which is really a small percentage, that gives us right to apply the method for sentinel lymph node detection and biopsy for predicting axillary status and to predict the real situation of the other nodes in the axillary pit.

Key words: axillary lymphadenectomy, breast cancer, skips metastasis

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Introduction

Axillary status is an important prognostic factor for the breast carcinoma. The introduction of a minimum invasive procedure for determining the axillary status, detection and biopsy of the sentinel lymph node (SLND), gives us the possibility to remove only one node. This can predict condition of the other nodes. (1, 2) The possibility of the occurrence of the skip metastasis in the axillary pit, situation where metastases from breast cancer skip, jump lymph nodes which are on the way of spreading, and to go to next level of lymph nodes, can give wrong result for the occupancy at the axillary pit. (3) This is the reason to explore our materials for persistence of the skip metastases and if the same persist how many are present in our material.

Aim

The aim of the study was to detect persistence of the skip metastases from breast cancer in axillary pit in the operative materials of patients surgically treated by one surgeon in the year 2015.

Material and Methods

We analyzed, in the retrospective study, histopathological results of 144 patients surgically treated for breast cancer at the University Clinic for Thoracic Surgery in 2015, by one surgeon, whereby intraoperatively level (1-3) of the lymph nodes in axillary pit were determined and marked. Radical surgical treatment of the breast (radical mastectomy or quadrantectomy) was done at patients, followed with radical lymphadenectomy of three levels of axillary pit. Each level of the axillary pit was marked, as later can be examined separately. All parameters, of the patients´ history and parameters from histopathological findings were put in the computer program Statistica 7, where the statistical analysis were done. The basic statistical analysis was done.

Results

There were analyzed 144 patients, with mean age of 57.3 years, with an average size of the tumor of 29,54mm + 18.89, with an average removed of 15.45 lymph nodes, from first level were removed mean 7,88; from second level were removed mean 4,95 and from the third level - 2,61.

Thus positive lymph nodes for metastatic deposits in whole axillary pit were mean 3.76, positive from the first level were mean 2,23; from the second level were positive mean 1,16 and positive from the third level were 0.37.

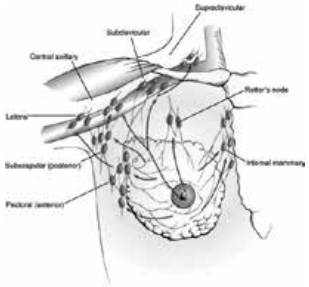
Only in two patients (1.38%) there were detected skip metastasis (affected 1-2 nodes in the first level and positive nodes in the third level, but there was no patient's positivity in the third level if there was no positive nodes in the first and the second level).

Table 1. *The main characteristics of the analyzed patients (n= 144) M±SD*

	Mean	**SD**
Age	57.3	12.8
	Mean	**SD**
Tumor size (mm)	29.54	18.9
	N	%
Axillary status		
N0	64	44.4
N+	80	55.6
Axillary pit level	Negative pit findings	Positive pit findings
I	64 (44,4%)	80 (55,6%)
II	90 (62,5%)	54 (37,5%)
III	121 (84,0%)	23 (16,0%)
Axillary pit level	Mean negative nodes	Mean positive nodes
I	5.65	2.23
II	3.80	1.16
III	2.43	0.37
Histology	**N**	**%**
Ductal	117	81.2
Lobular	4	2.8
Other	23	16.o
Grade	**N**	**%**
1	7	4.9
2	110	76.4
3	27	18.7
Stage	**N**	**%**
0	1	0.7
I	26	18.1
II	71	49.3
III	46	31.9

