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Apotel® 1000mg/6.7ml

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)**
Сите пациенти беа индуцирани со i.v. thiopentone 5mg/kg, i.v. fentanyl 2μg/kg, i.v. vecuronium 0.1mg/kg
Постоперативниот резултат на болка беше мерен со **Визуелна Аналогна Скала (ВАС) од "0-10"**. Исто така беше забележувана и **постоперативната употреба на tramadol** како спасувачки аналгетик. Инциденцата на **постоперативно гадење и повраќање (ПОГП)** и други компликации исто така беа забележувани во пост оперативниот период.
Резултатот на постоперативната болка беше забележуван во интервали 15 мин, 30 мин, 1 час, 2 часа, и 6 часа.

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

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

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

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

Табела3: *Споредба на ПОПГ помеѓу двете групи*

ПОГП	
I Група П	II Група НС
0	4

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

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

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

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

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WHEN EARLY RECOVERY REALLY MATTERS

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CONTENT

"HYBRID THINKING"

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During millions of years of biological evolution, the living world of planet Earth constantly went through the process of adaptation and natural selection. So, Darwin realized that the birds of Galapagos are the same species, but with other variations (adapted to the conditions in which they lived) that he met on other islands. That is why in his book "On the Origin of Species" he will underline: "The same species of birds adapt and change race to the changing world."

Evolutionary development and adaptation are also characteristics of humans. With biological evolution, the brain cortex in humans has constantly adapted and developed. The cerebral cortex is the center of the most important nerve centers for all human activities. These centers are interconnected by nerve connections that transmit information that is further analyzed, synthesized and memorized. Doesn't the human brain resemble today's computers?

How does the modern man function today?

Today's man is in the process of transhumanism with the goal of improving human well-being in every aspect through technological and scientific advances. That is why we have accelerated human evolution with the help of various inventions such as computers, mobile phones, nanorobotics... Artificial intelligence (AI) is such an example of transhumanism. AI is being integrated into every profession, every segment of human life.

Where is medicine in this process of transhumanism?

In medicine, we have accelerated biological and technological evolution. Evidence-based medicine is the basis of modern medicine. But AI enables new dimensions in this segment. AI is dynamically transforming medical practice. There are specially designed software solutions that facilitate the clinical practice of doctors with the help of AI. Quick solutions are offered in the medical decision-making process (10-15 seconds), from disease identification to differential diagnosis, treatment... All these facilitate and improve the clinical knowledge of doctors, real-time up to date academic and medical support is enabled, the precious time of doctors is optimized, but the most importantly, the quality of medical health care is improved. AI is gradually closely connecting the global medical community by sublimating the latest knowledge and scientific achievements in the field of medicine. With the help of AI, CT and MRI diagnostics are already facilitated, AI quantification of the coronary vasculature in cardiology, anesthesia monitoring, control of anesthesia, event and risk prediction, calculating and administering drugs, influences in the construction of individualized therapy, AI constructed archiving of medical records... With the further development of even more modern software, the impact of AI will be inevitable and even more common.

The future is here. We have accelerated personal adaptation to new technologies. But all of that requires a change in our thinking. That is why we have also developed another type of thinking - Hybrid thinking. The power of working together. Hybrid thinking is already a reality. Hybrid thinking analyzes, synthesizes, and harmonizes views across disciplines into coordinated and coherent frameworks. Perhaps the most plastic way to explain hybrid thinking are the following tulip pictures showing one person thinking, two persons and comprehensive, interdisciplinary, and open hybrid thinking.

Thinking of one person, Thinking of two persons, Hybrid thinking

What is the opposite of hybrid thinking?

Narrow, non-cooperative, homogenized, incomprehensive, exclusive, orthodox ... thinking.

In modern medicine, there are already procedures where hybrid thinking has been developed or is being developed. Such is the example of hybrid cardiological-cardiosurgical procedures where the heart team is composed of a non-invasive and invasive cardiologist, cardiac surgeon, anesthesiologist, nurses... The heart team with hybrid thinking and joint work from different professional disciplines becomes "One" for the benefit of the patient. Such is the case with heart or liver transplantation when the whole process requires the involvement and hybrid thinking of a huge team of medical and non-medical personnel. The same is the case with cancer teams. There are many examples. The further development of hybrid thinking will lead to even greater rise in hybrid procedures, transplantation...

Interestingly, there are already studies of hybrid thinking in the world. By stimulating hybrid thinking, students, who are our future, should also be stimulated to express themselves critically towards new ideas or an area they are interested in, as well as working together as teams.

The world is changing faster than ever. Throughout history, some have built walls, but some have torn those walls down. Let us be the harbingers of those who break down the mental walls and embrace, adapt, and apply the new future. Let's be active participants in the changing World.

ORIGINAL ARTICLE

DIASTOLIC DYSFUNCTION IN GESTATIONAL HYPERTENSION/ PREECLAMPSIA

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Abstract

Introduction: Hypertensive disorders in pregnancy including preeclampsia are present in 10% of pregnancies and are one of the biggest reasons for both maternal and fetal morbidity and mortality.
Materials and Methods: The study was undertaken at the University Clinic for Gynecology and Obstetrics in Skopje, North Macedonia. After initial assessment, 81 patients were enrolled in the study after signing a written consent. Patients were divided into two groups depending on whether they had hypertension or not. In the hypertensive group 51 patients were enrolled and 30 normotensive pregnancies were used as controls.
Results: Based on the values of the parameters of diastolic function obtained with PDA of the transmittance flow and the values of the parameters obtained with TDI of the longitudinal movement of the mitral ring, diastolic dysfunction was found in 17 (33.2%) pregnant women of the studied population, LV function ($p < 0.001$). In the pregnant women from the examined group in whom the presence of LV diastolic dysfunction was identified, the disorders were of mild degree, that is type of delayed relaxation of LV in all 17 pregnant women.
Conclusion: Early recognition and management of symptoms are essential. Women who suffer from hypertensive disorders in pregnancy require close monitoring after delivery.

