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I.V. Paracetamol

БЕЗБЕДНА АНАЛГЕЗИЈА

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)**
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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.

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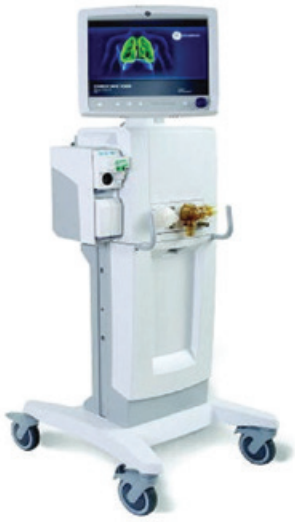

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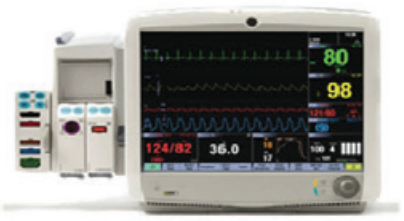

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CONTENT

BRAIN DEATH SCINTIGRAPHY: IS IT WORTHWHILE?

Daniela Miladinova, MD, PhD

Institute of Pathophysiology and Nuclear Medicine "Acad. Isak S. Tadzer", Faculty of Medicine, University "Ss. Cyril and Methodius", Skopje, North Macedonia

The concept of brain death (BD) was for the first time announced in 1968 at Harvard Medical School, when irreversible coma was defined as a new criterion for death. There was obvious need to improve resuscitative and supportive measures in seriously injured patients, but at the same time to decrease the burden on the patients' care, their families and hospitals treating the individuals whose hearts were beating, but brain was irreversibly damaged. Also, diagnosis of BD was crucial in the process of harvesting organs for transplantation (1).The National Conference of Commissioners on Uniform State Laws approved and recommended for enactment to all the states in the USA - the document named Uniform Determination of Death Act (UDDA) in 1980, whereby the BD was defined as irreversible cessation of circulatory and pulmonary functions and irreversible cessation of all functions in the entire brain(2).American Academy of Neurology(AAN) summarized in 1995 statements for the determination of BD in adults (3). The first of the prerequisites is clinical or neuroimaging evidence of acute central nervous system failure. Additional conditions are: exclusion of complicating medical conditions, absence of drug intoxication and core body temperature of at least 32^{o}C. Once the prerequisites have been met, a clinical examination should be performed to assess: coma, absence of all brain stem reflexes and apnea. The apnea test is considered safe and is a critical part of the BD testing system. If in the first instance apnea test is not conclusive, a repeat clinical examination after 6hours is recommended by the AAN, although the interval sometimes could be shorter.

In the situation when specific components of the clinical examination cannot be performed or are unreliable, ancillary or confirmatory tests of BD are advisable (4).Also, these tests can be used to shorten the length of the observation period as it is of utmost importance in providing valuable organs for transplantation. For decades up till now, organ procurement programs have revealed close relation between organ transplants and BD diagnosis (5).

Confirmatory (ancillary) tests of BD are divided in two groups:

1. Tests to demonstrate the loss of bioelectrical activity (EEG, multimodality evoked potentials –MEP and electroretinography ERG). These investigations are highly resistant to drug intoxication and hypothermia and are widely used in the ICUs.
2. Tests to demonstrate absent cerebral blood flow (CBF): cerebral intravenous digital subtraction angiography, xenon enhanced computed tomography, MRI angiography, CT angiography, transcranial Doppler ultrasonography –TCD and radionuclide angiography).

Among them EEG, cerebral angiography and radionuclide angiography (scintigraphy) are considered the most preferred tests for BD diagnosis (3). Complete absence of intracranial circulation was emphasized as the most confident proof that the global loss of brain function is irreversible (6).Different nuclear medicine techniques that demonstrate loss of CBF are widely applicable in routine clinical practice. As the BD determination policies are changing over time and are not unique even in the same states, there were attempts to improve uniformity. Comparison of the policies in different institutions in the USA showed greater presence of scintigraphy, 88% in 2015 vs. 43% in 2008 in the analyzed BD guidelines (7).

Radionuclide Brain Perfusion Scan (RBPS) is a specific and widely available method for assessment of the cerebral blood flow as it could be performed with mobile bedside gamma camera. An important advantage of the scintigraphy is the fact that applied radiopharmaceutical does not damage the organs that might be harvested (8).The recommendations of different professional organizations are defining protocols for brain death scintigraphy (9, 10). No special preparation of the patient is necessary for RBPS. Recommended is tourniquet placement around the scalp, above the eyebrows, ears and around the posterior prominence of the skull. The pressure caused by the tourniquet is diminishing skull blood flow, so it could not be confused with the cerebral blood flow. If the patient is with history of head trauma or increased intracranial pressure a tourniquet should not be used. Ventilation of the patient during the RBPS should be kept normal, as hyperventilation is causing changes in CBF. For RBPS different 99mTc labeled radiopharmaceuticals could be used as 99mTc-ECD (ethyl cysteinate dimer), 99mTc-HMPAO (hexamethyl propylene amine oxime) or 99mTc-DTPA(diethylenetriamine pentaacetic acid). Although brain specific agents offer the advantage of evaluation of the regional brain tissue perfusion (ECD or HMPAO) and are preferable, there is no clear evidence that they are more accurate in diagnosis of BD than nonspecific tracers (as DTPA< glucoheptonate or pertechnetate). Nonspecific tracers are not crossing brain blood barrier and provide information only on vascular flow. Flow images are acquired at the time of tracer injection, after application of 550-1100MBq 99mTc-DTPA, 370-1100MBq 99mTc-HMPAO or 370-1100MBq 99mTc-ECD. The recommended dose in children is 11.1MBq/kg or the minimum dose of 185MBq for brain specific agents. Flow images are essential for nonspecific tracers, but for brain specific agents they are also important as they confirm the lack of brain blood flow when the brain is not visualized on delayed images. Delayed images with specific tracers are acquired 20 minutes after the injectionin anterior, left lateral, right lateral and posterior position. Planar scintigraphy requires anterior and posterior image to separate activity in the right and left hemisphere and at least one lateral view to distinguish cerebral from cerebellar flow (11). The absence of radionuclide activity within the brain is consistent with the diagnosis of BD, but it is not sufficient to allow this diagnosis and should be correlated to other findings. Relatively increased nasal region perfusion “hot nose sign” is consequence of external carotid artery flow. Absence of internal carotid artery flow is leading to increased external carotid artery flow and subsequent perfusion in the nasal region. Hot nose sign is the most probably result of the diverted activity secondary to occlusion of the internal carotid artery through the external carotid artery branches, when some activity appears in the brainstem, and to a lesser extent in nasopharynx (12). As RBPS

is used in combination with other tests and physical examination findings, the final report of a positive study would be "shows no evidence of brain perfusion" rather than "demonstrates brain death". If there is a small amount of remaining activity revealing perfusion, repeating BRPS study should be considered (13). Planar dynamic and static images with brain specific agents (ECD/HMPAO) allow evaluation of cerebrum, basal ganglia, thalami and cerebellum. Performed in special context based on clinical findings, BRPS is confirming BD with high level of certainty. SPECT image is not easily available as it needs special equipment (dual head gamma camera) and is not offering clear advantage over planar images when they are performed following the accepted protocols. With the advantage of tomographic reconstruction, it is easy to differentiate activity in scalp, parotid or neck muscle from the activity in the brain. If activity in brain stem is visualized, the question about brain stem viability is concerned and should be interpreted very carefully, comparing it with other ancillary tests. Apart from limited availability, the use of 18F-FDG scan as a tracer that is assessing brain glucose metabolism, is promising test for BD confirmation (14).

Scintigraphic examination improves specificity of determining BD and diminishes possibility of error. BRPS might have important role in showing absence of perfusion to a skeptical family who is not willing to accept the diagnosis of BD(15).

In children and in neonates, the protocols for BRPS are slightly different. SPECT is a method of choice, and imaging criteria of BD are accepted as nonvisualization of cerebrum and cerebellum, named as "empty skull". There is no perfusion in the brain, whereas other tissues (scalp, skin, nasopharynx–hot nose sign, lung, heart, liver). If there is suspicion for some faint perfusion, either in the cerebrum or the cerebellum imaging, SPECT study should be repeated (16).

Early and correct diagnosis of BD is very important as the cadaveric transplantation will be improved in the situation when donor organs are removed on time. Use of 99mTc-HMPAO SPECT is increasing, and BRPS is becoming confirmatory BD test of choice in adults, as well as in children and neonates.

Moskopp discussing the future of the concept of BD and organ donation, proposed these topics to become essential part of the school curricula for biomedicine and ethics (17). Teachers, students and especially experienced physicians have to never stop explaining pathophysiology of the end of life to the family members of BD patients. It should be realized in understandable language and caring manner, without expecting to be understood and accepted in the very beginning, as it is the only way to increase the number of donated organs for cadaveric transplantations and to save more lives.

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OCCURRENCE OF PERIOPERATIVE HYPOXEMIA DURING ONE LUNG VENTILATION

Kokareva A[1, 2], Jovanovski- Srceva M[1,2], Stevic M[3], Nedxati J[1,4], Kondov G[1,4] Ognjanova E[2]

[1] Medical Faculty,"Ss. Cyril and Methodius" University, Skopje, Republic of North Macedonia

[2] University Clinic for TOARILUC, Skopje, Republic of North Macedonia

[3] Medical Faculty, University of Belgrade, Serbia; University Clinic for Children's Diseases, Belgrade, Republic of Serbia

[4] University Clinic for Thoracic Surgery, Skopje, Republic of North Macedonia

ABSTRACT

Background: One Lung Ventilation (OLV) remains standard procedure for thoracic surgery. However, this procedure increases the risk of hypoxemia and desaturation that can influence patients' mortality and morbidity. The aim of this study was to evaluate the occurrence of desaturation SpO_2 <93% in patients going pulmonal resections and to analyze the patients' profiles.

Material and Method: In a retro-prospective study were included all data of patients who underwent OLV for segmentectomy, lobectomy and bilobectomy, ASA I-III, with EF>50%, FEV_1>40%, PaO_2>60mmHg and who went standardized anesthesia protocol. Patients with prior radio or chemotherapy, with renal, hepatic, endocrine and coagulations disturbances were excluded. In all patients we evaluated demographics, clinical data, surgery data and the occurrence of desaturation (SpO_2 <93%), 10 minutes, 30 and 40 minutes after OLV.

Results: Desaturation occurred in 20% of the patients 10 minutes after the OLV, in 32.5% of the patients in the 30th and in 25% of the patients after the 40th minute. Significant number of patients underwent right sight lobectomy. In none of the patients OLV was stopped and no lethal outcome was registered.

Conclusion: In our study desaturation occurred from 20-32.5% of the patients who underwent OLV during the first 40 minutes in respect to the time. Desaturation mainly occurred in patients with right thoracotomy.

Key Words: Desaturation, hypoxemia, OLV, thoracic surgery.

Introduction

In the era of evidence-based medicine, new techniques, approaches and technologies are emerging in relation to thoracic surgery. Despite these expansions and progress of the technological novelties, one lung ventilation (OLV) remains gold standard during pulmonal surgery. This allows better surgical approach and better outcome in these patients, with all of the pathophysiological consequences (1,2).

During OLV where one lung is ventilated while both are perfused, different pathological mechanisms are triggered like: ventilation - perfusion V/Q mismatch, hypoxic vasoconstrictive

perfusion (HPV) - as compensatory mechanism, change in the end tidal CO_2, which along with the side intervention, surgical manipulation, large blood vessels in surgical field, lead to high levels of hemodynamical and respiratory disturbances. The most relevant, the most researched and important during these surgeries is the occurrence of perioperative hypoxemia (3,4,5).

Perioperative hypoxemia means a decrease of arterial oxygen saturation, but in the limits below what are differently reported. The most accepted and utilized definition of hypoxemia perioperative is a decrease of arterial oxygen saturation <90%, but this limit is not universally used. However, desaturation below 90% should be a sign of hypoxia and different measures should be used in order this hypoxemia not to have detrimental consequences on patient's mortality and morbidity (1,5,6).

When talking about the desaturation during OLV, a significant number of researches have been studied different methods of hypoxemia improvement, but studies for its occurrence are scattered (6). Furthermore, these studies preferably debate and are concentrated on the factors that may predict it or measures that may improve desaturation during OLV.

To our surprise, the most of the studies that have elaborated perioperative hypoxemia, never reported, or confirmed the incidence for desaturation occurrence, and furthermore to our knowledge, this is the first study done and reported from the Republic of North Macedonia with this data. Therefore, the aim of this study was to evaluate the occurrence of perioperative desaturation during one lung ventilation in patients undergoing lung segmentectomy, lobectomy, evaluation of their demographic and clinical characteristics, as well as to discuss some preoperative and perioperative literature issues that may increase the risk for it.

Material and Method

This is a retro-prospective evaluation study of patients who underwent one lung ventilation for pulmonary lobectomy, bilobectomy or segmentectomy in general anesthesia at the Clinic for Thoraco-vascular Surgery in Skopje for the period from January 2018 to October 2021. Study included medical records of elective patients who underwent standardized anesthesia protocol, patients with ASA (American Society of Anesthesiologist) I-III; cardiovascular stability and EF (Ejection Fraction)>50%, preoperative level of PaO_2>60mmHg and preoperative functional tests where (Forced Expiratory Volume in the 1st second) FEV_1 was >40%. The study excluded all patients in whom pulpectomy was planned or was done during surgery, patients with renal, hepatic, hemostatic and endocrine disturbances and patients who underwent prior radio or chemotherapy. The study was approved by the Clinical Institutional Board.