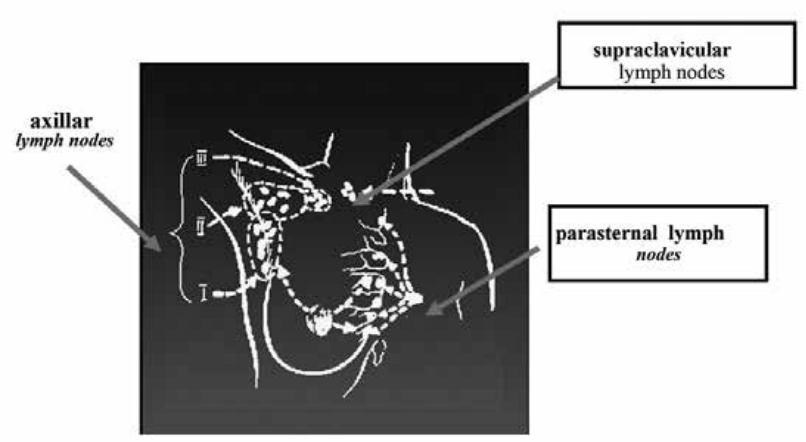
Discussion

Lymph drainages from the breast are well documented up to now, where main drainage (80-95%) is in the lymph nodes in the axillary pit, and the small amount especially from the medial parts of the breast were drained in lymph nodes located parasternaly, to lymph nodes located along arteries mammary intern. Minimal amount of lymph liquid was derivated to contra-lateral breast and subdiaphragmatic. (4,5)



Picture 1. *Lymph drainage of the breast*

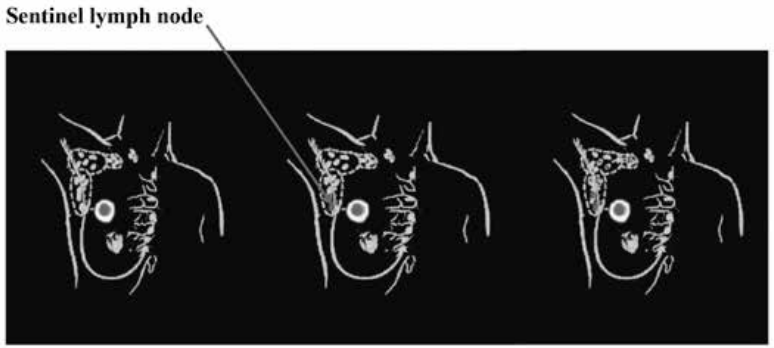
Lymph drainage in the lymph nodes in axillary pit is in five gropes of nodes (pectoral, subscapular, lateral, central and subclavicular). From practical and surgical point of view lymph nodes in the axillary pit are derived in three levels: I level (laterally from lateral border of minor pectoral muscle, II level contains lymph nodes that were under minor pectoral muscle, and III level (top of the axilla) where the lymph nodes were located in medial position from the medial border of the minor pectoral muscle.(4)



Picture 2. *Spread of lymph drainage from the breast*

In the past there were made several studies with the aim to examine the lymph drainage of the breast. They were performed on cadavers, but also in the patients, where different fluids as radiocoloid or different types of colors-metilen blue were used.(1,2,5) These studies were more frequent especially after 1990, after introducing the sentinel node biopsy technique. In these studies, lymph drainage was presented to be mainly through lymphatic that gone to axillary pit

80-98%, 5-20% to lymph nodes which were up to a. mammary intern, retrosternally, especially from medial parts of the breast, retromammary in dept were detected at 17% and 3-6% were spread to contra lateral breast, and small amount drainage were in subdiaphragmatic lymph nodes.(6) Much more were examined the way of spreading of lymph in the axial, and it was seen that mainly there was successive spread, first in first lymph node in the I level- named sentinel lymph node, than in other lymph nodes in I level, than in lymph nodes in II level and at the end in lymph nodes in III level. After that, the spread is in supraclavicular lymph nodes. This is the basic thesis for introducing sentinel lymph node biopsy technique. (1,2,5) Giving radiocoloids in the breast (subareolar, perialeolar, intraparenhimic, peritumoral), these radiocoloids were detected after 2-4 hours in the first drainage lymph node-sentinel lymph node in axillary pit. The same situation is also with giving color-vital blue or metilen blue, where giving perareolar or peritumoral 10 to 20 minutes before surgery, there were detected colors in the first drainage lymph node- sentinel lymph node, in the axillary pit. (1, 2) Detection, extraction of this lymph node, and histological examination of this lymph node make possible to detect, thus the breast cancer involve this lymph node or if this lymph node was not involved with metastases, it is possible to assume that the other lymph nodes were not involved with metastases and in these patients it is possible not to do axillary lymphadenectomy. (1,2)