Key Words: *gestational hypertension, diastolic dysfunction, preeclampsia,pregnancy.*

Introduction

Hypertensive disorders in pregnancy including preeclampsia are present in 10% of pregnancies and are one of the biggest reasons for both maternal and fetal morbidity/mortality (1). According to the WHO (World Health Organization), 16% of maternal mortality in developing countries is due to pregnancy related hypertension. The key issue is that half of these could have been prevented if treated on time (2).

Pregnancy is a dynamic process associated with significant physiological changes in the cardiovascular system. Maternal inability to adapt to these physiological changes can expose underlying, previously silent, cardiac pathology, which is why some call pregnancy “the nature’s stress test”. Cardiovascular disease in pregnancy is the leading cause of maternal mortality in North America (3).

The hemodynamic changes in pregnancies complicated with hypertension depend on the type and severity of hypertension and previous chronic diseases. In some pregnancies cardiovascular changes can precede the actual hypertension (4).

The accurate assessment of cardiac function during pregnancy is important. In the past, studies on the maternal cardiovascular system focused mainly on systolic function (5). However, myocardial relaxation is an energy-dependent process and diastolic dysfunction has been shown to precede impairment of systolic function in the evolution of most of the cardiac diseases (6). New studies have suggested that diastolic dysfunction is a major cause of congestive heart failure, and the majority of people with congestive heart failure have preserved left ventricular systolic function (7).

The best method in evaluation of left ventricular (LV) diastolic function involves measurement of transmittal inflow velocity by pulsed wave Doppler echocardiography. It has been in use for the past several decades to evaluate heart function in pregnant women (8).

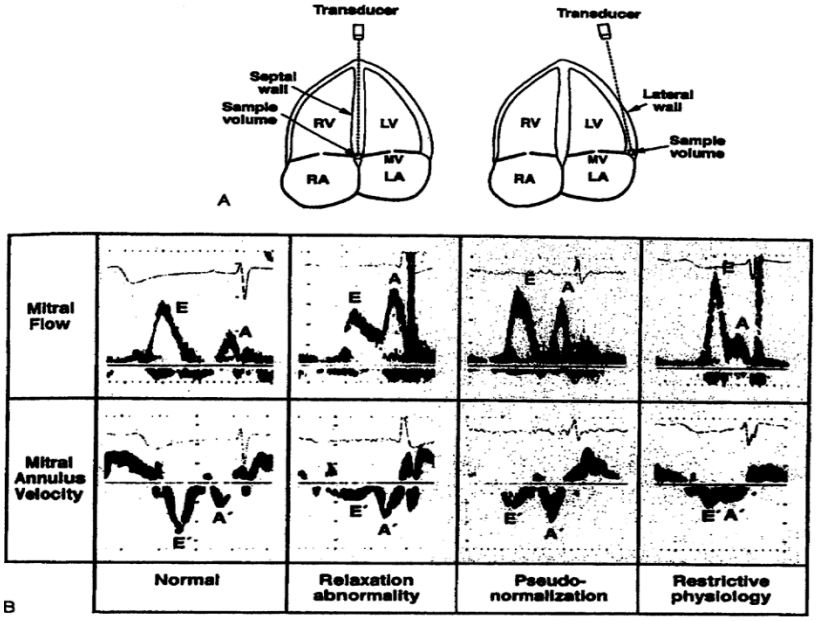
If we can identify any form of cardiac dysfunction along with its severity during early pregnancy, it may be possible to prevent progression of the condition and save mother from severe morbidity of acute heart failure (9). The aim of the study is to evaluate diastolic changes in pregnancies with gestational hypertension/preeclampsia.

Materials and methods

The study was undertaken at the University Clinic for Gynecology and Obstetrics in Skopje, Republic of North Macedonia. After initial assessment, 81 patients were enrolled in the study after signing a written consent. The patients were divided into two groups depending on whether they had hypertension or not. In the hypertensive group 51 patients were enrolled, and 30 normotensive pregnancies were used as controls. The initial examination was done at the 28thg.w. Subjects were classified as hypertensive if BP was ≥140/90 on two different occasion 6 hours apart.[i] The predetermined exclusion criteria for the study were: diabetes, maternal cardiovascular disease, alcohol and tobacco use. Gestation was confirmed by the last menstrual period and ultrasound measurement. BP was measured using the standard auscultatory method with the help of pneumatically operated mercurial type sphygmomanometer. BP was measured in the left arm in the sitting position with the arm at the level of the heart. Echocardiographic examination was done at the University Clinic for Cardiology with GE Vivid echocardiograph machine. M-mode studies were performed at the level of the aorta, left atrium and LV at midposition between the tips of the mitral valve. Systolic parameters studied were left ventricle end systolic diameter (LV ESD), left ventricle end diastolic diameter (LV EDD), stroke volume (SV), CO(cardiac output), left ventricular mass (LVM)and posterior wall thickness (PWT) in long-axis parasternal view. Diastolic parameters studied were E wave, A wave, E/A ratio, isovolumetric relaxation time (IVRT).

A total of 3 echocardiographies were made in the 28thg.w., 2 weeks after delivery and 6 months after delivery. The idea of the study was to determine heart's function during and after pregnancy, to evaluate diastolic function even after the pregnancy has ended to see whether heart changes still exist. In patients with diastolic dysfunction 6 months postpartum further checkups were organized with cardiologists.

Table of Diastolic Changes



1.Normal diastolic function,
2.Disturbed (abnormal) relaxation or light abnormal relaxation,
3.Pseudonormal type of diastolic dysfunction,
4.Restrictive type of diastolic dysfunction.

Results

Statistical analyses of data were donewith SPSS 21.0.For testing of normal distribution of data Shapiro - Wilk´s test was used. Categorical variables were shown with absolute and relative numbers and for describing quantitative variables descriptive statistics were used. For comparison of analyzed variables between evaluated and control group, Student's t-test was used as a test of significance. For comparison of (0.1 and 2 control) Paired sample test was used. For describing categorical variables x^2 test was used. The probability value ($P < 0.05$) is described as significant.