In all patients, demographic data, type of surgery, preoperative conditions (diseases), smoking, functional parameters and postoperative complications were evaluated. Additionally, we analyzed the occurrence of perioperative desaturation during one lung ventilation in the first 40 minutes after the lung was isolated, the need to stop OLV during the same time frame, the duration of OLV and the duration of desaturation. We defined desaturation as a drop of SpO_2 below 93%, while the fraction of inspirated O_2 of 50% (FiO_2 0,5) (7).

Anesthesiologic protocol: All patients underwent standardized preoperative evaluation with laboratory, heart, pulmonal evaluation, arterial blood gas analyzes. Perioperative, all patients

would have standardized monitoring of arterial blood pressure, heart rate, saturation (SpO_2), capnography ($EtCO_2$) FiO_2 and ECG.

Induction in anesthesia was after preoxygenation and premedication with fentanyl (3μ/kg), propofol (1-2mg/kg) and rocuronium for intubation (0.6mg/kg). Anesthesia was maintained with continuous propofol (6-7mg/kg/h) fentanyl by need and rocuronium. After adequate ventilation, in patients who had left side process right side double lumen tube (DLT) was placed and vice versa. Confirmation of the DLT was performed by auscultation and bronchoscopy. All patients were placed in lateral decubitus position after intubation and when the thoracic wall was stated to be opened a clamp was put and OLV was started with PCVG regime, respiratory volume of 5 ml/kg ideal body weight (IBW) and frequency of 14 or according to the $EtCO_2$ (35-45mmHg) during FIO_2 of 0.5.

Results

According to the inclusion criteria a total of 40 patients were included in the evaluation with average age of 62,2 years. The most of the patients were male (52%), ASA II (50%) and with BMI 25.35. The most of the patients had history of smoking (87.5%), hypertension (30%), diabetes mellitus was present in 8.75% of the patients and COPD in 30% of the evaluated patients. Data are shown in Table 1.

Table 1. *Demographic data of the patients*

Data	N=48
Age(years)mean± Sd	62.2±9.3SD
Gender	
M(n)**/F(n)**	21/19
BMI **(mean±** Sd**)**	25.35±3.8Sd
ASA	
1**/2/3**	7/20/13
COPD (pts)	12
Hypertension(pts)	17
Diabetes Mellitus(pts)	9
Smokers(pts)	35

BMI- Body Mass Index; ASA- American Society of Anesthesiologists status; COPD-Chronic Obstructive Pulmonary Disease; pts - number of patients.

In the most of the patients right-side intervention was done (62.5%) with the placement of left DLT. In a larger percentage of the patients single lobectomy (52.5%) was done. Preoperative

blood laboratory tests were within the normal range, normal hemoglobin, leucocytes and platelets, as well as other laboratory findings. Functional pulmonary tests showed average FEV_1 of 82.32%.

Table 2. *Clinical data of the patients*

Side of the surgery	
L(n)	15
R(n)	25
Type of surgery	
Lobectomy(pts)	21
Bilobectomy(pts)	16
Segmentectomy(pts)	3
Preoperative hemoglobin(means)	134.63+15.6 Sd
FEV_1(%) (mean±Sd)	82.32+17.9 10.57+2.3Sd
PaO_2 (mean±Sd)	

FEV_1-Forced Expiratory Volume in the first second, PaO_2- arterial blood oxygenation.

During the surgery and OLV desaturation was found in 20% of the patients in 10 minutes after OLV, in 32.5% of the patients at 30 minutes after OLV and in 25% of the patients - 40 minutes after OLV. After 40 minutes of the OLV nonsignificant number of patients had desaturation.

Table 3. *Desaturation SpO_2<93% in different times during OLV*

SpO_2<93%	
10 min after OLV	8pts
30 min after OLV	13pts
40 minutes after OLV	10
>50 min after OLV	2
The need to stop OLV	/
Unwanted perioperative circulatory events	/

One Lung Ventilation (OLV); pts-patients.

Clinical postoperative complications, like segmental atelectasis, were found in 15 patients and pneumonia in 4 patients. OLV was not stopped during surgery in none of the patients. None of the patients had lethal outcome or need for prolonged mechanical ventilation.

Discussion

Our study included 40 patients and showed that desaturation of SpO_2 below 93% during the first 40 minutes of OLV occurred in 71.5% (31) of the patients. However, this number include all the patients with SpO_2 during the 40-minutes interval, that statistically does not mean that all of them had that level of saturation because this number of patients is sum of all who developed and not extracted the same patient who by chance had desaturation in the first 10 minutes and continuing in the next time period. Therefore, the incidence of 71.3% desaturation is not the exact and real number for occurrence of desaturations. If we present by the exact time frame, we can see that in our study 20% (8) of the patients developed desaturations 10 minutes after OLV, 32.5% (13) after 30 minutes and 25% (10 patients) after 40 minutes of OLV.

When we discuss these results, several issues emerge in relation to high percentage of patients that had desaturation. Mainly, we have to mention that the literature does not give similar study done by similar method of measuring desaturation. Additionally, the most of the studies that reported desaturation or hypoxemia have limits of saturation either higher than in our study (<95) or lower (<90%), so, therefore the right consensus of desaturation is not well-established which led to different incidence of its occurrence (7,8).

As for example, Guenoun T. *et al.* have reported that the occurrence of hypoxemia during OLV is around 5%, but their study is interventional study that was interested in predictive values of preoperative hematocrit, PaO2 and during the intervention they took blood samples every 15 minutes after OLV (7). In their study they confirmed that preoperative PaO_2 had predictive values for arterial hypoxemia occurrence in 5% of the patients with multivariate logistic regression. Since their study is using different methods and materials, our results cannot be directly compared.

Young M. *et al.* debated that desaturation (not the same definition used) occured in 58% during OLV and there was a need for increase of the inspired fraction of FIO_2 to 1, in order to remain the SpO_2 above 95% (1). In conclusion to this study, it is obvious that larger number of patients did have desaturation during OLV than commonly reported 10%. This study's results even show that desaturation in our study occurred less than in their study.

New study of Yoon S. et al. has confirmed 25% of hypoxemia occurrence like in our study, but in this more pronounced study, authors have evaluated the intermittent hypoxemia for 20 minutes and hypoxemia was defined as SpO_2 <95% (8).

Furthermore, the side of the surgery is always one of the factors that highly influence the occurrence of the desaturation and hypoxemia during OLV (2,4,6). Since the right lung is larger than the left lung, it is confirmed that during left thoracotomy less hypoxemia will occur (4). Schwarzkopf K. *et al.* have confirmed that when ventilating on FiO_1 during OLV, mean arterial oxygen tension (PaO) is 280mmHg during left thoracotomy and only 170mmHg during right thoracotomy (9). When this knowledge is transferred to our study where 62.5% (25 patients) had right lobectomy, we cannot exclude this factor as a factor for higher incidence of desaturation.

Several preoperative lung abnormalities are also additional factor for OLV desaturation (4,5). COPD and the level of functional preoperative tests are also marker that can point out why some patients develop desaturation (6,7). Slinger *at al.* confirmed that the lower is the level

of the forced expiratory volume in the first second, the better the oxygenation will be (3). In our study FEV_1 was on average above 82% and additionally COPD was found in 30% of the patients.

Nevertheless, some novel researches impute that some new anatomical landmarks can be crucial factors for prediction and less occurrence of desaturation during OLV. The length of the left main bronchus measured on computer tomography and length less than 40mm, are nowadays studied as new predictors (6).

Pathophysiology of OLV desaturation is a complex issue debated for decades. Its occurrence overthought differently reported, is still a big issue and more and more new researches are done. In this context we have to mention that novel studies are more focused on predicting factors for hypoxemia occurrence and its treatment, than to its incidence.

As for the surgery discussed in our study the most of the patients had lobectomy and bilobectomy done which by itself means that the volume of the perfused lung is lower which complicate the whole oxygenation profile.

As for our study we must be realistic and to point out something. We measured only SpO_2 as a factor for hypoxemia which certainly might not be the most relevant measurement method. We must mention that this is a pilot study as part of a larger study that investigates more complex measurements to show the level of desaturation. However, some other studies do report the same measurement with different results as mentioned above.

In conclusion we can say that during OLV different percentages of desaturation occurred, the higher incidence of desaturation is after the 30^{th} minute of OLV, and the patients that have right side thoracotomy experience higher incidence of desaturation.

Limitation and Benefits

Our study has several limitations. Firstly, the number of patients in the study was not large, so the results may not present the population studied. Secondly, the study does not corelate the preoperative factors to the perioperative occurrence of hypoxemia, and additionally does not show a hypoxemia with confirmation of artery blood gas analysis. Thirdly, the additional factors like the side and type of operation time of the surgery and time of the OLV, are not elaborated and statistically corelated to the desaturation (only observationally). However, this study also has several benefits. It opens a door for the larger study, it is the first study reported from R.N. Macedonia and shows pattern for starting a large, randomized study.

Conflict of Interest: denied by the authors.

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EFFECT OF CYP2B6 POLYMORPHISM ON PROPOFOL IN PATIENTS UNDERGOING ABDOMINAL HYSTERECTOMY

Ivanov E[1], Sterjev Z[2], Karadjova D[1], Shosholceva M[3], Krstevska J[1], Pop-Stefanija V[1], Tomova E[1]

1. University Clinic for Gynecology and Obstetrics,
2. Pharmaceutical Faculty, Skopje,
3. University Clinic for Surgical Diseases "St. Naum Ohridski", Skopje

Abstract

Understanding why individuals respond differently to drug therapy is one of the most intriguing questions in modern medicine and pharmacology. The main premise is that individual differences in genetic variables in genes encoding metabolic enzymes, molecular transporters and propofol molecular binding sites are implicated in the sensitivity to the effects of propofol, a commonly used intravenous anesthetic. The goal of this research was to see how polymorphisms in the cytochrome P450 2B6 isozyme CYP2B6 gene impacted the propofol therapeutic outcomes in patients subjected to abdominal hysterectomy.

This study included ninety patients ranging in age from 29 to 74 years old and from various ethnic backgrounds. TaqMan SNP genotyping analysis on Stratagene MxPro 3005P real-time polymerase chain reaction was used to determine the presence of polymorphisms (qPCR). The genetic variations were distributed inside the Hardy-Weinberg equilibrium. The allelic frequencies of polymorphic variations and genotype distributions across adult and elderly patients, as well as patients of different ethnicities, were not significantly different ($p>0.05$).

According to our findings, the CYP2B6 gene variations did not cause any statistically significant effects on the analyzed clinical parameters i.e., doses for induction in anesthesia, additional doses, induction time and awakening time after anesthesia and adverse effects of propofol.

Key Words: *CYP2B6* gene, Pharmacogenetic, Propofol.

Introduction

One of the most challenging areas of research in clinical pharmacology, pharmacy, pharmacoepidemiology and especially pharmacogenetics, is the attempt to understand why individuals respond differently to drug therapy. Problems with drug therapy can be divided into two main categories. The first problem is that the drugs are not equally effective in all patients. If the effectiveness of the drug could be predicted in advance, an inter-individual variation on the drug would be avoided in patients in whom the drug does not work sufficiently, and at the same time the costs would be reduced. Another major therapeutic problem is the occurrence of adverse effects, which is especially important in the fields of medicine where drugs of a small therapeutic range are used, including anesthesiology and intensive care (1).

It is certainly an intriguing question why two patients receiving the same drug in the same dose and for the same indication react differently.

Interindividual variability in response to drugs in anesthesia patients has long been considered the rule, not the exception. Historically, differences in patients' responses have been interpreted by a variety of factors, such as age and gender, previous illnesses and comorbidities, drug interactions, type of surgery and nutritional status.

The incidence and potential for serious adverse reactions in anesthesiology are increased due to the narrow therapeutic indices of the drugs used and the previously mentioned high interindividual variability in drug responses. Genetic factors greatly contribute to these severe adverse reactions.

The foundations of genetics have been laid since the time of Mendel when the gene was considered a factor of inheritance. Polymorphism is a discontinuous genetic variation that results in the appearance of different forms or species of individuals between members of the same species. Genetic variations may be responsible for altering enzymes for metabolism or for transporting proteins, affecting absorption, distribution and bioavailability. Propofol (2,6-diisopropyl phenol) is a sedative or hypnotic drug whose effect depends on the dosage.

The beginning of his hypnotic action is very fast. After a dose of 2.5mg/kg, anesthetic sleep occurs in 90-100 seconds. The length of sleep depends on the dose used and lasts after a bolus of 2 to 2.5mg/kg for about 5 to 10 minutes (2). In lower doses, it leads to a state of sedation and amnesia. Age significantly affects the prescription of the dose for anesthesia. If it is calculated on the basis of body weight, this dose is the highest in children up to two years of age, and then decreases with age. Women require slightly higher doses than men (3,4).

Propofol is naturally metabolized by enzymes, mainly in the liver, and the metabolism is almost complete, leaving less than 1% unchanged drug excreted in the urine. During abdominal surgery, such as liver transplantation, there is evidence of extrahepatic metabolism which, the most likely, takes place in the kidneys. Metabolic capacity depends not only on enzyme capacity, but also on liver blood circulation and oxygenation. The clearance of propofol exceeds the blood circulation in the liver, which indicates the existence of additional, extrahepatic metabolism. This particularly high clearance is likely to contribute to relatively rapid recovery after continuous infusions. Conjugation in the liver results in the production of inactive metabolites that are eliminated by renal clearance.

There are two main manners in which propofol is metabolized: direct glucuronidation followed by propofol glucuronide (PG) production or hydroxylation and quinol (*Q*) production (5).

The *UGT1A9* and *CYP2B6* genes possess large numbers of *SNPs*, causing numerous interindividual differences in propofol response in different patients. So far, 38 alleles (variants) of the *CYP2B6* gene have been found (6).