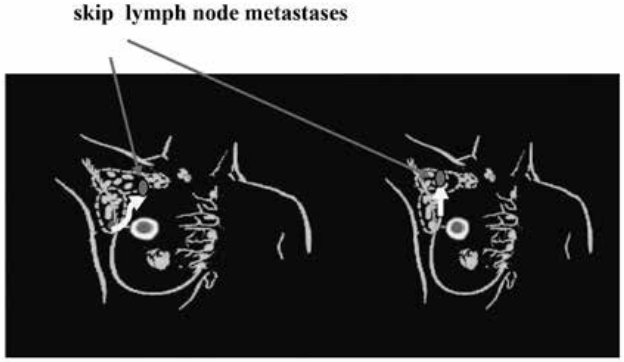


Picture 3. *Normal spread of metastases, radiocoloid and methilen blue from breast to axillary lymph node*

But in practice, it is not so easy, and the spreading is not always in this way. So, in the literature, in the study Pasta detected SLND in 86% in the lymph node of I level, 8,6% in II level and 2,8% in III level.(7) Heuts detected SLND in 98% in axillary pit, in 20% in the lymph node according a. mammary intern.(8,9,10,11) In patients with previous surgery before, especially if the surgery was in the upper lateral quadrant, there was present no sentinel lymph node in axillary pit. In few cases, in examination with static Gama camera, it was shown that after giving radiocoloids, the contrast was gone down in the subdiafragmatic parts of the body.(6,7)

The appearance of the abnormal spread of the metastases in lymph nodes in axillary pit is not well examined. There were few hypothesis, that as abnormal lymph channel that goes directly

from breast to second or third level of lymph nodes, or abnormal lymph channel that avoids some lymph nodes in normal way of lymph drainage in the axillary pit.(3, 12)



Picture 4. *Abnormal, discontinued (skip) spread of metastases from breast to axillary lymph node*

In the literature there were few publications about the skip metastasis. Sun J- analyzed 1502 patients and detected skip metastases in 7,9% of all analyzed patients, or in 14,6% of the patients with positive metastases in axillary lymph nodes.(3) This is situation that gives large percent of false negative detected SLND (up to 25%). Also he couldn't associate the appearance of the skip metastases with any factor. (3)

Rossen PP- analyzed 1228 cases with breast cancer and detected skip metastases at only 1,6%, and this condition is not associated with the size of the tumor, its localization or the histology.(12)

Loyd LR- detected skip metastases in1,6% of all patients, or 3,2% at positive for metastases axillary lymph nodes. This percent is relatively small to decide to do axillary lymphadenectomy at all patients.(13)

So, the technique of detecting and biopsy of the first drainage lymph node (sentinel lymph node) has possibility to give wrong results, which were result of spreading to other pools (parasternal, contra lateral breast, subdiafragmatic spread), but also of appearing of skip metastases in the other parts of axillary pit. These are the reason for success rate of detection of sentinel node to be in the range between 80 to 99%, with possibility of false negative results of 3 to 10%.(1,2)

In our study we detected skip metastases in only two cases (1,36%) or 2,5 % of patients with positive axillary findings, which is low, and we can use SLND biopsy safely.

Conclusion

The percentage of skip metastasis in our study was 1.38%, which is really a small percentage, that gives us right to applay the method for sentinel lymph node detection and biopsy for predicting axillary status and to predict the real situation of the other nodes in axillary pit.

Conflict of Interest

We have no conflict of interest to declare.