Table 1. Parameters of diastolic dysfunction determined with PDA (pulse doppler) on transmittal flow and pulse wave TDI e' velocity (sm/sek) of longitudinal movement of the mitral ring in evaluated and control group.

	Evaluated group (n=51)	Control group (n=30)	P value
E wave, m/s	0.67±0.04	0.78±0.02	< 0.005‡
A wave, m/s	0.62±0.12	0.57±0.04	0.05‡
DT, ms	215.1±16.8	191±4.8	< 0.005‡
E/A ratio	1.08±0.23	1.5±0.07	<0.01‡
E', cm/s	8.3±1.9	9.4±0.8	<0.05‡
E/E' ratio	9.9±2.0	8.2±0.5	< 0.05‡
PS, mm	34.6±3.7	28.9±1.6	<0.001‡

‡Student's t-test

In Table 1, Doppler echocardiographic parameters define diastolic function in pregnancies with hypertension and in control group.

Student t-test has shown significant statistical difference between the two groups when E wave speed ($p<0.005$), E/A value (($p<0.01$), DT($p<0.005$), speed of longitudinal movement of the mitral ring - E'($p<0.05$) and E/E' value($p<0.05$).

The Chi-square-test has shown statistical difference ($p<0.001$) between the two groups, in ratio to diastolic dysfunction, defined by PDA (pulse doppler) parameters and TDI velocity (Table 1).

Table 2. Diastolic function in both group defined by parameters of pulse wave (PDA) doppler of transmittal flow and TDI velocity(sm/sek) of longitudinal movement of the mitral ring in evaluated and control group.

	Evaluated group (n=51)	Control group (n=30)	P
Diastolic dysfunction			
No(n,%)	29(56.9%)	29 (96.7%)	<0.001†
Yes(n,%)	22(43.1%)	1(3.3%)	
Delayed relaxation	19 (37.2%)	1 (3.3%)	
Pseudonormal type	3 (5.9%)	0	
Restrictive type	0	0	

†Chi-square test

The Chi-square test showed us a statistically significant difference between the two groups, in terms of the presence of diastolic dysfunction of LV, defined according to the parameters of PDA.

Based on the values of the parameters of diastolic function obtained with PDA of the transmittal flow and the values of the parameters obtained with TDI of the longitudinal movement of the mitral ring, diastolic dysfunction was found in 22 (43.1%) pregnant women of the study population, in addition in the normotensive group diastolic dysfunction was found in 1 (3.3%) patient ($p <0.001$).

In patients in whom the presence of LV diastolic dysfunction was identified, the disorders were mild, that is a type of delayed relaxation of LV in 19 (37.2%) pregnant women, and moderate in 3 (5.9%) pregnant

women. In the control group only one patient (3.3%) had delayed relaxation or a mild degree of diastolic dysfunction.

The first control was performed in all respondents 2 weeks postpartum.

Table 3. Parameters of diastolic dysfunction determined with PDA on transmittal flow and TDI (sm/sek) of longitudinal movement of the mitral ring in evaluated and control group on the first control.

	Evaluated group (n=51)	**Control group (n=30)**	**P value**
E wave, m/s	0.67±0.04	0.77±0.02	< 0.05‡
A wave, m/s	0.60±0.12	0.57±0.06	0.06‡
DT, ms	208.3±18.8	196.5±5.3	< 0.005‡
E/A ratio	1.28±0.23	1.52±0.07	<0.01‡
E', cm/s	8.7±1.6	9.6±0.7	<0.05‡
E/E' ratio	9.0±2.2	7.8±0.6	< 0.05‡
PS, mm	33.5±4.1	28.9±1.6	<0.001‡

‡Student's t-test

Table 3presents Doppler echocardiographic parameters that define diastolic function in pregnant women with preeclampsia or gestational hypertension and the control group (the first control).

Student t-test showed us a statistically significant difference between the two groups in terms of E wave velocity, E/ A ratio, DT, speed of the longitudinal movement of the mitral flow - E'i and E / E 'ratio.

The Chi-square test showed a statistically significant difference (p <0.001) between the two groups, in terms of the prevalence of LV diastolic dysfunction, defined according to the parameters of PDA and TDA (Table 3).

Table 4. Diastolic function in both group, defined by parameters of transmittal profile, gained with PDA (pulse wave) and TDI of longitudinal movement of the mitral ring in evaluated and control group on the first control.

	Evaluated group (n=51)	**Control group (n=30)**	**P**
Diastolic dysfunction			
No(n,%)	34(66.7%)	30 (100%)	<0.001†
Yes(n,%)	17(33.3%)	0	
Delayed relaxation	17 (33.2%)	0	
Pseudonormal type	0	0	
Restrictive type	0	0	

†Chi-square test

The Chi-square test showed us a statistically significant difference between the two groups, in terms of the presence of diastolic dysfunction of LC, defined according to the parameters of PDA.

Based on the values of the parameters of diastolic function obtained with PDA of the transmittal flow and the values of the parameters obtained with TDI of the longitudinal movement of the mitral ring, diastolic dysfunction was found in 17 (33.2%) pregnant women of the study population. LV function ($p < 0.001$). In the pregnant women from the examined group in whom the presence of LV diastolic dysfunction was identified, the disorders were of mild degree, that is type of delayed relaxation of LV in all 17 pregnant women.

The examined echocardiographic findings presented in Table 5 and 6 refer to the second control. This control was performed in all respondents 6 months postpartum. Unfortunately, some of the respondents did not respond to the last echocardiographic control, namely 8 patients from the study and 4 patients from the control group did not complete the second control. The same parameters were examined again.

Table 5. Parameters of diastolic dysfunction determined with PDA on transmittal flow and TDI of longitudinal movement of the mitral ring in evaluated and control group on second control.