The *CYP2B6* gene encodes several cytochrome P 450 enzyme superfamilies (*CYP2A*, *CYP2B*, and *CYP2F*). These enzymes belong to the monooxygenases, they catalyze reactions in the synthesis of cholesterol, steroids and other lipids, as well as the biotransformation reactions of many drugs, including propofol. Propofol is often used in combination with other drugs, such as

opioids and other anesthetics, and has been shown to inhibit their metabolism. Enzymes encoding this gene are responsible for the detoxification and biotransformation of drugs, their interaction and/or inhibition. As there is frequent interindividual variation in *CYP2B6* gene expression, it is considered a highly polymorphic *P450* gene with several complex haplotypes and different ethnic and racial variants. The high variability of this gene is due to the influence of genetic factors, including the polymorphism of the *CYP2B6* gene and non-genetic factors. Variants of alleles of this gene usually encode an enzyme whose activity is reduced or completely absent (7). Some previous studies have suggested that its expression is present only in part of the human liver, but recent studies have shown that the *CYP2B6* gene is present in all liver cells in adult patients (6).

The motive for our research is the pronounced interindividual variability in the response to propofol and the search for possible reasons for this phenomenon. The differences in the dosage, as well as in the reactions and effects of propofol anesthesia, are based on differences in the genes responsible for metabolism, the transport and the receptor to which it binds.

The objectives of the scientific study were to determine the effect of *CYP2B6* gene polymorphisms on the pharmacodynamics of propofol during general anesthesia in abdominal hysterectomies i.e., determining whether and to what extent the gene profile has an effect on propofol dosing in patients undergoing abdominal hysterectomy, determining the effect of single nucleotide polymorphism (SNP) for CYP2B6, variations observed in the clinical response to propofol, analysis and comparison of patients in relation to the doses of propofol administered, as well as obtaining information that would be useful in the future adjustment of anesthesia with the individual DNA of patients.

Material and Methods

This research is a cohort, prospective and longitudinal study. It was performed at the Clinic for Gynecology and Obstetrics of the University "Ss. Cyril and Methodius" Skopje and at the Center for Biomolecular Analysis of the Faculty of Pharmacy, University "Ss. Cyril and Methodius" in Skopje, Republic of Macedonia, in the period from October 2016 to November 2017.

Ninety (90) patients planned for abdominal hysterectomy were included in this study. All patients signed an informative consent to participate in the study.

Inclusion criteria were: age from 25-80; body weight within 20% above and below ideal; ASA 1-2-3. Exclusion criteria were: allergy to propofol, soy or peanuts, alcohol and drug dependence, chronic diseases such as psychiatric, liver or kidney diseases.

Propofol was administered according to the standard protocol based on the status and individual characteristics of the test group, as well as empirical medical data obtained from the instructions for use (0.1–0.15mg/kg/min., iv for 3–5 minutes). This is a non-interventional study that included the use of propofol according to a standard dosing protocol and monitoring the clinical response in patients during general anesthesia for this indication. The patients were not divided into groups and did not deviate from the usual plan for anesthesia. All data were entered in the anesthetic record card as an integral part of the mandatory medical documentation and subsequently analyzed.

After the appropriate preoperative preparation, a peripheral intravenous line was placed before the anesthesia was started. Non-invasive monitoring (TA, ECG, pulse, SatO2 and capnography) was used to monitor vital functions, and entropy was used to monitor the depth of anesthesia. General endotracheal anesthesia was performed as follows: introduction, midazolam 0.1mg/kg, fentanyl 2mcg/kg, propofol 1% given at a rate of 400ml/hour to achieve SE entropy values of 40 to 60 with monitoring of loss of eyelash reflex (dose from 1.5 to 2.5mg/kg), rocuronium bromide (0.4-0.6mg/kg), maintenance (propofol 50-150mcg/kg/min, repeated boluses of rocuronium bromide 0.3mg/kg, fentanyl 2mcg/kg, ventilation of the lungs with oxygen and nitric oxide in a ratio of 50:50%). At the end of the intervention, the reversal of neuromuscular block was achieved with 2.5mg of neostigmine and 1mg of atropine, after which, the patient was extubated and transferred to the recovery room.

The study also analyzed the adverse effects of opioids: nausea, vomiting and the degree of sedation. Adverse effects were monitored 24 hours after surgery. The presence of nausea was assessed by the following nausea assessment scale: (0 - no nausea, 1 - mild nausea, 2 - moderate nausea, 3 - severe nausea). Sedation was assessed according to the Ramsey sedation score (0 - awake, 1 - anxious, 2 - cooperative, oriented, 3 - reacts to commands, 4 - reacts to tactile stimuli, 5 - weak and slow reaction to verbal and tactile stimuli, 6 - doesn't respond to strong and painful stimuli).

Before the start of anesthesia, blood was sampled and DNA extractions were analyzed - 4ml of blood with EDTA as an anticoagulant. Genomic DNA was extracted from a total of 90 patients who underwent abdominal hysterectomy during total intravenous propofol anesthesia at the University Clinic of Gynecology and Obstetrics in Skopje. Genotyping was performed in the laboratory at the Center for Biomolecular Pharmaceutical Analysis, Faculty of Pharmacy, University of Skopje.

Results

The study included 90 female patients, who underwent abdominal hysterectomy. Patients ranged in age from 29 to 74 years, with a mean age of 51.5 ± 8.8 years. The bodyweight of the patients varied from 48 to 131kg, on average 77.7 ± 16.6kg. In the ethnic structure, there were 66 Macedonians (73.3%), 23 Albanians (25.6%), and one Turk (1.1%). According to the ASA (American Society of Anesthesiology) classification, ASA 1 status was in 9 (10%), ASA 2 status in 70 (77.8%) and ASA 3 status in 11 (12.2%) patients. There were 17.8% (16) of the patients with a history of comorbidities (six hypertensive patients), three were obese and had diabetes, two were obese, two were diabetic and hypertensive, and one had diabetes mellitus accompanied by thrombophlebitis, one with cirrhosis of the liver and the last patient with comorbidity was obese and had hypertension.

Distribution of CYP2B6 genotypes in patients is given in Table 1, while demographic characteristics of female patients with the CYP2B6 genotype regarding age, body weight, BMI and nationality are given in Table 2.

Table 1. *Distribution of CYP2B6 genotypes*

CYP2B6	*N* (%)
GG genotype	53 (58.89)
GT genotype	32 (35,56)
TT genotype	5 (5.55)

Table 2. *Demographic characteristics of female patients with the CYP2B6 genotype*

Variable	CYP2B6			***p value***
	GG genotype	GT genotype	TT genotype	
	(n=53)	(n=32)	(m=5)	
Age				
mean±SD	52.4 ± 7.9	49.9 ± 8.5	54.2 ± 17.4	P = 0.37 *ns*
Body weight				
mean±SD	75.0 ± 13.4	79.8 ± 17.1	92.6 ± 32.6	*p* = 0.054 *ns*
BMI				
mean±SD	29.5 ± 5.6	30.4 ± 6.0	36.2 ± 12.8	*p* = 0.07 *ns*
Nationality. n (%)				
Macedonian	39 (73.58)	25 (78.12)	2 (40)	P = 0.3 *ns*
Albanian	13 (24.53)	7 (21.88)	3 (60)	
Turk	1 (1.89)			

P *(Analysis of Variance),*
P *(Fisher exact)*
GG - homozygotes with two normal alleles
GT - heterozygotes with one normal and one mutated allele
TT - homozygotes with two mutated alleles

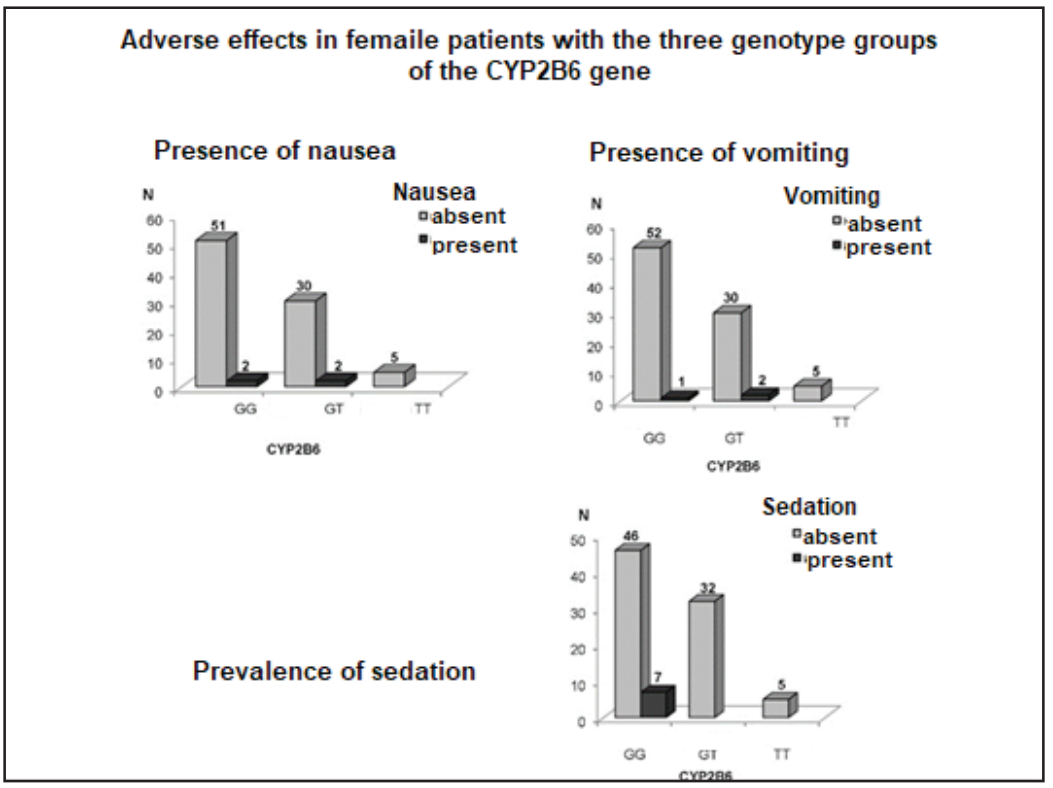
Table 3. *Correlation between CYP2B6 genotype and the induction time, the time to reaching entropy value 40-60, time under anesthesia, the awakening time and the total time from the onset to the end of anesthesia*

Variable	CYP2B6			***p value***
	GG genotype	GT genotype	TT genotype	
	(n=53)	(n=32)	(m=5)	
Induction time (sec)				
mean ± SD	97.4 ± 139.9	74.2 ± 47.4	54 ± 13.4	$p = 0.6$ *ns*
median (IQR)	60 (60-120)	60 (35-95)	60 (60-60)	
time to reaching entropy value 40-60 (sec)				
mean±SD	32.2 ± 19.8	30.12 ± 9.9	22.4 ± 9.8	$p = 0.3$ *ns*
median (IQR)	30 (20-40)	30 (24.5-35)	20 (15-30)	
Time under anesthesia (min)				
mean ± SD	101.45 ± 47.2	107.1 ± 46.3	71.4 ± 26	$p = 0.17$ *ns*
median (IQR)	95 (75-120)	107.5 (77.5-122.5)	75 (50-92)	
Awakening time (min)				
mean ± SD	15.2 ± 7.9	12.3 ± 5.4	11 ± 3.1	$p = 0.06$ *ns*
median (IQR)	15 (10-17)	10 (10-15)	10 (10-13)	
total time from the onset to the end of anesthesia (min)				
mean ± SD	116.6 ± 46.7	119.4 ± 46.7	82.4 ± 27.8	$p = 0.13$ *ns*
median (IQR)	114 (88-135)	117.5 (90-130)	90 (60-105)	

p (Kruskal – Wallais)
GG - homozygotes with two normal alleles
GT - heterozygotes with one normal and one mutated allele
TT - homozygotes with two mutated alleles

The presence of adverse effects like nausea, vomiting and sedation are given in Image 1.

Image 1. *Adverse effects of patients with three genotype groups of the CYP2B6 gene*



The consumption in genotip CYP2B6 is given in Table 4, while the corelation between propofol consumption and the age of patients and propofol consumption and BMI of patients with genotype CYP2B6 is given in Table 5.