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АПСТРАКТ

Вовед: Аксиларниот статус е значаен прогностички фактор кај малигномот на дојка. Воведувањето на минимално- инвазивната процедура за определување на аксиларниот статус, детекција на жлезда стражар, овозможува отстранување на една жлезда која ќе ја манифестира состојбата на останатите жлезди. Постоењето на можност за појава на скокачки метастази може да даде погрешна претстава за зафатеноста на жлездите во аксиларната јама.

Цел: Анализа на историите и патохистолошките резултати од 144 пациенти оперирани од еден хирург во 2015 година од малигном на дојка со цел да се процени колкав е процентот на скип метастази во нашиот материјал.

Материјал и метод: Анализирани се патохистолошките резултати од 144 пациенти оперирани од еден хирург, при што интраоперативно се определени и маркирани спратовите (1-3) на лимфни жлезди во пазувната јама.

Резултати: Во анализата се опфатени 144 пациенти, со средна возраст од 57,3 ± 12 години, со просечна големина на тумор од 29,54мм ±18,89, со просечно извадени 15,45 лимфни жлезди, а само од III спрат 2,61. Притоа, позитивни на метастатски депозит биле средно 3,76±6,25, а позитивни од III спрат биле 0,37±1,26. Само кај два пациенти (1,38%) се детектирани скокачки метастази (зафатена 1-2 жлезди во прв спрат и позитивна жлезда во трет спрат, а нема ниту еден пациент позитивен во трет спрат а да нема позитивни резултати во прв и втор спрат).

Заклучок: Процентот на скокачки метастази во нашиот материјал е 1,38% што е навистина мал процент, кој овозможува сигурна примена на методот на детекција на жлезда стражар во пазувната јама.

Клучни зборови: детекција и биопсија на жлезда стражар, скип метастази, статус на аксиларана јама.

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HEPATIC RESECTION SURGERY AND THE ANESTHETIC APPROACH

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ABSTRACT

Liver resection can be associated with increased likelihood of massive bleeding. The blood loss presents major intraoperative issue. Bleeding is usually present in cirrhotic patients, but can be faced even in the patients with normal liver function undergoing massive liver resection. Correction of preoperative abnormal coagulation's tests, strong interaction between the surgeon and the anesthesiologist, and finally the anesthesia technique, may successfully reduce the bleeding intensity and blood transfusions requirements. This review will be focused on the anesthesiologist's role in minimizing the blood loss during hepatic resection in our case.

Key words: anesthesia, intraoperative bleeding, liver disease, low CVP

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Introduction

Massive bleeding is a major concern of liver resection. An increased intraoperative transfusion of blood components and large amounts of fluids can be administered due to massive bleeding. The tendency to overfill vascular bed and large amount of blood transfusions is recently reported to be associated with worst outcome and increased mortality rate (1-4). Decreased liver function, liver failure, major liver tissue trauma, and primary liver tumor, may be associated with abnormal coagulation. We report a case of a patient undergone to left lobe resection for suspected hepatic cell carcinoma.

Case Report

The patient K. J., 75 years old white man, with no previous medical history, was recovered in our institute and diagnosed with left liver lobe tumor. The preoperative consult was unremarkable. Cardiac, respiratory, and liver examinations were within limits. Blood gases and the other biochemistry examination were within normal limits. The angio-CT scan examination (Fig 1, 2) revealed left lobe tumor sized 65 × 52 mm. Tumor marker Ca 19-9 was 91240 U/ml (normal values ≤ 35 U/ml).