	Evaluated group (n=43)	**Control group (n=26)**	**P value**
E wave, m/s	0.72±0.04	0.78±0.02	< 0.05‡
A wave, m/s	0.59±0.12	0.56±0.14	0.06‡
DT, ms	210.3±18.8	194.5±4.7	< 0.05‡
E/A ratio	1.32±0.23	1.57±0.05	<0.05‡
E', cm/s	8.8±1.7	9.5±0.9	0.05‡
E/E' ratio	8.6±2.5	7.6±0.6	< 0.05‡
PS, mm	30.75±3.12	29.67±1.71	0.05‡

‡Student's t-test

Table 6. Parameters of diastolic dysfunction determined with PDA (pulse doppler) on transmittal flow and TDI of longitudinal movement of the mitral ring in evaluated and control group on second control.

	Evaluated group (n=43)	**Control group (n=26)**	**P**
Diastolic dysfunction			
No(n,%)	31(71.9%)	26 (100%)	0.003†
Yes(n,%)	12 (28.1%)	0	
Abnormal relaxation	17 (33.2%)	0	
Pseudonormal type	0	0	
Restrictive type	0	0	

†Chi-square test

We found diastolic dysfunction in 12 of the 43 subjects from the population with gestational hypertension or preeclampsia (28.1%), 8 pregnant women did not complete the study at the last control. In the control group 4 patients did not report at the last control and nopositive finding was observed from the available respondents in this group ($p < 0.001$) (Table 5).

Disscusion

The left ventricular diastolic dysfunction is defined as the inability of the heart to fill with normal blood volume without increasing ventricular filling pressure. Left ventricular diastolic function and left ventricular filling pressure were calculated and graded using standard diagnostic algorithms (11,12)

Diastolic dysfunction usually occurs before systolic dysfunction in the evolution of ischemic/ hypertensive cardiovascular disease and it is of prognostic importance in predicting long-term cardiovascular morbidity (13).The American College of Cardiology has highlighted the importance of identifying asymptomatic cardiac dysfunction for early intervention and improvement of outcome (14).Heart failure is a progressive condition, which begins with risk factors for left ventricular dysfunction and progresses further to asymptomatic changes in cardiac structure and function, finally evolving into heart failure (15). Diastolic dysfunction precedes the onset of systolic dysfunction in 50% of cardiac diseases, which further precedes the onset of heart failure (16).

The Olmsted study described the predictive significance of left ventricular diastolic dysfunction using multivariable adjusted analyses (17). One year post-delivery, diastolic dysfunction was present in 11.5% of women with pre-eclampsia, in 22.7% of women with early-onset pre-eclampsia and in 1.9% of women whose pre-eclampsia developed after 34 weeks.

In our study, diastolic dysfunction at the entrance of the study was identified in 43.1% of the evaluated pregnant women, at the first control the percentage decreased to 33.3% and at the last control - 6 months after delivery was 18.1%. In our study, pregnant women were not divided into early and late preeclampsia due to the low number of patients. In other studies, in preterm preeclampsia, diastolic dysfunction is found in more than 50% of cases at the entrance to the study (18). The one-year control study showed diastolic dysfunction in 14% of term preeclampsia compared to 40% in preterm preeclampsia. In our study, upon entering the study, diastolic dysfunction was identified in one pregnant woman in the control group, but it was not observed in the next two controls. In studies where diastolic dysfunction was observed in part of normotensive pregnant women, it normalized within 3 months after delivery (19).The changes that persist for more than a year have number of cardiovascular consequences, and these results seem to be specific to early onset preeclampsia (<34 g.w.), but not in term preeclampsia (20).

Conclusion

Early recognition and management of symptoms are essential. Women who suffer from hypertensive disorders in pregnancy require close monitoring after delivery. This has been shown especially in early onset preeclampsia. Up to 40% of those patients fit the criteria of B-stages heart failure (left ventricular diastolic dysfunction/abnormal relaxation).These are young active women who don’t know that they have an underlying risk for chronic hypertension and future heart failure. Close cooperation between obstetricians and cardiologists is needed, so that these patients are not lost in the system.

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ORIGINAL ARTICLE

EVALUATION OF THE SURGICAL TREATMENT OF LUNG CANCER

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Abstract

Lung cancer is the most common malignancy in men and in the entire human population. It is considered that 2,200,000 new patients are detected annually in the world (Globcan 2020), 475,000 in Europe (Globcan 2020), i.e. 1,135 in the Republic of North Macedonia (Globcan 2020). The treatment is multimodal, and several factors influence its choice.
Surgical treatment is one of the modalities of treatment and its application depends on numerous factors - histological structure of the tumor, stage of the disease, satisfactory respiratory reserves, satisfactory cardiac reserves, general condition of the patient, etc. At the clinic for thoracic and vascular surgery in 2022, only 59 patients were surgically treated, which is 85% of the total surgically treated in the Republic of North Macedonia. Out of the 59 patients, 44 (74.6%) were men. The average age of the operated patients was 64.22 years, and 37 (62.7%) underwent neoadjuvant chemotherapy preoperatively to reduce the tumor and stage of the disease.
Patients who were operated on were mostly in IIIA stage 16 (27.12%). The small percentage of operated patients, 7.7%, and the particularly high percentage of operated patients at an advanced stage indicates that patients are detected at an advanced stage of the disease, which is a contraindication for surgery. Introduction of screening for lung cancer using computed tomography in risk groups will significantly change the therapeutic approach to this group of patients, as well as the outcome of their treatment.

Key Words: *lung cancer, screening, surgery,..*

Introduction

Lung cancer is the most common malignancy in men and in the entire human population, but also is on the first place according to the mortality rate. It is considered that 2,200,000 new patients are detected annually in the world (Globcan 2020), i.e. 1,135 in the Republic of North Macedonia (Globcan 2020), out of which only 59 patients were surgically treated at the thoracic and vascular surgery clinic in 2022, which is 85% of the total surgically treated in the Republic of North Macedonia (1).

Lung resection is one of the procedures in the treatment of lung cancer (2-4).

The extensiveness of the disease (clinically advanced stage), histological structure (small cell carcinoma), limited respiratory reserves, limited cardiac reserves, deterioration of the general condition, make lung resection impossible. That is why only 10% of newly diagnosed patients with lung malignancy undergo surgical intervention with lung resection (4).