Table 4. *Consumption in genotip CYP2B6*

Variable	CYP2B6			***p value***
	GG genotype	GT genotype	TT genotype	
	(n=53)	(n=32)	(m=5)	
Propofol for introduction to anesthesia/ mg				
mean±SD	154.94 ± 39.8	148.12 ± 41.9		$p = 0.31$
median (IQR)	150 (120-200)	150 (120-190)	120 (70-150)	
Additional propofol dose to maintain anesthesia/ mg				
mean±SD	134.15 ± 47.3	133.12 ± 51.6	108 ±	$p = 0.34$
median (IQR)	100 (100-200)	100 (100-200)	100 (70-100)	
Total intraoperative consumption of propofol/ mg				
mean±SD	289.1 ± 62,7	281.25 ± 78.8	230 ± 106.8	$p = 0.24$
median (IQR)	300 (250-330)	250 (225-350)	220 (140-250)	

p (Kruskal – Wallais)
GG - homozygotes with two normal alleles
GT - heterozygotes with one normal and one mutated allele
TT - homozygotes with two mutated alleles

Table 5. *Correlation between propofol consumption and age of patients and propofol consumption and BMI of patients with genotype CYP2B6*

Correlation	*Spearman rho*	*p*	*Spearman rho*	*P*
Initial propofol dose				
GG genotype	-0.34	0.012 *sig*	0.24	0.09 *ns*
GT genotype	-0.467	0.007 *sig*	0.02	0.9 *ns*
TT genotype				
Additional propofol dose				
GG genotype	-0.221	0.11 *ns*	0.047	0.73 *ns*
GT genotype	-0.13	0.48 *ns*	0.13	0.46 *ns*
TT genotype				
Total propofol dose				
GG genotype	-0.368	0.007 *sig*	0.20	0.12 *ns*
GT genotype	-0.338	0.058 *ns*	0.07	0.7 *ns*
TT genotype				

GG - homozygotes with two normal alleles
GT - heterozygotes with one normal and one mutated allele
TT - homozygotes with two mutated alleles

Discussion

The genetic polymorphism of the *CYP2B6* gene (cytochrome *P450 2B6*) and its relation with ethnicity, gender and genotypes, have been examined frequently. *CYP2B6* is one of the best-known polymorphic cytochrome *P450* genes in humans. It is currently known to have 30 defined alleles with over 100 described polymorphisms. Cytochrome enzymes participate in the metabolism of almost all drugs used in anesthesiology. The polymorphic nature of the cytochrome *P450* gene (*CYP2B6*) greatly influences the individual drug response and the possibility of adverse reactions. Ilic et al. find large inter-individual differences between individuals of different ages, genders or ethnicities (8). However, the authors conclude that their data do not indicate the possibility of clinically significant gender differences in the *CYP2B6* gene polymorphisms present, or that their methods were not sensitive enough to detect such slight differences. Ethnic differences in *CYP2B6* activity were also observed in human liver

microsomes. In this study, no association was found between *CYP2B6* genotypes and groups of different gender or ethnic groups. It has been suggested previously that a possible cause of ethnic differences in *CYP2B6* activity might be differences in genotypic frequency. It was thought that differences in allelic frequency could be partly explained by differences between ethnic groups observed with respect to the liver microsomal activity. The variability of *CYP2B6* activity and the expression of differences may depend on the combination of polymorphisms present in the individual. However, as no interactions between genotype and ethnicity were found, there was no direct evidence to suggest that there were differences in the genotypic effects between different ethnic groups. Changes in *CYP2B6* gene activity may direct toward differences in systemic exposure to drugs that metabolize *CYP2B6*, leading to variations in therapeutic and toxic responses to these drugs in certain populations. Given the fact that this study compared respondents of different racial backgrounds (Belarusian and African American), it is not surprising that in our study there are no differences in the results obtained for respondents of Macedonian and Albanian descent, who are similar and without racial differences (8). The effects of *CYP2B6* gene genotypes on the rate of propofol elimination in the elderly patients' population were also studied in the works of *Eugene A* (9). This analysis revealed that patients with the *CYP2B6* AA and AG allele eliminated propofol at a rate of CL AA _ AG=9.1ml/kg/min, while patients with the GG allele eliminated propofol at a rate of CL GG=24.2ml/kg/min. The clinical risks of a propofol overdose in the elderly patients, regardless of *CYP2B6* genotype, are described in a case report published by *Yonekura et al*. in December 2016 (10). In this case, the authors defined certain genotypes of *CYP2B6* as predisposing factors in a 71-years-old patient who experienced a three-hour delayed awakening from anesthesia. In a retrospective analysis of 17,540 patients, of whom 4,033 were over 65 years of age, the patients older than 70 years developed increased hypertension depending on the dose of propofol. Furthermore, a study conducted by *Mikstacki* and co-workers reported that variations in the *CYP2B6* gene, as well as body mass index (*BMI*) were associated to the rate of propofol metabolism and affected the optimization of anesthesia (11,12).

Single nucleotide polymorphisms (SNPs) in *CYP2B6* may contribute to inter-individual variability in the rate of propofol metabolite formation.

In our results, we did not find differences between different genotypes of the *CYP2B6* gene and entropy rate, as well as induction time and the time of awakening, which is consistent with data from other authors (13).

Even though *in vitro* studies suggest an effect of some *CYP2B6* gene polymorphisms on the activity of enzymes involved in propofol metabolism, no individual differences in propofol pharmacokinetics were observed (14-17). This is consistent with our results, as well as those of Johom et al., whereby no association was found between *CYP2B6* and *GABRE* genotypes and propofol clearance (18).

In our studies, we examined the correlation between the CYP2B6, GABRE and ABCB1 genotype genes with the most common propofol adverse effects: nausea, vomiting and unwanted prolonged sedation. Characteristically, there is no difference between the percentage of adverse effects and the affiliation of patients to certain genotypes of the examined genes. It is not yet

precisely defined in the available literature whether propofol metabolites are associated to drug adverse effects, or which present enzymes and products of gene polymorphisms are responsible for the occurrence of propofol adverse effects (19,20). It can be assumed that such adverse effects would be exacerbated by anesthesia in patients without measuring BIS or entropy. That is why, some patients would be unnecessarily exposed to a dose of propofol different (higher) than that required to obtain BIS<70, especially if they have hypotension, bradycardia, possible prolonged sedation, nausea and vomiting in the early postoperative period.

One of the weaknesses of the considered studies that are similar to ours lies in the large number of anesthetics and other drugs that patients receive during the operative period. The most important of these are opiate analgesics, which are known to be associated to postoperative nausea and vomiting, as well as prolonged sedation in the early postoperative period (21,22).

Conclusion

According to the distribution of the three genotypes of the *CYP2B6* gene, the GG *genotype*, which consisted of two normal alleles, was present in more than half of female patients. *CYP2B6* genetic polymorphism did not have a significant effect on the duration of induction, the time to entropy value of 40-60, or the time of awakening. The total dose of propofol was negatively correlated to the age of patients with homozygous normal *GG* genotype for the *CYP2B6* gene, and the *CYP2B6* genetic polymorphism did not have a significant effect on the occurrence of adverse effects. However, the observed trend of possible influence of CYP2B6 variants requires continuation of these studies in a larger number of patients.

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SURGICAL PATIENTS WITH PACEMAKER – MULTIDISCIPLINARY CHALLENGE

Georgiev A[1], Janusevski F[1], Nikolov I[2], Gavrilovska – Brzanov A[3], Stojanovski S[4], Jovanovski Srceva M[3]

[1]University Clinic of Cardiology, Medical Faculty, University "Ss. Cyril and Methodius"- Skopje
[2]University Clinic for Nephrology, Medical Faculty, University "Ss. Cyril and Methodius"- Skopje
[3]University Clinic for Traumatology, Orthopedic, Anesthesia, Reanimation, Intensive Care and Emergency, Medical Faculty, University "Ss. Cyril and Methodius"- Skopje

ABSTRACT

Running anesthesia during surgery in patients with pacemaker has always been a challenge. The pacemaker malfunctions are rare, but if they occur, they can cause life-threatening consequences for the patient. The opinion of the cardiologist, the technical examination of the pacemaker and a good anesthetic assessment before surgery are vital for the outcome of the surgical treatment. Hereby, we present a case of successful anesthesia management in a patient with left kidney tumor who underwent a radical nephrectomy of the left kidney in general endotracheal anesthesia, and we discuss possible and general implications of the pacemaker from multidisciplinary aspect.

Key Words: general anesthesia, pacemaker, pre/peri/postoperative management, radical nephrectomy.

Introduction

The first pacemaker was used clinically in 1958. Around one million pacemakers are implanted worldwide each year, out of which more than 200,000 in the United States alone. It is estimated that 1.5 million Americans today have a pacemaker. The most of the patients with implanted cardiac pacemakers are older (1,2).

Pacemakers are intended for people which have arrhythmias with a constant or intermittent very slow or very fast heart rate. The pacemaker as a "guardian of the heart" enables patients to have a normal heart rate of 60 to 100 beats per minute. The average lifespan of a pacemaker lithium battery is 7-10 years depending on how much battery is used. The last decade we are witnessing a fast technological development in the world, especially in medical technology. Major technological improvements have been made to pacemaker systems (2).

Surgical procedures and anesthesia in these patients should always be considered with emphasized caution. Despite the advanced technology built into pacemakers, the possibility of complications and possible technical problems should always be taken into account. Continuous technological improvements also lead to confusion in the follow-up of these patients, especially when they need some surgical treatment. Proper preoperative preparation and proper anesthesia

management of the patient are key to the positive outcome of surgical treatments in a pacemaker patient. Anesthesiologists and surgeons face various difficulties regarding pacemakers such as: the choice of anesthesia technique, the continuous monitoring of these patients, the possibility of electrical interference with the pacemaker, possibilities for pacemaker dysfunctions, how far the electrocautery should be from the pacemaker, the usage of magnetic resonance imaging etc. (3,4)

Case Report

We present this case report of a 79 years old male patient with a computed tomography diagnosis for neo-infiltrative change of the left kidney, interpolar to the lower pole with a diameter of 120x100mm. The patient underwent a radical nephrectomy of the left kidney with a general endotracheal anesthesia (OETA).

From his past illnesses, the patient had regulated hypertension with continuous antihypertensive therapy, and had a prostatectomy 10 years ago. Due to the appearance of a total AV block, a permanent pacemaker was implanted eight months ago. The patient received a single-chamber pacemaker VVIR with a ventricular electrode with active fixation of the right ventricular septum. This type of pacemaker is on ventricular demand pacing. The ventricle is paced, sensed, and the pulse generator inhibits pacing output in response to a sensed ventricular event. The patient went for regular technical examinations of the pacemaker after the pacemaker was placed.

Before the operation, the patient underwent anesthesia preoperative evaluation, regular cardiac examination with ultrasound of the heart (with preserved global systolic function and ejection fraction (EF) 62%) and technical examination of the pacemaker and cardiac positive opinion for the operation with a recommendation to use a bipolar electrocautery during surgery.

A complete laboratory analysis and hemostasis of blood was also performed and an X-ray of the lungs and heart was made, and all were within the normal range. Prior to the operation, the anesthesiology team checked the functionality and placement of the necessary equipment, such as the defibrillator and transcutaneous pacing equipment. The earthing plate was neatly placed on the patient's thigh. General anesthesia was induced with preoxygenation, fentanyl and propofol. The patient was intubated with rocuronium bromide. Cardiac monitoring was performed on Datex Omeda integrated monitoring in (five electrodes placed on standard) II lead with adjusted J point. Patient was under continuous monitoring of blood pressure, heart rate, oxygenation, temperature and $EtCO_{2.}$ Surgery and anesthesia went uneventful, and nephrectomy was done. Postoperative recovery went uneventful additionally and another check of the pacemaker was done before release of the patient from the hospital.

Discussion

The pacemakers are very beneficial and life-saving devices for patients who need them. As a "guardian of the heart" they provide quality and normal life in these patients. Due to the increasing representation of the elderly population in the world, the number of pacemaker implants is expected to continue to grow. The new generations of pacemakers are quite safe, but still have the possibility of their malfunction during surgical treatment.

Patients with pacemakers must be carefully evaluated before surgery. The most often these are elderly patients with cardiomyopathies and with constant drug treatment. They are often associated to other diseases. That is why they are challenging patients to administer anesthesia for any anesthesiologist (5,6).

One of the main concerns during surgery is the possibility of electromagnetic interference (EMI) which can lead to pacemaker's failure with subsequent hemodynamic instability and heart rhythm disturbances, that can end fatally. Electromagnetic interference usually occurs directly generated by the surgery electrocautery used. It can also be indirectly, which is rare and is transmitted through the atmosphere when using surgical electrical appliances (3,4,6,7,8,9,10). Improper use of the electrocautery can damage the pacemaker system. This can lead to inhibition of the pacemaker in on-demand mode, can change the threshold, reprogram the pacemaker in automatic safe reversion mode, can cause ventricular fibrillation or other rhythm disturbances. And in some case of inadequate use, the electrocautery can lead to thermal pacemaker's electrode damage (6,9,11,12). To prevent the occurrence of EMI, it is necessary to carefully use the electrocautery which should be bipolar, to use it at least 15cm away from the pacemaker system, to limit its use with an one-second burst at ten-second intervals, use of the lowest possible power, correct placement on the earthing plate to minimize possible flow through the pacemaker system, as well as to provide continuous cardio monitoring for early detection of cardiac arrhythmias or possible pacemaker's malfunction (3,5,6).

A second concern of physicians about pacemaker patients is the possibility of using magnetic resonance imaging (MRI) for diagnostic purposes in these patients. For many years, MRI has been banned in patients with implantable heart electronics devices. But, in 2008 Medtronic promoted the first magnetic resonance imaging conditional pacemaker system Enrhythm MRI. This pacemaker system, like the others that followed, was approved by Food and Drug Administration and is recommended by the American and European Society of Cardiology. These pacemaker systems enable MRI to be performed on patients with a pacemaker. In other pacemaker patients who have a non-magnetic resonance imaging conditioning pacemaker system, an MRI can be performed, but with special protocols and only in those patients who are not pacemaker dependent. Of course, the recommendation for MRI in these patients should be highly selective by appropriate doctors and institutions (3,13,14,15,16).

From the aspect of anesthesia, electrolyte imbalance should also be considered in these patients. Electrolyte and metabolic disorders as hyperkalemia, hyperglycemia, alkalosis and acidosis increase the pacing threshold and possible loss of capture which can be fatal in these patients. Therefore, pre-operatively, this health condition in these patients (who are often with cardiomyopathies treated with diuretics and other drugs) must be considered and corrected in a timely manner (17,18,19,20).

In the patient we present, the pacemaker was implanted for complete heart block. He was pacemaker dependent. During the operation, the use of the electrocautery was far from the pacemaker system. The radical nephrectomy of the left kidney also passed successfully without any obstacles in the pacemaker's work. Postoperatively, the patient was also continuously monitored. After the operation, the technical control of the pacemaker showed its good functional condition.

Conclusion

The knowledge of pacemaker technology, as well as careful anesthesia and cardiological preoperative assessment, are crucial to the surgical outcome of the pacemaker patients. All measures to prevent electromagnetic interference should be taken during the operation. Modern pacemakers minimize the possibility of interference if all preventive measures are applied.