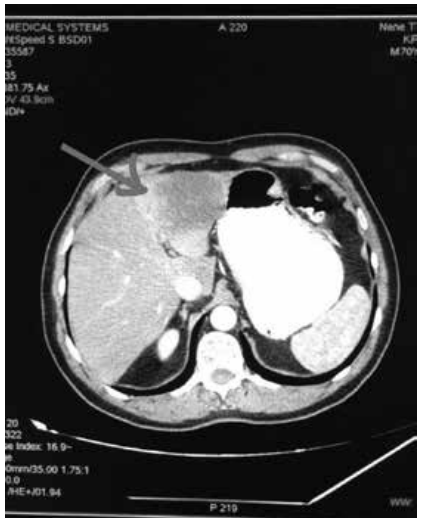

Fig 1

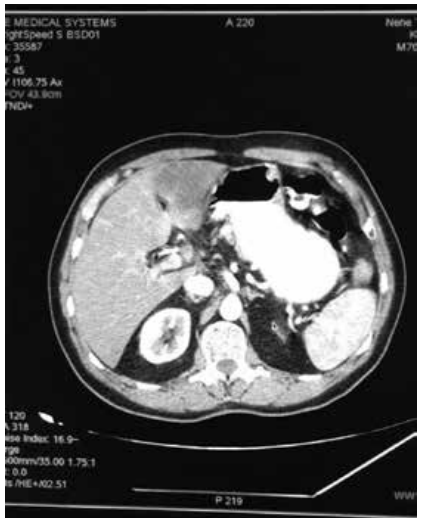

Fig 2

The patient was premedicated with oral Diazepam 10 mg the night before the surgery, and morphine sulfate 10 mg intramuscularly 30 minutes before the induction of the anesthesia. In operating room, after peripheral venous cannula was inserted, right radial artery and right internal jugular vein were cannulated with a 20G arterial cannula and 7.5 F central venous catheter. A fast track anesthesia was made (Fentanyl 5 mcg/kg, Propofol 2 mg/kg, cis-atracurium 0.15 mg/kg). Monitoring included standard monitoring, central venous pressure and invasive blood pressure monitoring. The anesthesia was maintained with propofol and remifentanil infusion, and cis-atracurium was used as needed. The anesthesiologist tended to maintain CVP 5-6 cm H2O. The surgical technique consisted of large incision (Fig 3), preparation of the liver and large vessels (Fig 4), and anatomic left lobe resection (Fig 5, 6). After the resection, left lobe was sent for histopathology examination (Fig 7). During the surgery, the estimated bleeding amount was 2000 ml in 10 minutes due to damage of one suprahepatic vein. There were administered 3 blood unites, 3 FFP units, crystalloids (saline, ringer) 2000 ml, and 1000 ml of colloids. Norepinephrine and dopamine infusions were used to stabilize hemodynamics. Tranex was administered to enhance the coagulation. After 6 hours of surgery, the patient was successfully extubated in OR with normal vital signs. After the surgery the patient suffered a transitory liver dysfunction demonstrated by albumin level of 2.1, PT 33.6%, INR 1.945, AST 712, and ALT 2356. Hepatic function was normalized in the 4-th postoperative day. The patient was discharged uneventful on 8-th postoperative day, being referred to the gastrohepatologist and the oncologist for further follow up.