The use of neoadjuvant oncology therapy in a certain percentage increases the chance of lung resection. Of course, perhaps the introduction of a screening program with computed tomography enables the detection of lung cancer in the earliest stage of the disease, which significantly increases the percentage of lung resections (5,6).

The aim of this paper is to determine the characteristics of patients with lung cancer, type of tumor, type of lung resection through the analysis of operative material of patients operated at the University Clinic for Thoracic and Vascular Surgery in 2022. At the same time, measures should be proposed to increase the percentage of operated patients from lung malignancy.

Material and Methods

In 2022, 59 patients with proven lung malignancy were surgically treated at the Thoracic and Vascular Surgery Clinic. The study did not include patients in whom lung malignancy was not proven, as well as patients in whom the surgical intervention was for the purpose of diagnosing changes, exploration and so on.

Descriptive parameters (gender, age), tumor localization, pathohistological finding, TNM descriptors, preoperative application of neoadjuvant therapy, stage of disease resulting from TNM descriptors, surgical approach, type of lung resection and removed part of lung were analyzed.

The parameters are entered into a database in the Excel program. Standard computer programs Statistics 10 were used for statistical analysis.

Results

At the Clinic for Thoracic and Vascular Surgery in 2022, 59 patients were operated for lung cancer. Out of them, 44 (74.6%) were men, and 15 (25.4%) were women. The age of the patients was from 40 to 79 years, with an average age of 64.22 years.

All patients were operated under general anesthesia, using a double-lumen tube.

Among the pathohistological findings, squamous cell carcinoma was most common - in 32 (54,2%), followed by adenocarcinoma - in 19 (32.2%). The results of the distribution of patients by gender and pathohistological findings are shown in Table 1.

Table 1. Distribution of type of lung cancer according to gender of patients.

Pathohistology	Male	Female	**Total**
Squamos cell	27 (45.8%)	5 (8.5%)	**32 (54.2%)**
Adenocarcinoma	11 (18.6%)	8 (13.6%)	**19 (32.2%)**
SCLC	0	1 (1.7%)	**1 (1.7%)**
Another	6 (10.2%)	1 (1.7%)	**7 (11.9%)**
	44 (74.6%)	**15 (25.4%)**	**59 (100%)**

The following table shows the results of distribution of disease stage descriptors T (tumor size), N (involvement of lymph nodes with metastases) and M (presence of systemic metastases).

Table 2. Distribution of patients according T stage, N stage, M stage and TNM stage.

	T	**N**	**M**		**stage**	**TNM**
0	1 (1.7%)	37 (62.7%)	57(96.6%)		I	11 (18.6%)
1	11 (18.6%)	17 (28.8%)	2 (3.4%)		IIA	13 (22.0%)
2	24 (40.7%)	5 (8.4%)			IIB	9 (15.2%)
3	14 (23.7%)				IIIA	19(32.2%)
4	9 (15.2%)				IIIB	5 (8.4%)
					IV	**2 (3.4%)**
Total	**59 (100%)**	**59 (100%)**	**59 (100%)**			**59 (100%)**

The tumor size in the lung ranged from 0 to 90mm, mean value 45.12mm.

The tumor was mostly located in the upper lobe, in 23 (39%) and in the right lung, in 31 (52.5%).

Oot of the operated patients, preoperative neoadjuvant chemotherapy was applied in 37 patients (62.7%), in order to reduce the stage of the disease, so that lung resection could be performed.

Open anterolateral thoracotomy was the most often applied, in 49 (83%) of the patients.

Of the lung resections, lobectomy was the most often used, in 45 cases (76.27%). The surgical approach and type of lung resection are attached to Table 3.

Table 3. Distribution of patients presented by type of surgical approach and type of lung resection according to TNM stage.

TYPE							
⇩ STAGE⇨	**I**	**IIA**	**IIB**	**IIIA**	**IIIB**	**IV**	**Total**
Thoracotomy	9	10	8	16	4	2	**49 (83%)**
VATS	2	3	1	3	1	0	**10 (17%)**
	11	**13**	**9**	**19**	**5**	**2**	**59**
Wedge	1	1	0	0	1	0	**3 (5.1%)**
Lobectomy	9	11	7	14	2	2	**45 (76.3%)**
Bilobectomy	0	1	0	2	0	0	**3 (5.1%)**
Pulmectomy	0	0	2	2	2	0	**6 (10.2%)**
other	1	0	0	1	0	0	**2 (3.4%)**
	11 (18.6%)	**13 (22%)**	**9 (15.3%)**	**19 (32.2%)**	**5 (8.5%)**	**2 (3.4%)**	**59 (100%)**

Complications of the type: prolonged air leak in 10, incomplete re-expansion in 9, bronchopneumonia with atelectasis in 8, encapsulated effusion in 4, which were resolved with conservative treatment, were detected in the patients.

No death outcome was detected in any patient in-hospital.

Discussion

Resection is the primary mode of treatment for stage I and II NSCLC and an important component of the multimodality approach to stage IIIA disease (2-4,7).

Standard resections include removal of the lobe involved with tumor and systematic evaluation of ipsilateral hilar and mediastinal lymph nodes (2-4,8).

According to Globcan, in 2020, 1,135 patients with lung malignancy were detected in the Republic of North Macedonia, unfortunately only 59 (5.2%) cases were treated surgically, which is 85% of the total surgically treated patients with lung malignancy (1).

First of all, the reason for such a small number of operated patients is the detection of lung cancer in an advanced stage. Namely, the indication for surgery are patients of I, II and part of IIIA stage from the group of non-small cell cancer type. Contraindicated for surgery are also patients with detected small cell cancer, which are represented by 20%, except for the earliest stage (4,7).

The large respiratory reserves of the lungs, clinical symptoms that are not characteristic of lung cancer at the beginning, are the reason for detection of lung cancer in an advanced stage, which are inoperable at the time of diagnosis.