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ANESTHETIC CHALLENGES FOR MAJOR HEPATECTOMY

Kiprijanovska B[1], Spirovska T[1], Toleska M[1,2], Ognjanova V[1], Rushiti Q[2,3]

[1]University Clinic for Traumatology, Orthopedic, Anesthesia, Reanimation, Intensive Care and Emergency, Skopje, Republic of North Macedonia
[2]University "Ss. Cyril and Methodius", Faculty of Medicine, Skopje, Republic of North Macedonia
[3]University Clinic for Digestive Surgery, Skopje, Republic of North Macedonia

ABSTRACT

Hepatic resection is the treatment of choice for many liver diseases. However, it is a large and complex operation with a high risk of side effects in the patients, and it is a challenge for both surgeons and anesthesiologists. This paper presents a case of successfully performed right hepatectomy in a 45-years-old woman with the finding of a giant liver hemangioma, larger than 10cm, placed near the inferior vena cava and the challenges faced by the anesthesiologists when guiding such a patient during the entire perioperative period. The main concern was the risk of massive blood loss, which might significantly increase the rate of morbidity and mortality. During liver resection, central venous pressure (CVP) was optimally maintained below 5cmH2O to reduce blood loss. The cell salvage technique was used to minimize heterologous blood transfusion. Epidural anesthesia can be safely applied in patients undergoing major hepatic resection, provided that they have corrected perioperative hemostasis. The surgical approach after Belghiti "liver hanging maneuver" performed by the surgeons in our case may involve transient compression of the inferior vena cava that cause profound hypotension. Therefore, a successful outcome requires close collaboration between the anesthesiology and surgical team by sharing decisions throughout the operation and following and implementing the latest evidence-based recommendations.

Key Words: *central venous pressure (CVP), giant hemangioma, right hepatectomy.*

Introduction

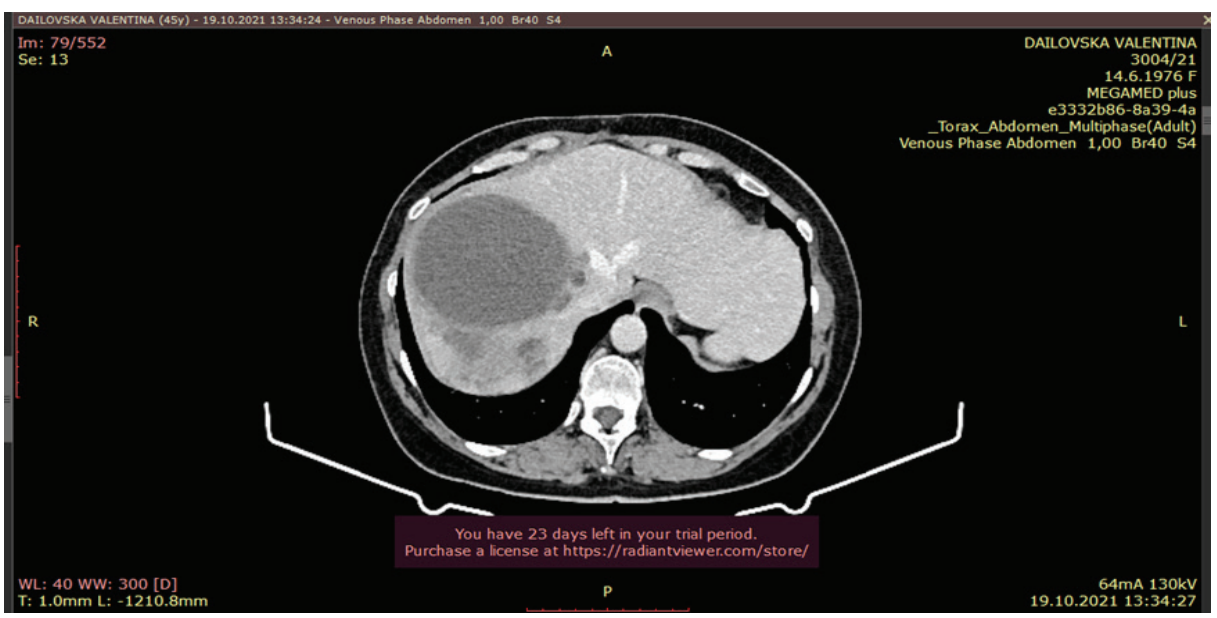
Hemangiomas are the most common benign liver tumors occurring in up to 20% of the population and are usually incidental findings. Current guidelines recommend following the condition and performing surgery for symptomatic patients with giant hemangiomas (larger than 10cm), rapidly growing or when the diagnosis remains inconclusive. Giant liver hemangiomas can cause abdominal pain, congestive heart failure, Kasabach-Merit syndrome (KMS), a rare, life-threatening consumption coagulopathy, and spontaneous or traumatic rupture with a high mortality rate (36-39%) (1,2). The liver is the only solid organ in the human body that can regenerate after tissue loss; hence hepatic resection may be used as the treatment of choice for benign and malignant primary hepatobiliary tumors, hepatic metastases, transplant donation

and hepatic trauma. However, hepatic resection is considered a large, technically complex, high-risk operation with the possibility of severe perioperative complications in these patients. Significant morbidity ranges from 17% in benign to 27% in malignancies, with a mortality risk of up to 5% (3).

Case Report

A 45-years-old woman with a 105×120mm giant hemangioma located in the right lobe of the liver, near the inferior vena cava, was planned for a right hepatectomy at the Clinic for Digestive Surgery (Figure 1). Three mounts before, the patient underwent selective trans-arterial embolization without success. She complained of progressive abdominal symptoms. Her comorbidities included high blood pressure controlled by therapy with ACE inhibitor and varicose veins of the lower extremities. Therefore, the patient was allocated to the second ASA classification group, and according to the Child-Pugh points system, it was determined to be in Group A. Twelve hours before surgery, the patient received low molecular weight heparin and wore tight-fitting compression stockings to prevent venous thromboembolism. Prior to surgery, a Th8-Th9 epidural catheter was placed for perioperative pain treatment, and she was given antibiotic prophylaxis with a third-generation cephalosporin.

Figure 1. *Computed tomography with angiography (CTA) scan of the abdomen and pelvis, showing oval lesion with hemangioma features demarcated in the right lobe of the liver.*



The operation was performed under general anesthesia combined with regional, invasive hemodynamic monitoring and cell salvage technique for autologous blood transfusion. After standard induction to anesthesia, the patient was intubated, placed on a controlled, protective mechanical ventilation (respiratory volume 6ml/kg and positive end-expiratory pressure lower than 5cmH2O), and the central venous line was accessed through the right internal jugular vein

to monitor the central venous pressure continuously. A high-flow transfusion catheter up to 2L/min was placed through the same vein. In addition, the left brachial artery was catheterized for invasive monitoring of arterial blood pressure. Anesthesia was maintained with sevoflurane, a mixture of bupivacaine 0.25% and fentanyl 0.2mg administered continuously through the epidural catheter at 2-4ml/hour depending on the hemodynamic parameters and repeated doses of rocuronium by indication. BIS and EMG monitoring controlled the depth of anesthesia and neuromuscular block, respectively. The operation lasted around 3 hours.

Central venous pressure was constantly monitored and maintained below 5cmH2O during hepatic resection with restrictive fluid intake (4-6ml/kg per hour balanced crystalloids), furosemide, and occasionally nitroglycerin infusion. When the mean arterial pressure dropped below 65mmHg, an intravenous bolus of phenylephrine 50-100μg was given. After resection, the circulating volume was made up with a balanced crystalloid solution with a flow rate of 8ml/kg per hour and 50ml albumin 20%. At the end of the operation, the patient received 480ml of autologous blood from the cell saver device and two units of donated fresh frozen plasma according to hemostasis results. She also received 250ml of mannitol 10%, 1g of vitamin C and 10ml of calcium 10%. As a result, the patient had adequate urinary output. The acid-base status showed mild metabolic acidosis (pH=7.3) and lactate values below 2mmol/L, corrected by improving perfusion. Blood samples were taken several times to control the hematocrit, acid-base balance, serum electrolytes, glycemia and hemostasis. Throughout the procedure, she was warmed with a blanket of forced, warm air, and warmed infusion solutions were used. After the conversion of the neuromuscular block and extubating in the operating room, the patient was transferred to the post-anesthesia care unit (PACU) and after 3 hours on the ward.

The postoperative period passed without any significant symptoms, except for the expected slight increase in serum transaminases (AST and ALT), which were normalized after a short time and were in the reference range on the day of discharge. In addition, prothrombin time (PT) and blood sugar levels remained within normal limits. Postoperative pain was treated with patient-controlled epidural analgesia. The patient was discharged home in good general condition on the 7-th postoperative day.

Discussion

Preoperative assessment and preparation should be individually tailored to the needs of each patient based on existing comorbidities and liver function. They ought to optimize their clinical condition and increase physiological reserves. The Child-Pugh Scoring System is a predictive tool for assessing patients with chronic liver disease, and predicts the risk of developing hepatic failure and chance of mortality. This system has become of great use in hepatobiliary surgery. It is based on serum albumin, bilirubin, prothrombin time, and subjective evaluation of ascites and encephalopathy. Class A patients are generally considered safe candidates for elective surgery (4).

The main concern of the anesthesiologists during liver resection is the danger of severe blood loss because the liver is a greatly vascularized organ with a total blood flow of 1.5L/min (5). There should be adequate availability of blood products depending on the extent and complex

nature of the resection, preoperative anemia and coagulation status. Before surgery, the exact location and vascularization of the tumor formation can be confirmed by imaging investigations allowing planning of the surgical approach. A nomogram created by Sima and colleagues consisting of number of resected segments, lesion type, resection of other organs, preoperative hemoglobin value and platelet count, can predict blood loss and transfusion requirements (6).

Several studies indicate a reduction in CVP below 5cmH2O, thus and hepatic venous congestion, resulting in a more favorable operating environment for the surgeon during liver resection that decreases blood loss and the need for transfusion (7,8). Therefore, this practice is also accepted at our institution. Early intraoperative restrictive fluid intake (4-6ml/kg per hour balanced crystalloids) is used to lower CVP, and diuretics or nitrate infusions are administered if necessary. However, mean arterial pressure should be maintained above 65mmHg due to adequate perfusion of the remaining liver and other vital organs. Risks of reduced CVP may include cardiovascular instability, possible air embolism, and, theoretically, increased risk of postoperative renal dysfunction (9,10). Some patients require individualized management plan to maintain cardiovascular stability. The ERAS (Enhanced Recovery after Surgery) program is committed to keeping CVP below 5cmH2O with careful intraoperative monitoring (11). A balanced crystalloid solution should be preferred to 0.9% saline or colloids to maintain intravascular volume and avoid hyperchloremic acidosis and renal dysfunction, respectively. If possible, 20% albumin should be used as the volume expander (11,12). The strategy of protective mechanical ventilation with an air volume of 4-6ml/kg and positive end-expiratory pressure (PEEP) equal to or less than 5cmH2O, avoids the excessive increase in intrathoracic pressure and consequently increases in CVP. Sympathetic blockade and vasodilation during epidural anesthesia may also help maintaining lower CVP. Epidural anesthesia can be safely used in patients undergoing major hepatic resection, provided they have corrected perioperative hemostasis. There is no evidence of increased adverse events (13). In addition, epidural anesthesia and analgesia reduce operative stress, provide opioid-free postoperative analgesia, and aid in early mobilization and postoperative rehabilitation.

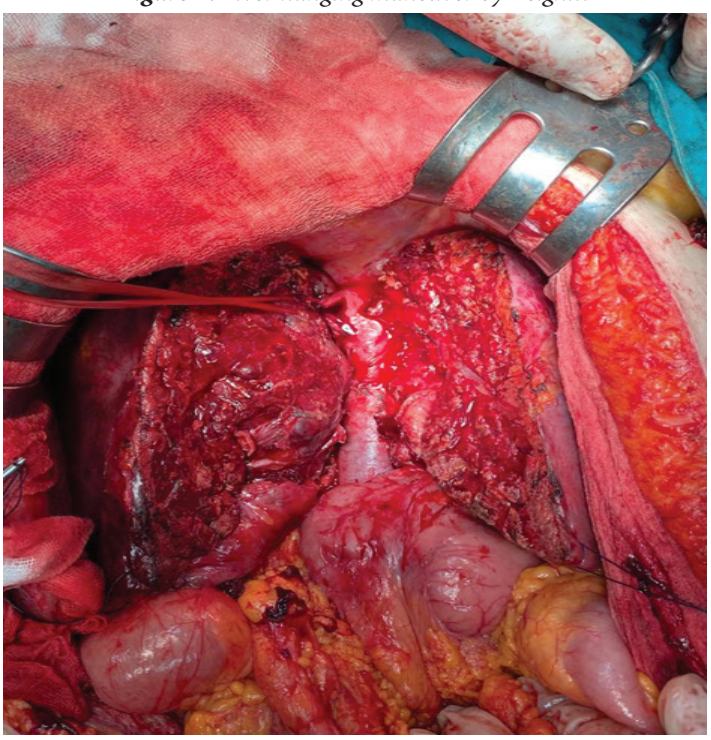
Red blood cell salvage techniques can be helpful in minimizing the need for a blood transfusion by 40% without causing cardiovascular, neurological and immunological adverse clinical outcomes (14).

The frequent measurements of arterial gas, serum electrolytes, serum ionized calcium and glycemia are necessary to detect and adequately treat metabolic disorders. Coagulation can be monitored by thromboelastography (15). Therapy with specific blood products should be given depending on the results of thromboelastography and standard laboratory tests for hemostasis. The benefits of antioxidants for reducing free radicals and preserving renal function have not yet been proven (16,17).

There is small number of evidences to favor the choice of a particular anesthetic. Nitric oxide should be avoided as it causes intestinal distension, and there is a possible risk of air embolism. An anesthesiologist should carefully select anesthetic drugs that minimize the effects of reducing surgically induced hepatic blood flow. Short-acting drugs should be preferred (18).