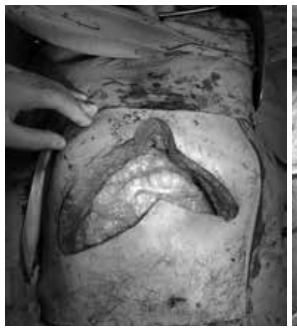

Fig 3

Fig 4

Fig 5

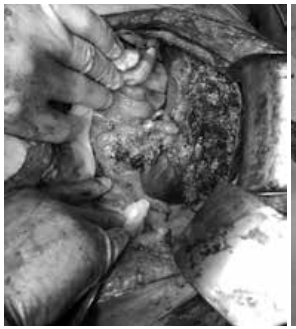

Fig 6

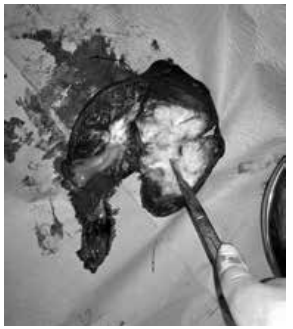

Fig 7

Discussion

Monitoring

Liver surgery and especially large liver resection needs careful and strict monitoring. It is recently reported that standard monitoring according ASA guidelines is mandatory, but invasive monitoring of central venous and arterial blood pressure are routinely recommended. Arterial access is of great importance not only to measure the blood pressure, but for frequently blood gases and biochemistry analysis as well. The recommended monitoring was performed in our patient. Two large-bore intravenous cannulas are usually inserted in order to facilitate fluid administration, as we did in our case. Central venous pressure (CVP) monitoring can serve as guide for fluid management and hemodynamic manipulation. In the patients with cardiac dysfunction it is not so reliable, but can be assembled with the other methods judging for circulating volume. A hyperdynamic state with increased cardiac index, decreased systemic vascular resistance, and augmented splanchnic blood flow may persist preoperatively (5). This increased blood supply to the residual liver parenchyma ensures rapid growth. Signs and symptoms of the heart failure can easily be overlooked as they mimic those of cirrhosis and liver failure. Transthoracic echocardiography is useful to measure right ventricular systolic pressure and also shows the cardiac changes. We had no access on TEE. Rapid infusion and cell saver devices are generally useful. Thromboelastography (6) and Rotating Thromboelastometry are useful to monitor all the coagulation's disorders, but unfortunately we did not have this device in our department. We used standard laboratory monitoring of coagulation profile. Thromboelastometry (TEM, previously named rotational thrombelastometry/-graphy) presents the viscoelastic method for blood coagulation testing (7) TEM tests all the interactions of coagulation factors, anticoagulant drugs, blood cells, platelets, and fibrinolysis. TEM is performed with the ROTEM whole blood analyzer (Tem Innovations GmbH, Munich). They allow testing in the presence of therapeutic heparin concentrations and provide differential diagnostic information to support decisions in therapy. Application of TEM at the point of care (POC) or in emergency laboratories became gold standard. TEM gives information about both hypo- and hyperfunctional stages of coagulation and hyperfibrinolysis. Close coagulation monitoring during liver surgery can decrease the amount of bleeding and blood transfusion (8). Strict monitoring helps the anesthesiologist to maintain good hemodynamic profile and fluid balance. Avoiding overfilling can minimize bleeding and blood transfusions (9). The use of cell saver machine can minimize bleeding and blood transfusions too (10). Antifibrinolytics has been recently extensively studied (11-13). Hyperfibrinolysis may be faced liver surgery and orthotopic liver transplantation (OLT), increasing intraoperative blood loss. Epsilon aminocaproic acid (EACA), tranexamic acid (TA), and aprotinin are used in order to minimize bleeding. We administered 2 grams of Tranex (tranexamic acid) during surgery. Antifibrinolytics must be used very carefully in order not only to reduce bleeding and blood transfusions, but also to take present thromboembolism risk.

Stabilizing Hemodynamic

Portal hypertension and hyperdynamic profile are responsible for increased risk of bleeding, but our patient had no altered liver test and no previous hepatic dysfunction or illness. It is reported that hepatic venous pressure plays an important role in blood loss during liver surgery. So controlling CVP is a crucial method in order to reduce intraoperative bleeding (14, 15). Several authors recommended a CVP under 5 cm H2O (16, 17). Massicotte et al supported that plasma avoidance, fluid restriction and low CVP, phlebotomy, minimizing blood transfusions, may improve survival after liver transplantation (18, 19). We tended to maintain CVP under 5-6 cm H2O. Using total intravenous anesthesia (propofol and remifentanil), and nitroglycerine, we induced venodilation. Being very careful to administer right amount of fluids, we avoided overfilling the patient. So low CVP was due to vasodilation, avoid overfilling, and avoid PEEP. Excessive decreased CVP can induce hemodynamic instability and increased risk for air embolism (20), and usually treated with fluid boluses, vasoconstrictors (phenilephrine, norepinephrine), and/or inotropes as dopamine, epinephrine. In our patient we used norepinephrine and dopamine according to hemodynamic parameters, associated with small boluses of ephedrine and phenilephrine. Intraoperative period was unremarkable till the dramatic moment of massive bleeding (2000 ml in 10 minute) due to suprahepatic vein damage.