Preoperative evaluation of pulmonary reserves (gas analyses, ventilation tests), as well as evaluation of cardiac reserves (echocardiography and, if necessary, coronary angiography), further exclude from operative treatment the patients with a high risk of surgery.

According to the pathohistological diagnosis of the tumor, squamous cell carcinoma is the most common, especially in operated male patients where it is represented by 61,4%. Contrary to this, in women operated for lung cancer, adenocarcinoma dominates, which is represented by 53,3% .

According to the stage of the disease in the operated patients, the most often they were operated in IIIA stage - 19 (32.2%), which indicates that they were operated in an advanced stage, even more knowing that 37 patients (62.7%) were preoperatively treated with neoadjuvant chemotherapy in order to downsize the tumor and the stage.

Lobectomy remains the preferred operation and it is associated with better survival and lower locoregional recurrence, but there is increased interest in the role of sublobar resections (2,3,7-9)

In our study, 45 (76.3%) of the patients were treated with lobectomy and lymphadenectomy, 3 with bilobectomy and 6 with pulmectomy due to disease progression in more than one lobe.

Results after anatomical lobectomy for early stage, NSCLC were good. In the large ACOSOG Z0030 trial, disease-free survival at 5 years was 68% for resected early-stage patients. The operative mortality following lobectomy is reported to be 1 to 3% with pneumonia and respiratory failure as the overwhelming causative factors (2,3,7-9).

For early-stage disease, the evolving surgical treatment goals were aimed at decreasing of morbidity and mortality through less invasive approaches including video-assisted thoracoscopic surgery (2,3,7-9).

The most large series of lobectomy by VATS describe a similar pattern of perioperative complications as the open approach, but at reduced rates of complications, especially at early stage (2,7,9).

VATS has been established as a safe and less morbid alternative to open resection, but skepticism remains about its oncologic effectiveness (8).

From what has been presented so far, it clearly follows that the main problem is late-diagnosed patients with lung cancer. Accordingly, consideration should be given to introducing lung computed tomography screening in at-risk populations. With the introduction of screening, it is expected that the percentage of patients with early-stage disease who will undergo surgery will rise to 25 to 40% (5,6).

Conclusions

The small percentage of patients with lung cancer that were operated, as well as those operated in an advanced stage of the disease, should encourage the introduction of screening of the risk population.

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ORIGINAL ARTICLE

DELAYED COMPLICATIONS FOLLOWING LONG-TERM CENTRAL VENOUS CATHETER PLACEMENT IN PEDIATRIC ONCOLOGY CASES

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Abstract

Introduction: Modern chemotherapy protocols in pediatric oncology necessitate the deployment of central venous catheters. The duration of catheter usage ranges from several months to a year. Typically, long-term central venous catheters (LCVC), including external tunneling (ETLCVC) and totally implanted (TILCVC) variations, are employed for this purpose.

Aim: This study aims to assess the superiority of ETLCVC over TILCVC and to evaluate the occurrence of delayed complications, specifically focusing on catheter occlusion, dislocation of the catheter and catheter – related thrombosis, following the placement of central venous catheters.

Material and Methods: This prospective interventional clinical study encompassed 120 pediatric patients, aged 2-14 years, diagnosed with leukemia, lymphomas and solid tumors. The participants were stratified into two groups (n=60). Group 1 received ETLCVC, whereas Group 2 underwent TILCVC placement. An informative interview was conducted with the eligible patients' parents, and written consent for study participation was obtained.

Results: In the group of patients with an implanted ETLCVC, four patients had a dislocation of the catheter, three patients had a catheter occlusion, two patients had a catheter – related thrombosis. In the group of patients in whom a TILCVC was implanted, one patient had an dislocation of the catheter, one patient had catheter occlusion, and there wasn't any patient with catheter – related thrombosis.

Conclusion: Incidence of delayed complications (catheter occlusion, dislocation of the catheter, and catheter – related thrombosis) in our study were more frequent in patients in whom ETLCVC was applied, but this difference did not have statistical significance.

Key Words: *Delayed complications from long-term central venous catheters, long-term implanted central venous catheters, pediatric oncology patients.*

Introduction

Pediatric patients diagnosed with malignant diseases represent a rare occurrence, yet approximately 80 cases are reported annually in our country, necessitating the placement of a long-term central venous catheter (1). These diseases rank as the second most common cause of death in patients aged 12 months and older (2). The psychological impact of these illnesses can contribute to future complications, underscoring the importance of understanding how young patients cope with their conditions and the duration of their treatment.

In the field of pediatric hemato-oncology, various types of fully implanted long-term central venous catheters, such as external tunneling and totally implanted catheters, are employed (3). The selection of an appropriate catheter for pediatric oncology patients is influenced by their specific needs, taking into account factors like planned treatment duration, anticipated catheter usage and institutional capacity (4). It is recognized that cytostatic drugs exert a vascular irritating effect, placing a progressive strain on the venous system. Consequently, frequent peripheral venipunctures can induce behavioral and physiological reactions linked to pain or anxiety (4).

Due to the inadequate peripheral venous vascular system in children, it becomes necessary to insert a long-term central venous catheter for secure central venous access during cytostatic treatment (5). Given that the duration of treatment can extend from several weeks to several years, especially in cases like leukemia where the process lasts an average of two years, long-term central venous catheters play a crucial role in facilitating the daily administration of chemotherapy. These catheters serve as essential tools for safely infusing chemotherapeutic agents, supportive medications, blood products, hydration, and total parenteral nutrition (6). By avoiding frequent painful punctures of peripheral veins, long-term central venous catheters are believed to alleviate daily stress and enhance the quality of life for pediatric patients (7,8).

Pediatric oncology patients with long-term central venous catheters, require specialized treatment. The placement of central catheters can be accomplished through various techniques, including "blind" percutaneous venipuncture guided by anatomical landmarks, percutaneous puncture with ultrasound guidance, and cannulation of peripheral venous lines. However, catheter placement entails inherent risks and potential complications, depending on the chosen venipuncture site, technique, and catheter type (9,10). Immunocompromised pediatric oncology patients are particularly susceptible to complications (6).