The surgical team in our case performed a surgical approach by Belghiti "liver hanging maneuver," a method of passing a tape along with the retrohepatic avascular space and suspending the liver during parenchymal transection (Figure 2). Surgical manipulations during this approach may involve transient compression of the inferior vena cava that reduces venous return and causes profound hypotension (19). They didn't use any vascular occlusion techniques, such as temporary occlusion of the hepatic inflow (Pringle maneuver) or total vascular exclusion (TVE). Therefore, communication with the surgical team regarding surgical manipulation and management of hemodynamics is key to achieving a successful outcome.

Figure 2. *Liver hanging maneuver by Belghiti*



Postoperative hepatic failure (POLF) the most often occurs in patients after major resection who have a small volume of the remaining liver. POLF should be recognized as early as possible. It's manifested by the development of jaundice, encephalopathy and coagulopathy. The treatment consists of a goal-directed resuscitation of the systemic organ failure, artificial liver support systems, and liver transplantation as the last choice for this fatal condition (20,21,22). However, adequate preoperative assessment and preparation of the patients, precise intraoperative surgical and anesthesia techniques and improved postoperative care will help to prevent this complication.

Since 2016, the ERAS program guidelines have been developed to accelerate the functional recovery of patients undergoing liver surgery. In these guidelines, a total of 23 recommendations are suggested, including not using prophylactic nasogastric tube and abdominal drainage, targeted fluid therapy, early oral administration and rapid postoperative mobilization (11).

Conclusion

A successful outcome requires close collaboration between the anesthesiology and surgical team by sharing decisions throughout the operation and following and implementing the latest evidence-based recommendations.

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THE CORRELATION BETWEEN THE BODY MASS INDEX AND THE INFLAMMATORY MARKERS IN THE HOSPITALIZED PATIENTS WITH COVID-19

Markovska Z[1], Stavridis S[2,3], Mijakoski D[3,4], Malinovska Nikolovska LJ[5], Meshkova I[1], Stoleski S[3,4]

[1]Department of Anesthesiology and Intensive Care, City General Hospital "8th of September", Skopje, Republic of North Macedonia

[2]University Clinic of Urology, Skopje, Republic of North Macedonia

[3]Faculty of Medicine, "Ss. Cyril and Methodius" University, Skopje, Republic of North Macedonia

[4]Institute of Occupational Health of Republic of North Macedonia, Skopje, Republic of North Macedonia

[5] Department of Pediatric Cardiac Surgery, "Acibadem Sistina" Hospital, Skopje, Republic of North Macedonia

ABSTRACT

The Guidelines for COVID-19 pneumonia emphasize the need for nutritional assessment of obese individuals.

Methods: This prospective observational study extract data for 100 patients aged between 22 and 72 years (mean aged 59±60 years) with confirmed COVID-19 pneumonia who were hospitalized in City General Hospital "8th of September" in Skopje, Macedonia**.** Data extracted included: demographics (age, gender), laboratory marker (c reactive protein), clinical outcomes (length of hospital stay, type of disease, length of homestay). We used an online calculator for Body mass index (BMI) for the assessment of body fat for each patient.

Results: Among 100 patients who were admitted to the hospital, 66% were obese. We found a significant interaction between BMI and increased CRP concentration and a severe type of the disease. Increased BMI was associated to the length of homestay, but the length of the hospital stay did not correlate significantly with obesity.

Conclusion: BMI is a reliable indicator and easy screening method of body fatness. However, further studies for the standard nutritional assessment tool in patients with COVID-19 are still needed.

Key Words: Body mass index, COVID-19, C reactive protein, obesity.

Introduction

Hospitalized patients with COVID-19 pneumonia are at high risk of derangements in nutritional status, both for malnutrition and obesity (1). The European Society for Clinical Nutrition and Metabolism (ESPEN) created recommendations for the nutritional management of obese patients with COVID-19 infections (2). Increased amounts of adipose mass adversely

affect skeletal muscle metabolism and immune function, leading to a higher risk of infection, progressive reduction of muscle protein synthesis and further organs' damage (3). Body fat is biologically active and has an active role in producing pro-inflammatory factors. Among them, IL-6 stimulates the production of C-reactive protein in the liver (4). The release of IL-6 from adipose tissue may induce low-grade systemic inflammation in persons with excess body fat. Furthermore, the expression of ACE2 as the target site for COVID-19 in adipose tissue, is larger than that occurring in the lung tissue (5). Some studies demonstrate that angiotensin-converting enzyme 2 (ACE2) expression can be modulated by a diet (6). Obesity has also adversely affected clinical outcomes: mortality, propagation and length of hospital stay (7). Therefore, it is important to perform body fat assessment systematically in all patients at hospital admission. In the present study, we applied Body mass index (BMI) as an indicator of body fat. BMI is calculated as the patient's weight in kg divided by the square of her/his height in meters. The aim of this study is to determine whether serum C-reactive protein level is higher in obese patients with confirmed COVID-19 pneumonia.

Material and methods

This prospective observational study received approval from the Ethics Committee of City General Hospital 8th of September in Skopje according to the situation for emergency caused by the infectious disease (8). Adult patients affected by SARS-CoV-2 infection between 22 and 72 years (mean aged 59±60 years) who were admitted to the hospital emergency unit were included in this study. Clinical COVID-19 diagnosis was confirmed in the extracts from nasopharyngeal swabs using reverse transcriptase-polymerase chain reaction (Rt-PCR). Demographic data (age, gender) were recorded at the hospital admission. Body fat and inflammatory status were assessed within 48 hours of admission. We used an online calculator for Body mass index (BMI) for the assessment of body fat (https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htm). Laboratory marker CRP for assessment of inflammatory status was assessed by the quantitative method, the capillary tube method using a blood sample from the peripheral vein. The requested sample volume of serum for the assay was 1.0ml. The serum sample was obtained from whole blood that has been centrifuged with the help of serum separator vacutainers. Obtained serum samples were stored in the fully automated instrument Abbott Architect plus c 4000. At the same time uncap and load reagent, type CPPVaR1, was stored in the reagent racks. The instrument calculated the results automatically by pressing the CRP tests for all specimens' bottom on it. The reference range was 0.0-5.0mg/l. Patients were classified according to the World Health Organization classification in correlation to BMI, into the following groups: normal BMI (18.5-24.9), overweight (25-29,9), and obesity class (>30 BMI) respectively. The overweight and obese group were merged into one group, the obese group (BMI>25). Data for clinical outcomes (length of hospital stay, type of disease) were extracted after hospitalization from the medical documents. Patients were classified according to the National's Institute of Health COVID-19 treatment guidelines (https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/) in correlation to the clinical severity into the following

groups: mild, moderate, severe and critical illness. The severe and critically ill groups were merged into one group (severe). The length of hospital stay (LOS) was calculated according to an average number of days from the day of admission till the day of disgorge. The length of the homestay (LHS) was calculated according to an average number of days from the beginning of the symptoms to the day of admission to the hospital.

Results

The sample characteristics of 100 patients with COVID-19 in the BMI analysis are shown in Table 1.

Table 1

	Normal BMI group≤25 (N=34)	Obese group BMI>25 (N=66)	Statistic, *p* value
Age (years) (mean± SD)	59.68 ± 16.43	59.91± 11.83	*t*=-0.073 *p*=0.942
Gender - n (%) Male (n=65) Female (n=35)	 26 (40) 8(22.9)	 39 (60) 27(77.1)	χ^2=2.979, *p*=0.084
Type of disease - n (%) 1 Mild (n=47) 2 Moderate(n=23) 3 Severe (n=30)	 22 (46.8) 7 (30.4) 5 (16.7)	 25 (53.2) 16 (69.6) 25 (83.3)	χ^2=7.583, p=0.023
Length of hospital stay (days) (mean ± SD)	15.09± 10.19	11.33± 5.97	*t*=1.981 *p*=0.054
Length of home stay (days) (mean ± SD)	2.88 ± 2.68	4.73 ± 4.4	*t*=-2.217 *p*=0.029
CRP (mean ± SD) mg/L	88.11± 63.79	130.14± 80.6	*t*=-2.643 *p*=0.006

We applied a t-test for independent samples for continuous variables and a chi-square test for categorical variables. A p-value of <0.05 was considered statistically significant. The associations of BMI with age (*t*=-0.073, *p*=0.942) and gender (χ^2=2.979, *p*=0.084) were non-significant. BMI was likewise not associated to the length of hospital stay. The median length of hospital stay was 15.09 ± 10.19 and 11.33 ± 5.97 days in the normal group and obese COVID-19 patients respectively. BMI was significantly associated to CRP (*t*=-2.643, *p*=0.006), the type of disease (χ^2=7.583, *p*=0.023) and homestay (4.73 ± 4.4*vs*. 2.88 ± 2.68) (*t*=-2.217, *p*=0.029). Severe type of disease was 16.7% and 83.3% in the normal and obese group respectively. The obese group had a higher CRP level (130.14± 80.6) and longer homestay (4.73 ± 4.4) compared to the normal group.

Discussion

ESPEN emphasizes the need for nutritional assessment of patients with COVID-19 pneumonia with significant recognition on obese patients. Among the nutritional screening tools, body mass index (BMI) is one of the recommendations. Based on BMI calculation in our study we estimated that 66% of patients with COVID-19 pneumonia were obese. It has been shown that expansion of adipose tissue in obesity is accompanied by the accumulation of immune cells such as macrophages. Among pro-inflammatory factors: adiponectin, IL-6, and TNF-α are produced by macrophages (9). The overexpressed proinflammatory cytokines in obesity can explain the chronic low-grade inflammation state in obese patients (10). SARS COV 2 may infect fat cells and certain immune cells within them leading to further production of inflammatory mediators, as well as progression of pre-existing low-grade systemic inflammation (11). IL-6 is a key cytokine in the inflammatory response that stimulates the production of CRP in the liver (12). Similarly, we also determined a higher prevalence of low-grade systemic inflammation measured with CRP level in obese patients compared to the ones with normal-weight. In our study, obese patients had higher mean CRP levels compared to those who were with normal BMI (130.14 ± 80.6 vs 88.11 ± 63.79). The most importantly, besides the correlation between obesity and inflammation, we wanted to investigate also the additional determinants for higher CRP in obese patients. Our study extends these findings: the distribution of body fat measured with BMI is associated to CRP concentration, independently of the type of disease. Even among patients with a mild type of disease, a higher BMI is associated to a higher CRP concentration. Furthermore, several studies have shown a close relationship between obesity and the length of hospital stay (13, 14). In opposite, we noticed increased BMI is associated to the length of homestay, but not with the length of hospital stay. Among obese patients, the length of the homestay was longer than that of the normal group. Several possible reasons may explain why obese patients came late for admission. Obesity in itself might impair the respiratory system reducing lung compliance and gas exchange even before the inflammation sets in (15). So, the patients though that the present dyspnea was due to their obesity and that it was not a new symptom of illness. Moreover, we have already mentioned that obese patients already have increased pro-inflammatory cytokine even before the beginning of the symptoms (16). This increased immune response induces the body to generate excessive inflammation which may lead to an increased risk of severe illness when infection with SARS CoV- 2 is set in (17). The reported incidence of a severe type of disease with BMI >25 in our study was 25% compared to 5% in the normal group of patients. We did not divide the obese and normal groups into subgroups: death and survival group to determine the lethal outcome as a risk factor for LOS. Single CRP measurement is another limitation of our study. We assessed CRP within 48 hours of admission so, the CRP level did not represent the inflammatory state for the whole hospitalization.

Conclusion

According to the results of this study it can be concluded that BMI as a marker of the nutrition status should be included in the routine examination of patients with COVID-19 pneumonia because it helps in the prediction of progression of the illness.

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NON-INFECTIOUS ANTERIOR UVEITIS IN CHILDREN - A REVIEW OF THE LITERATURE

Velkovska B[1], Shekerinov Trpevska N[1,2], Kjaeva Nivichka J[1,2], Ivanova Cekov M[1], Petrushevska A[1]

[1] University Clinic of Eye Diseases - Skopje, Republic of North Macedonia

[2] Medical Faculty, University „Ss. Cyril and Methodius" Skopje, Republic of North Macedonia

ABSTRACT

Introduction: Uveitis is a challenging condition for ophthalmologists to treat, and it is considerably more challenging when the patient is a child.

Childhood uveitis is rather common, yet many cases go misdiagnosed due to the child's lack of cooperation, lack of subjective symptoms, non-expression of subjective symptoms, parental lack of information, and so on.

The purpose of this study is to highlight the most prevalent types of anterior uveitis in children, describe the most common clinical entities, and emphasize the significance of regular and thorough examinations of children who visit ophthalmology clinics.

Conclusion: While childhood uveitis is a challenging pathology for ophthalmologists to treat, the fact that there are many protocols for diagnosis and therapy, makes the ophthalmologist's job easier and gives him confidence in which way to go.

The need of regular ophthalmological examinations in childhood, bio-microscopy, and fundus inspection in mydriasis cannot be overstated.

Key Words**: children, non-infectious, uveitis.**

Introduction

Uveitis is less common in children than it is in adults, and diagnosing and treating it can be difficult because young children often show no symptoms, on one hand due to their inability to express themselves, and on the other hand due to the disease's truly asymptomatic nature. Because working with children is difficult, subtle signs like anterior chamber flare or vitreous can go unnoticed (1). The incidence of pediatric uveitis increased with age in a study conducted in county hospitals in the United Kingdom, rising from 3.15 per 100,000 in children aged 0 to 5 years to 6.06 per 100,000 in children aged 11 to 15 years (1).