As a conclusion CVP less than 5 cm H2O is generally recommended (21).This can be realized through fluid restriction, no aggressive unnecessary correction of coagulation's disorders (fresh frozen plasma, platelets), and avoiding all the above mentioned situations that can increased CVP.

Preventing further Liver Function Deterioration

Hepatic vascular supply is a contribution of venous blood from portal vein and arterial one furnished by common hepatic artery. Venous blood supplies 60% of blood influx and 40% of oxygen, whereas arterial blood 35-40% of total hepatic blood amount enriched with oxygen (60% of oxygen that goes to the liver). The anesthesiologist must ensure good volume status and mean arterial pressure 60-75 mmHg. This hemodynamic profile is essential to prevent hepatic further dysfunction. It is mandatory to avoid all the hepatotoxic drugs as acetaminophen and halogenated inhalator anesthetic drugs. Another mechanism contributing in hepatic damage is ischemia-reperfusion injury. Hepatic protection can be done by N-acetilcysteine. Nevertheless, stabilization hemodynamic and optimize liver tissue oxygenation are most important anesthetic measures (22). Gentle surgical manipulation and short ischemia period can help liver to maintain its functions.

Postoperative Care

Postoperatively we took care about hepatic and renal function, postoperative pain, possible hypoglycemia, and vital parameters. The incidence of hepatocellular insufficiency varies from

1-3% (23). Our patient suffered a transitory hepatic dysfunction, but the situation resolved in 4-th postoperative days. We avoided use of acetaminophen for controlling the pain as well.

Conclusions

Major liver resection presents a big challenge to the anesthesiologist. Intraoperative bleeding and liver function protection are important issues the anesthesiologist must address. Avoiding aggressive correction of preoperative coagulation's disorders, fluid restriction regimen, maintaining low CVP, can guarantee less bleeding and improved patient's outcome. Finally a multidisciplinary team (gastrohepatologist, surgeon, and the anesthesiologist) is mandatory to successfully treat these patients.

Acknowledgment

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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).

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Introduction section should include a literature overview in relevance to the elaborated problem. In this sections 3-5 key references are citied and this section should not be longer than 2 pages.

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).

Results are displayed in simple manner with text, images, tables and charts that are submitted in the text where author wants to stand, titled and numbered appropriately. Additionally, on separate document all carts images and tables are send together with the manuscript.

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

Conclusion section should not include more than 150 words and shoul be drown from the relevant elaborated results.

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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

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Macedonian abstract should include title (in capital letters) and all the needed features as the English abstract only written in Macedonian with Times New Roman, font size 12 with Macedonian support in Microsoft Word.

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I _____. Here by declare that the article _____ (NAME OF THE ARTICLE) has not been previously published (fully or partialy) previously.

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_____(FULL NAME AND SURNAMES OF THE AUTORS AND SIGNATURES) are responsible for the etic, profesional and scientific content of the study.

I _____(THE FIRST AUTHOR FULL NAME) declare Conflict of interest or declare non Conflict of interest.

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Apotel® 1000mg/6.7ml

I.V. Paracetamol

БЕЗБЕДНА АНЕЛГЕЗИЈА

менаџирање на болка кога сте загрижени за безбедноста

I.V. paracetamol за прв пат во Европа е применет во 2001 година, а денес поради неговата докажана безбедност и ефикасност е прв од избор **аналгетик и антипиретик.**

Предоперативна и Интраоперативна Аналгезија:
Предоперативна анелгезија е дефинирана како третман кој што започнува пред оперативниот зафат се со цел да се превенира воспоставувањето на централна сензибилизација на болка.
i.v. paracetamol е безбеден, добро толериран лек со докажана ефикасност како **предоперативна и интраоперативна анелгезија** за умерена до средна болка при оперативни зафати.
Голем број на клинички студии ја докажуваат ефикасноста на **i.v. paracetamol** како **преодоперативна и интраоперативна анелгезија**.