Complications may arise during the catheter application, immediately afterward, or after a certain period, allowing for classification as early (≤30 days) or delayed (>30 days).

Complications can also be categorized based on their severity, specifically as minor and major. Minor complications typically do not necessitate surgical intervention or specific medical therapy for a period shorter than 24 hours. On the other hand, major complications encompass issues that demand early surgical intervention or extended medical treatment requiring a hospital stay exceeding 24 hours, with the potential for life-threatening outcomes.

Problems may arise during the placement of the central venous catheter, often involving injury to surrounding vital structures or incorrect positioning of the catheter tip. Early complications commonly include cardiac arrhythmia (23% - 25%), accidental arterial puncture (0% - 15%), hemothorax (0.1% - 11%), pneumothorax (1% - 4%), and air embolism (11-14). Delayed complications in central catheter placement often involve migration, mechanical issues (9%), complications related to the catheter material (2%) (13,14), infections (15), thrombosis (50%) (16), and fibrin pooling in the catheter.

Traumatic, infectious, or thrombotic complications of this nature can pose life-threatening risks, lead to extended hospitalization, and undoubtedly incur additional costs for prolonged treatment (6,17-19).

In such instances, a non-functional central venous line is simply extracted, necessitating the placement of a new central venous catheter (20).

The dislocation of the catheter in a central venous catheter represents a commonly encountered delayed complication. This complication occurs after the initial placement of the catheter and involves the movement or displacement of the catheter from its intended position within the vascular system. Unlike some early complications that manifest during or shortly after the insertion procedure, dislocation tends to become apparent over time (20-23).

The dislocation of the catheter can result in its tip being improperly positioned, potentially leading to issues such as inadequate delivery of medications or therapies, as well as posing risks of damage to surrounding structures. Detection of catheter dislocation often involves diagnostic imaging techniques, such as X-rays, to ascertain the catheter's current location within the vascular system.

Managing catheter dislocation typically involves repositioning the catheter through appropriate medical interventions. Additionally, measures are taken to secure the catheter in its revised position to minimize the likelihood of further dislocation (21).

Given the importance of central venous catheters in the administration of various medical treatments, prompt identification and resolution of catheter dislocation are essential to maintain the efficacy and safety of ongoing patient care. Regular monitoring and follow-up assessments are crucial to identify and address any complications, including dislocation, in a timely manner, thereby optimizing the functionality and longevity of the central venous catheter.

Catheter occlusion in a central venous catheter is a prevalent delayed complication that can impact the functionality of the catheter over time. This complication occurs after the initial placement of the catheter and involves the blockage or obstruction of the catheter lumen, hindering the normal flow of fluids or medications through the catheter (22,23).

The occlusion of the central venous catheter can result from various factors, including the accumulation of blood clots, fibrin deposits, or precipitates of medications within the catheter lumen. Additionally, the formation of a thrombus around the catheter tip or within the blood vessels can contribute to occlusion.

Symptoms of catheter occlusion may include difficulty in aspirating blood or infusing fluids, changes in pressure readings during catheter use, or a noticeable decrease in the effectiveness of therapies administered through the catheter. Diagnostic measures, such as catheter patency checks and imaging studies, may be employed to identify and confirm the occlusion.

Addressing catheter occlusion often involves interventions to restore catheter patency. Healthcare professionals may use techniques such as instilling a thrombolytic agent or saline solution into the catheter, applying gentle catheter flushing, or employing mechanical devices designed to break down obstructions. In some cases, catheter replacement may be necessary if occlusion persists despite initial interventions (6,19,21).

Preventive measures include regular flushing of the catheter with appropriate solutions, adherence to prescribed flushing protocols, and ensuring proper care and maintenance of the catheter. Routine monitoring and assessment of the central venous catheter play a crucial role in early detection and management of occlusion, helping to sustain the catheter's effectiveness and minimize potential complications for patients requiring long-term intravascular access.

Catheter-related thrombosis in a central venous catheter represents a common delayed complication that can significantly impact the vascular access and overall well-being of the patient. This complication occurs subsequent to the initial catheter placement and involves the formation of blood clots within or around the catheter, obstructing the normal blood flow through the vessel.

The development of thrombosis in the central venous catheter is often multifactorial, influenced by factors such as prolonged catheter dwell time, hypercoagulability of the patient, and catheter-related trauma to the vessel wall. Thrombosis can manifest in various forms, including the formation of clots within the catheter lumen, around the catheter tip, or extending into the larger blood vessels (22,23).

Patients with catheter-related thrombosis may experience symptoms such as swelling, pain, or discoloration at the catheter site, as well as difficulty in aspirating blood or infusing fluids through the catheter. Diagnostic measures, including imaging studies such as ultrasound or venography, are often employed to confirm the presence and extent of thrombosis (20-25).

Managing catheter-related thrombosis involves a combination of anticoagulation therapy and interventions to address the underlying causes. Anticoagulant medications may be administered to prevent the extension of the clot and reduce the risk of further complications. In some cases, the removal or replacement of the catheter may be necessary to eliminate the source of thrombosis (20-26).

Preventive measures to reduce the risk of catheter-related thrombosis include regular assessment of catheter function, adherence to anticoagulation protocols in high-risk patients, and ensuring proper catheter placement techniques. Healthcare professionals play a crucial role in monitoring and promptly addressing any signs of thrombosis, contributing to the maintenance of vascular access and the overall safety of patients relying on central venous catheters for medical treatment (26,27).

Aim of the study:

The main goal of this study is to assess the frequency of delayed complications in patients utilizing two distinct types of long-term central venous catheters. The first type involves tunneling, specifically the Hickman-monolumen and Broviac-multilumen catheters. The second type comprises totally implanted long-term central venous catheters, specifically the Bard-port. The study aims to provide valuable insights into the incidence of complications that occur beyond the initial placement period, offering a comprehensive understanding of the safety and efficacy profiles of these two catheter types in clinical practice.