The classification is based on the SUN nomenclature (Standardization of Uveitis Nomenclature), which was standardized in 2005 and is accepted by ophthalmologists across the world. In general, the following criteria are used to classify uveitis: anatomical classification (based on where the inflammatory process is located), clinical course (acute, chronic, recurrent), etiology (infectious and non-infectious), and histopathological findings (granulomatous and non-granulomatous) (2).

According to this classification, anterior uveitis is localized to the anterior chamber and includes iritis, iridocyclitis and anterior cyclitis. Intermediate uveitis affects the corpus vitreous, and includes: pars planitis, posterior cyclitis, and hyalitis. Posterior uveitis affects the retina and choroid, and includes focal, multifocal and diffuse chorioretinitis, retinochoroiditis, retinitis and neuroretinitis. Panuveitis is defined as involvement of all structures i.e., anterior chamber, vitreous, retina and choroid (2).

According to the clinical course, onset and duration, uveitis is divided into acute, recurrent and chronic. Acute uveitis is considered to be uveitis with a rapid onset and limited duration. Recurrent uveitis is with episodes of exacerbation and remission, inactive for more than 3 months without therapy. Chronic uveitis lasts longer, with a gradual onset and exacerbation of symptoms less than three months after discontinuation of therapy (2, 3).

Blurred vision is the most common subjective symptom of the patients due to cells and flare in the anterior chamber or vitreous. Pain and photophobia are also common, mainly due to ciliary muscle spasm, although anterior chamber infiltration, corneal epithelial edema and pupil muscle involvement may also contribute to light sensitivity (1, 3).

Slit lamp examination reveals cells in the aqueous humor, which are diagnostic of iritis and are often accompanied by flare due to the presence of albumin. Although cells in the anterior part of the vitreous serve as evidence of cyclitis, they are rarely seen in isolation and are of limited clinical significance (3).

The pathology of anterior uveitis can be granulomatous or non-granulomatous. Granulomatous inflammation is associated to large endothelial precipitates (KPs), appearing like fat globules, named mutton-fat KPs which are composed mainly of epithelioid cells deposited on the corneal endothelium (3, 4).

Granulomatous uveitis tends to be chronic and is often associated to systemic conditions and autoimmune reactions. It may also be associated to infectious etiologies such as syphilis, Lyme disease, tuberculosis (TB) and herpes viral infections (3, 4). Herpes infections usually cause non-granulomatous uveitis in acute cases and granulomatous uveitis in chronic cases (4).

In contrast, non-granulomatous inflammation tends to be associated to smaller lymphocyte cells in the anterior chamber. The most commonly it is presented as acute and idiopathic or associated to human leukocyte antigen B27 (HLA-B27) conditions (4).

Clinical entities in childhood

Juvenile idiopathic arthritis

JIA is an inflammatory arthritis that affects children under the age of 16 and lasts for at the least 6 weeks. Other causes such as infection, metabolic processes and neoplasms need to be ruled out. In a 3:1 ratio, female children are more likely to be affected than male children. It is the most common cause of anterior uveitis in children (5).

There are four subtypes of JIA: persistent oligoarticular (affected 4 or fewer joints involved during disease), prolonged oligoarticular (4 or fewer joints affected during the first 6 months, and then 5 or more joints affected after that), polyarticular with positive rheumatoid factor and

polyarticular with negative rheumatoid factor. The incidence of JIA in the United States and Canada is estimated at 0.041 to 0.061 per 1000 children (5).

Thirty to sixty percent of all children with JIA in the United States and Europe are oligoarticular, with a peak age of 2 to 4 years, while the polyarticular form of JIA has a bimodal onset, the first at 1-4 years, and the second at 6-12 years. The ratio of females to males in the oligoarticular form of JIA is 3:1 (5).

Anterior uveitis occurs in 20% of the oligoarticular form and 55% of the polyarticular form. It is manifested as chronic progressive iridocyclitis. It may start asymptomatically, usually detected on routine examination. Even in exacerbations, with 4+ cells in the anterior chamber, there are rarely cells in the vitreous. Detected late, sometimes even initially detected complications: band keratopathy, cataract, strabismus (6).

It is manifested as chronic, non-granulomatous, affecting both eyes in 70%, and it is unusual for a unilateral to become bilateral within a year. The finding is usually symmetrical (5). Cells and flare are seen in the anterior chamber, and the first sign is an irregular or miotic pupil. The eye is usually calm. In acute exacerbations, dusty endothelial precipitates may be seen, but no hypopyon. Posterior synechiae can be seen in long-term uveitis. Very rarely "mutton fat" precipitates (6).

In 10% of the cases, it passes with mild symptoms and persists for up to 1 year. In 50% - it is moderate and lasts more than 4 months and in 25% it is very severe, lasts for several years and does not respond to treatment, ending with complications (5, 6). Complications include: cataract, band keratopathy, secondary glaucoma, cystoid macular edema, optic neuropathy, ERM, traction ablation, NVD (6). Early immunomodulatory treatment reduces the risk of ocular complications and vision loss (6).

Uveitis associated to Morbus Behcet

The peak of the disease is between 3 and 4 years. Recurrent oral ulcers, which are part of the diagnostic criteria, usually do not appear at early age, but appear after 16 years. There are no internationally accepted criteria for early childhood diagnosis. According to a recent report by the International Register of Patients Suspected of Morbus Behcet, recurrent oral ulcers occur in up to 83% of cases studied, with 62% of those cases confirming the diagnosis. Uveitis was found in 34% of this group, which is significantly lower than in adults (7).

Multisystem disease, characterized by recurrent episodes of oral and genital ulcers and vasculitis, may involve small, medium and large blood vessels. Usually found in Mediterranean people, it occurs along the "old silk road", and is closely related to HLA B-51 (8).

Various skin lesions may be seen during the course of the disease, including erythema nodosum, superficial thrombophlebitis, papulopustular lesions, pseudofolliculitis, acne-shaped lesions and rarely extragenital ulcers. Gastrointestinal ulcers, neurological involvement and vascular disease are life-threatening complications of the disease (9).

Uveitis is the most common ocular manifestation, affecting up to 50% of patients. Early ocular manifestations include episcleritis, scleritis, conjunctival ulcers, keratitis, orbital inflammation, isolated optic neuritis, and extraocular muscle paralysis (8).

It is presented as bilateral non-granulomatous panuveitis and retinal vasculitis. The anterior segment shows ciliary hyperaemia, hypopyon in 10-30% of cases. The hypopyon forms and disappears quickly, it is not dense, it accumulates and moves by turning the head, unlike the hypopyon in HLA B 27 uveitis, where it is thick and sticky and does not move. Hypopyon indicates involvement of the posterior segment of the eye, in contrast to HLA B 27 where inflammation is confined to the anterior segment (7, 9).

The average age of onset of pediatric Behcet uveitis is in late childhood (10-15 years). There is a male predominance in the pediatric age group, similar to Behcet uveitis in adults (9).

Panuveitis was the most common manifestation of Behcet in childhood, in previous research. Complications of the disease include cataracts and optic atrophy. Treatment is with topical and systemic corticosteroids, as well as with immunosuppressive therapy in patients with more severe clinical manifestations (9).

Tubulointerstitial nephritis and uveitis syndrome (TINU)

TINU is an uncommon syndrome that accounts for 1.7% of all cases of adult uveitis. However, it is more common cause of uveitis in children and adolescents with a mean age of 15 years (10, 11). The clinical diagnosis of TINU is based on systemic symptoms such as fever, weight loss, abdominal and joint pain, and arthralgia associated to renal dysfunction, confirmed by elevated urea and creatinine, proteinuria, microhematuria and glycosuria (11).

The pathogenetic mechanism is considered to be a defect in cellular immunity, and infectious causes have been reported, including previous infection with Epstein Barr virus, Herpes Zoster and Chlamydia (11). Uveitis manifests as bilateral, usually granulomatous. It responds well to topical corticosteroid therapy (12).

Sarcoidosis

Sarcoidosis in children is a rare multisystem granulomatous inflammatory disorder. While older children may show signs of pulmonary involvement, young children usually present it with a triad of arthritis, skin lesions and uveitis. Serum levels of the angiotensin-converting enzyme may be erroneous, as children normally tend to have higher levels than adults (13).

It is a multisystem, T lymphocyte-mediated non-specific granulomatous disease of unknown etiology. Ocular manifestations occur from 13 to 70% and are the most often anterior granulomatous uveitis, less often posterior uveitis, optic neuritis, their involvement of the skin of the eyelids is as granulomas, granulomatous conjunctivitis, involvement of the tear gland, episcleritis, scleritis, etc. Uveitis occurs from 30 to 70%, while conjunctival nodules up to 40% (14).

Early-onset sarcoidosis (EOS) has been reported in children under 5 years of age and is relatively rare. Blue and Jobs simultaneously described Blue Syndrome (BS) in 1985 as an autosomal dominant, inherited, granulomatous, inflammatory disease. It further became clear that BS and EOS are familial and sporadic forms of the same disease, respectively. BS is manifested in early childhood as a triad of granulomatous dermatitis, polyarthritis and uveitis (15).

The first symptom, in the first year of life, is a skin rash. At the age of 2 to 4 years, polyarthritis occurs. Uveitis occurs in 60% - 80% of patients at about 4 years of age (15). BS and EOS are characterized by the presence of non-caseating epithelioid and giant cell granulomas in the affected tissues. The treatment is the same as for others uveitis (14, 15)

Masquerade anterior uveitis

Masquerade syndromes are a group of disorders that either mimic chronic idiopathic uveitis or there is some non-immune disease that gives a clinical picture of intraocular inflammation. In children, the most common masquerade syndromes manifested as anterior uveitis are: leukemia, retinoblastoma, and juvenile xanthogranuloma (16).

Masquerade syndromes are divided into malignant and non-malignant. From malignant diseases, lymphomas and leukemias give a clinical picture of pseudo-uveitis. The presence of retinoblastoma and the rare form of medulloblastoma must be ruled out. Non-malignant diseases that may mimic uveitis include Coats, juvenile xanthogranuloma and persistent hyperplastic primary vitreous. Treatment focuses on treating the primary cause (17).

Traumatic uveitis

Uveitis can occur after a small, blunt, non-perforated trauma to the eye. If severe inflammation occurs in a minor injury, a predisposition such as HLA-B27 positivity should be considered. Slit lamp shows miosis, ciliary hyperemia and decreased intraocular pressure, and less commonly hyphaema (18).

Idiopathic uveitis

Idiopathic uveitis is diagnosed when no systemic cause is found. In a study by Ben Ezra et al., idiopathic uveitis is cited as the cause in 25.4% of 821 children and adolescents with uveitis. According the same authors, idiopathic uveitis should be a diagnosis of exclusion, once all systemic causes of ocular inflammation have been ruled out (19).

Discussion

Non-infectious pediatric uveitis is a group of inflammatory eye diseases that can lead to ocular complications and vision loss. Juvenile idiopathic arthritis (JIA) is the most common cause, but it also often occurs in other autoimmune conditions such as Behcet's disease or sarcoidosis. Idiopathic uveitis, where there is no associated systemic disease, is as common as JIA-associated uveitis (JIA-U). The classification of uveitis is usually by anatomical location, and anterior uveitis (AU) is the most common manifestation (20).

Several studies have shown an association with HLA class II gene polymorphisms to an increased predisposition in children carrying the HLA-DRB1 * 11, HLA-DRB1 * 13, and HLA-B27 alleles. While HLA-DR1 has been shown to have a protective effect (21).

In childhood, in addition to autoimmune and idiopathic uveitis, infectious uveitis also occurs. Infectious uveitis occurs in 6% to 33% of all cases of childhood uveitis and can be caused

by reactivation of a congenital or acquired infection in childhood (22). Because of its association to rubella, in a study of infectious uveitis in children, Fuchs heterochromic iridocyclitis (FHI) was classified as infectious uveitis (23). In the same study, ocular toxoplasmosis was cited as the most common cause of infectious uveitis in as many as 60% and all patients had chorioretinal lesions. The second most common cause was viral, with 30%, with VZV being the most common pathogen (39%). Five patients with VZV had anterior uveitis and two had acute retinal necrosis (ARN). Congenital CMV was detected in three immunocompetent children. One patient with CMV had anterior uveitis and cataracts, and the other two had chorioretinal scars (23).

Another interesting entity is postinfectious autoimmune uveitis. It manifests itself two weeks after streptococcal pharyngitis. It was firstly described by Cockington and Hahn in 1991. It is presented with bilateral uveitis and elevated serum antistreptolysin O (ASO) titers in more than 95% of the cases. The titer is usually elevated one week after group A streptococcal infection and peaks between 3 and 6 weeks. It decreases after 6 to 8 weeks, although some patients have elevated levels for longer periods of time (24, 25).

Regarding the diagnosis, it should start from complete blood count, HLA typing, RF, ANA, urine analysis, and additionally if we suspect sarcoidosis, lysozyme, chest X-ray and ACE. ACE levels tend to be elevated in the pediatric population compared to the adult population, so that elevated ACE alone cannot be diagnostic of juvenile sarcoidosis, so a chest X-ray and lysozyme level should be performed (26).

When infectious etiology is suspected, IgM and IgG toxoplasmosis and toxocariasis antibodies should be tested. When vasculitis is severe, additional tests for myeloperoxidase and proteinase 3 may be performed. Tuberculosis testing with a skin test can be done with a purified protein derivative or with a serum interferon gamma assay such as QuantiFERON-TB Gold. If syphilis is suspected, enzyme immunoassay, VDRL, RPR, FTA-ABS, TPPA, microhemagglutination essay are performed (26).

There are panel recommendations for the treatment of non-infectious uveitis, but larger randomized controlled trials are needed. Topical corticosteroids are used as the first line of treatment, but in refractory cases, methotrexate and/or biological therapy, usually inhibitors of tumor necrosis (TNFi) such as infliximab or adalimumab, are recommended (27).