КЛИНИЧКА СТУДИЈА:
Ефект од **предоперативен i.v. paracetamol** за постоперативни аналгетски потреби кај пациенти кои се подлежни на оперативни зафати. A Sreenivasulu, R Prabhavathi, 2015
Цел: Да се утврди ефикасноста на **предоперативната употреба на 1000mg i.v. paracetamol** кај постоперативните болки и анелгетски потреби кај пациенти подлежни на хируршки зафати.
Метод: 60 пациенти беа поделени во две рандомизирани групи од по 30 пациенти.
На I. Група им беше администрирано **ампула од 1000mg i.v. paracetamol разредена 0,9%NaCl** р-ор 30 минути пред индукција **(ГРУПА П)**,
На II. Група им беше администрирано **i.v. 0,9% NaCl р-ор 100мл** 30 минути пред индукција **(ГРУПА НС)**
Сите пациенти беа индуцирани со i.v. thiopentone 5mg/kg, i.v. fentanyl 2μg/kg, i.v. vecuronium 0.1mg/kg
Постоперативниот резултат на болка беше мерен со **Визуелна Аналогна Скала (ВАС) од "0-10"**. Исто така беше забележувана и **постоперативната употреба на tramadol** како спасувачки аналгетик. Инциденцата на **постоперативно гадење и повраќање (ПОГП)** и други компликации исто така беа забележувани во пост оперативниот период.
Резултатот на постоперативната болка беше забележуван во интервали 15 мин, 30 мин, 1 час, 2 часа, и 6 часа.

Резултат:

Табела 1: *Споредба на средниот резултат на болка (ВАС) помеѓу двете групи*

Интервали	I Група П	II Група НС	*P вредност*
15 мин	2.06 ± 0.63	2.61 ± 0.56	0.0006
30 мин	2.35 ± 1.17	3.84 ± 1.55	0.0001
1 час	2.42 ± 1.12	2.87 ± 0.99	0.0989
2 часа	2.13 ± 1.06	2.52 ± 0.89	0.1219
6 часа	2 ± 0.52	2.52 ± 0.89	0.0549

Табела 2: *Споредба за потребите од tramadol помеѓу двете групи*

Интервали	I Група П	II Група НС	*P вредност*
До 1 час	4 (12.90%)	15 (50%)	0.0002
1-2 часа	3 (9.68%)	2 (6.45%)	0.64
2-6 часа	1 (3.23%)	3 (9.68%)	0.301
Вкупно	**8 (25.81%)**	**20 (64.52%)**	**0.002**

Табела3: *Споредба на ПОПГ помеѓу двете групи*

ПОГП	
I Група П	II Група НС
0	4

Заклучок: Предоперативна администрација на **1000mg i.v. paracetamol** кај пациенти подлежни на оперативен зафат обезбедува **статистички задоволителна анелегизија**, и ја **намалува постоперативната употреба на tramadol**. Оттука **1000mg i.v. paracetamol** може безбедно да се администитрира како превенција при оперативни зафати.

i.v. Paracetamol + јак опоид	МНОГУ ЈАКА БОЛКА
i.v. Paracetamol + слаб опоид	ЈАКА БОЛКА
i.v. Paracetamol + NSAID i.v. Paracetamol + rescue medicine	УМЕРЕНА БОЛКА
i.v. Paracetamol + rescue medicine	СЛАБА БОЛКА

Мултимодално менаџирање на постоперативна болка
I.V. Paracetamol е атрактивна компонента за мултиодално менаџирање на болка.

- Синергистичко делување
- Зголемување на аналгетски ефект
- Значително намалување на болка
- Редукција на дозата на опоидни лекови за - 40% во првите 24 часа
- Намалување на несаканите ефекти поврзани со монотерапија на NSAID и опоидни лекови
- Ублажување на акутна и хронична болка

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