Conclusion:

Anterior uveitis in childhood is a challenge, both clinically, due to poor cooperation of the children, and diagnostically and therapeutically. Pediatric uveitis is usually mild or asymptomatic. What is facilitating is that there are numerous researches so far and established protocols for both diagnosis and treatment. Despite the fact that each case is unique, regular ophthalmological examinations in childhood are critical, which in addition to monitoring visual acuity and refraction, should always include a detailed biomicroscopic examination, mydriasis examination and fundus examination with indirect ophthalmoscopy.

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TATTOO AND SPINAL ANESTHESIA – SHOULD WE PUNCTURE OR NOT?

Panoska Avramovska A[1], Gavrilovska–Brzanov A[2], Jovanovski-Srceva M[2], Simevska S[1], Ivanovski O[3], Georgiev A[4], Stevic M[5]

[1]Department of Anesthesiology and Intensive Care, University Clinic for Gynecology and Obstetrics, Faculty of Medicine, "Ss. Cyril and Methodius" University, Skopje, Republic of North Macedonia
[2]University Clinic for Traumatology, Orthopedic Disease, Anesthesiology, Reanimation and Intensive Care Medicine and Emergency Department, Faculty of Medicine, Ss. Cyril and Methodius University, Skopje, Republic of North Macedonia
[3]University Clinic for Urology, Faculty of Medicine, "Ss. Cyril and Methodius" University, Skopje, Republic of North Macedonia
[4]University Clinic for Cardiology, Faculty of Medicine, "Ss. Cyril and Methodius" University, Skopje, Republic of North Macedonia
[5]Department of Anesthesiology, University Children's Hospital, Faculty of medicine, University of Belgrade, Republic of Serbia

ABSTRACT

The topic of tattoos and spinal anesthesia has not been so popular among anesthesiologists, yet still controversial for many of them when it comes to the question: should we puncture or not? Reviews of the literature for complications that may arise as a result of regional anesthesia over a tattoo are unconvincing due to the lack of real evidence-based material. However, theoretical risks do exist and are well explained, hence the anesthesiologist often confront the dilemma about puncturing through an inked skin. The case we present is a young man for an emergency testicular torsion surgery under regional anesthesia despite his tattoo covering his whole back. There were no complications related to the anesthesia technique of choice even a year after the surgery. Hence, spinal anesthesia through a tattoo should be considered safe in emergency or elective interventions.

Introduction

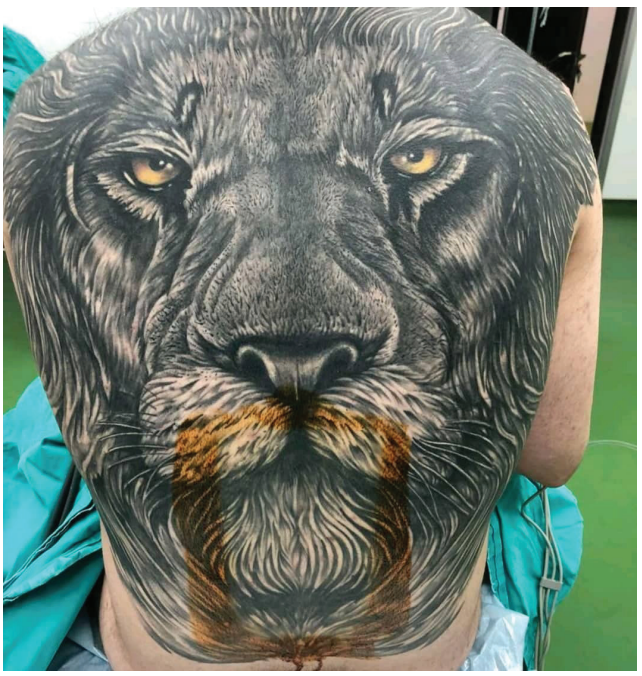
The prevalence of tattoos worldwide among young people vary from 10 - 29% with increased interest for tattooing in all regions over the course of fourteen years (1). Consequently, anesthesiologists at least once in their career will be confronted with the decision of whether they should perform a regional anesthesia over general anesthesia (2). The literature does not provide any real evidence about the possible complications of regional anesthesia over tattoo. Hence, the tattoos are only described as potential risk for occurrence when it comes to neuraxial anesthesia through a pigmented skin. Many of the described scenarios reveal the problem with tissue

coring that eventually may lead to epidermoid tumor in the epidural, subdural or subarachnoid space, as well as inflammatory or granulomatous immune response that can contribute to the outcome of late neurological complications (3). Moreover, local skin reactions such as allergy, irritation, edema and non-acute reactions such as pseudolymphoma, lichenoid, hepatitis B or C, have been described as a result of the tattooing process, but they were not anyhow related to the regional anesthesia performed. However, puncture is contraindicated if any of those symptoms are already present locally (4). In spite of what was stated, the theoretical risk of late neurological complications that may occur as a result of a needle puncture through a pigmented skin, made puncturing through a tattoo a real challenge for the on-duty anesthesiologist in our presented case report.

Case Report

A 21-years old patient was admitted in hospital for an emergency surgical procedure due to testicular torsion. He had one-month old tattoo of a lion covering his whole back with no evident signs of inflammation or skin irritation. Tattoo extensiveness would not allow spinal anesthesia to be performed without penetrating the pigmented tissue. Moreover, patient had a history of right-hand hemiparesis from birth, as well as medical neurology record of focal epilepsy controlled with a carbamazepine for over ten years, with no seizures in the last eight years. His vital parameters in the OR were TA=130/60mmHg, HR=100b/min, SaO2=100% and a regular electrocardiography record. After reviewing the literature and discussing with the patient, the theoretical risks between the neuraxial anesthesia on tattooed skin over the real existing risks of general anesthesia shortly after a meal, the regional anesthesia was a technique of choice. The patient was placed in a seated position, spinal puncture was done under aseptic conditions with a spinal needle 26G placed through a pigmented skin at the level L3-L4. Cerebrospinal fluid free flow was achieved in the first attempt and 15mg hyperbaric 0.5% Bupivacaine was applied to the subarachnoid space. Spinal block of Th10 sensory level was achieved in about 10 minutes. Due to the psychological condition of the patient who showed fear from the moment entering the OR, the spinal block was intravenously supported with 0.1mg Fentanyl and 2mg Midazolam right after incision. During the whole surgical procedure, the patient was closely monitored for any possible neurological changes or hemodynamic instability. The procedure went well with no complications. The sensory and motor functions were completely restored approximately three hours after the puncture. Patient was discharged from hospital three days later, without any post-surgical or complications from the regional anesthesia. Even a year after the surgery, he has not reported any symptomatology on his control examinations.

Figure 1. *Whole back tattoo in a young man with Dg. Testicular torsion, ready for spinal anesthesia.*



Discussion:

As we have previously stated, there is a limited literature evidence of real complications when it comes to neuraxial anesthesia and tattoo in the lumbar region. One of the theoretical possibilities is that the tissue coring may occur as a result of the needle passing through the pigmented skin. As far as the literature reveals, the concern is placed on ink fragments passing through the dura matter and causing inflammatory response of the immune system which can potentially cause neurological complications such as chemical meningitis or arachnoiditis (5). This is due to the possible risk of the chemical compounds of the ink itself such as 2-ethyl-5-nitroaniline, 2,5-dichloraniline and 4-nitro-toluene that can be toxic or cancerogenic. Nowadays, tattoo artists tend to use organic pigments which further decrease the chance of potential harm induced by a tattoo (5). Yet, the highlight is placed on the process of tissue coring when the needle passes over the inked skin and the chances of pigmented particles passing inside the epidural, subdural or subarachnoid space. Theoretically, this may lead to the formation of epidermoid tumor which again is hard to relate to the puncture as it may take many years to develop (6). This was described by Gardner et al, whereby three cases of intraspinal epidermoid tumor were reported as late complications of a spinal puncture. In all of the cases, patients have developed this type of tumor many years later, so it is a controversy if the epidermal tissue in the spinal canal was the real cause of the tumor or was it a result of iatrogenic factors (7). As a prevention, some studies suggest a superficial incision of the inked skin to be done before the puncture in order to provide pigment free area and prevent the pigment entering the deeper tissues. However, this may reflect on the look of the tattoo (3). In our case, considering the inability to modify the level of spinal puncture due to the extensiveness of the tattoo and no available ink free skin around the lumbar region, the puncture was done without an incision. Supporting our decision for

puncturing without an incision and opposite of what was previously stated; a study by Kluger et al. provides counter arguments. They are explaining the histological process of a peeling tattooed skin and how the deposited pigments in the epidermis are progressively lost over time, that superficial epidermal layers are peeled away, and the deeper particles in dermis are destroyed by the function of the macrophages and fibroblasts (8). Many studies have examined the type of needles for spinal puncture in relation to the squamous epithelial cell transport risk. Studies reported that unpigmented biological tissue was punctured and samples of the cerebrospinal fluid were investigated under microscope. It was discovered that significantly lower number of cells were found in samples where the spinal punctures were done with atraumatic needles in comparison to the number of transferred cells when using pencil point needles. The highest number of epithelial cells were found when Quincke needles were used (9,10). In our case, 26G needle was used and the CSF flow was achieved in the first attempt, meaning there was a minimal trauma of the dura. We assume that those two criteria may have contributed to the good satisfactory outcome and no complications reported even a year after the surgery. There is only one documented case of burning sensation, pain and tenderness over the extensive lumbar tattoo after performing an epidural for labor analgesia, with a normal neurological status and resolving symptoms the following day, linked to a possible deeper lumbar tissue irritation (11). Other study has reported a spinal epidural abscess related to a tattoo of the gluteal region and lower back as a result of an infected tattoo manifested with irritation and drainage (12). Adwani et al. reported a case of axillary lymphadenopathy and development of malignant melanoma that was mimicked by the presence of ink in the lymph nodes, thirty years after the tattoo was made (13). These last two cases were not related to regional anesthesia, but counted for complications that occurred as a result of already existing tattoo and problems arising from it. However, none of the above discussed scenarios were seen in our case, even though the highest risk was the potential of seizures in the perioperative or postoperative period due to the focal epilepsy already present from birth. A study from Koop et al. summarizes the results during a 14-years study period where they conclude that the majority of cases presented a seizure due to their underlying condition, but not as a result of the neuraxial anesthesia. Many of those that developed a seizure shortly postoperatively were cases with previously uncontrolled neurological condition (14). In our case, the likelihood of this outcome was very low knowing the fact that the patient had been on a well-controlled antiepileptic therapy for ten years without a seizure in the last eight years.

When it comes to anesthesiologists' opinion about lower back tattoos and neuraxial anesthesia, their approaches differ if faced with such situation. The highest percentage of anesthesiologists i.e 97% would definitely go for a regional anesthesia over a lower back tattoo if faced with an emergency cesarean section, especially if the parturient is classified as Malampati III or IV (15). In a survey from 2007, 65% declared themselves positive for puncturing over inked skin, while 35% would avoid it if possible (16). In a larger study from 2010, anesthesiologists were asked about their opinion on the given topic, so, 74.3% would definitely perform neuraxial block over the tattoo, 67.2% would try and puncture on ink free region, while 7.1% of them

would do it over the pigmented region. In the same study, 67% anesthesiologists were already in situation where they had to choose whether to puncture or not, whereby 61% of them performed such action on non-tattooed area, while 6% did not go for regional anesthesia (17). In another survey, out of all interviewed anesthesiologists, 57% would perform a regional block without a concern, while 42% of them would firstly go with an incision before taking the spinal shot. 39% would avoid this type of anesthesia as a precaution or would consider the risk of cell migration described in literature (18). In a New Zealand's survey, however, 65% of the anesthesiologist did not consider that making an incision would change anything in their approach, while 35% would agree to puncture the tattoo only with a previously made incision. 87% of the interviewed clinicians would not explain to their patients the theoretical risks of regional anesthesia over a tattooed skin (19).

Conclusion:

Although, there are few described conditions that may follow neuraxial anesthesia over tattooed skin, a real concern should not exist in relation to regional anesthesia and tattoos, as there is no up-to-date available evidence-based medical complications described in literature.

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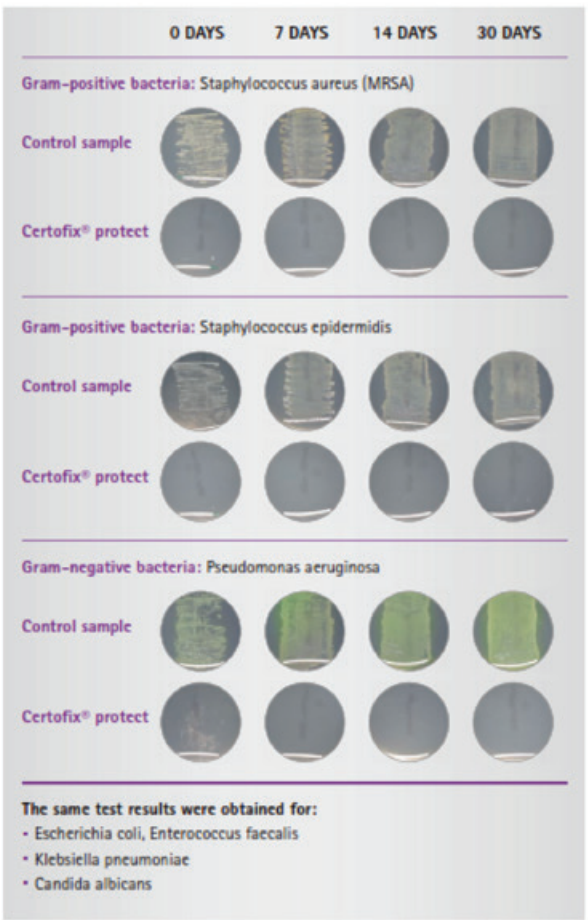

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