Material and methods

Our study is prospective, interventional clinical study performed on 120 hemato-oncology pediatric patients scheduled for chemotherapy using a long-term central venous catheter and conducted in the period from January 2021 to January 2023.

The study was performed at the University Clinic for Traumatology, Orthopedics, Anesthesia with Resuscitation and Intensive Care and Emergency Center (UC TOARILUC - KARIL) in collaboration with the University Clinic for Pediatric Surgery and the Clinic for Children's Diseases.

The study included pediatric patients who met the specified inclusion criteria, while those exhibiting factors for exclusion were not considered for participation. Enrolled participants comprised children with various conditions, including acute lymphoblastic leukemia, myeloid leukemia, non-Hodgkin and Hodgkin lymphoma, as well as solid tumors such as CNS tumors, rhabdomyosarcoma, Wilms' tumor, and bone tumors. The study encompassed individuals aged 2 to 14 years, with a body mass index (BMI) below 25 kg/m2, falling within American Association of Anesthesiologists (ASA) classes I to III. Inclusion criteria also specified patients with normal infectious markers, neutrophil and platelet counts, appropriate hemostasis, and those whose parents or guardians provided informed written consent for study participation.

Patients falling below the age of 2 or surpassing 14 years, those with a BMI exceeding 25 kg/m2, individuals with ongoing or suspected infections previously treated with broad-spectrum antibiotics, patients exhibiting elevated infectious parameters, those with hemostatic disorders, thrombocytopenia, neutropenia, anemia (Hb < 100g/l), individuals allergic to heparin, and pediatric patients with kidney or liver diseases were systematically excluded from the study.

The study involved the randomization of patients into two equally sized groups. The first group consisted of 60 pediatric oncology patients who underwent the application of a totally implanted long-term central venous catheter under general endotracheal anesthesia. The second group comprised 60 pediatric oncology patients who underwent the application of an external tunneling long-term central venous catheter under general endotracheal anesthesia.

Following collaborative discussions with colleagues from the Clinic for Children's Diseases and pre-operative preparations, a designated date for central venous catheter placement was established. One day before the procedure, patients underwent a thorough examination and anesthesia assessment at the UC TOARILUC anesthesiology outpatient clinic.

Upon admission to the Clinic for Pediatric Surgery, the invasive procedure commenced. Standard non-invasive hemodynamic monitoring, including ECG, non-invasive blood pressure, and pulse oximetry, was conducted in the operating room for pediatric patients. Following the induction of inhalation anesthesia (Sevoflurane-O2), a peripheral venous line was established for the administration of muscle relaxants and opioid analgesics. Subsequently, after endotracheal intubation and ensuring adequate hemodynamic and respiratory monitoring, the central venous catheter placement procedure was initiated.

The patient was appropriately positioned, adopting the Trendelenburg position, and the operating field was meticulously prepared using aseptic techniques. An ultrasound technique, employing the Siemens Acuson P500

with a linear probe, was utilized to identify anatomical structures for port placement. The central venous catheter placement in both study groups followed Seldinger's method, targeting the vena jugularis interna.

For patients in the first group, vena jugularis interna was punctured, securing venous access. A guide-wire was then inserted, through which a silicone dilator was threaded, ensuring its tip reached the venous blood vessel. Subsequently, a subcutaneous pocket was created along the middle clavicular line, 3-5 cm below the right clavicle. Following precise hemostasis, the silicone reservoir, connected to the silicone catheter, was positioned within the subcutaneous pocket. A subcutaneous tunneling procedure was employed to establish communication between the pocket and the vessel puncture site. The catheter was then passed through this subcutaneous tunnel, using a metal guide to reach the insertion site of the silicone dilator. The silicone catheter's tip was inserted into the venous blood vessel via the placed silicone dilator, reaching vena cava superior through vena jugularis interna. The silicone catheter's height was determined by measuring from the insertion site to the sternal angle between the manubrium and the body of the sternum. Closure of the subcutaneous pocket was achieved through surgical sutures. The fully implanted catheter's position was verified by aspiration through the silicone reservoir, with a positive test indicating the return of venous blood. At the procedure's conclusion, the catheter received a 2.5 ml injection of heparin solution (100 IU of heparin in 1 ml of physiological solution). The tip's position was confirmed through a native X-ray of the lungs.

For patients in the second group, who underwent the application of an external tunneling long-term central venous catheter, the initial phase mirrored that of patients in the first group. Venous access was established by puncturing the vena jugularis interna, and a guide wire was introduced, subsequently removing the metal cannula from the blood vessel. The silicone dilator, serving as a guide with its tip positioned in the venous blood vessel, was then threaded over the guide wire. A small subcutaneous incision of 1 cm was made in the middle clavicular line, 3-5 cm below the clavicle, after achieving adequate hemostasis. Following this, a subcutaneous tunneling procedure was performed from the surgical incision site to the insertion point of the silicone dilator.

Through the created subcutaneous tunnel, the silicone catheter was threaded from the surgical incision site to the positioned dilator with the aid of a plastic guide. Utilizing the guide dilator, the tunneling central venous catheter was introduced into the venous blood vessel, with its tip placed in v. cava superior. The outer portion of the catheter was secured with a surgical suture to the surgical incision. The tunneling central venous catheter featured a safety cuff (Surecuff-Tissue Ingrowth cuff) positioned in the subcutaneous tunnel 1-2 cm from the surgical incision. This safety cuff served to anchor the catheter to the surrounding subcutaneous tissue while acting as a physical barrier against the transmission of microorganisms. Procedures for verifying the position and height of the catheter aligned with those conducted for patients in the first group.

Following the interventional procedure and awakening from general anesthesia, patients from both groups underwent monitoring in the recovery room for one hour, where potential early complications were observed. After concluding the recovery room stay and undergoing X-ray diagnostics, patients were transferred to the Children's Disease Clinic for monitoring late complications arising from the invasive procedure. The initiation of prescribed chemotherapy could commence on the same day.

Results

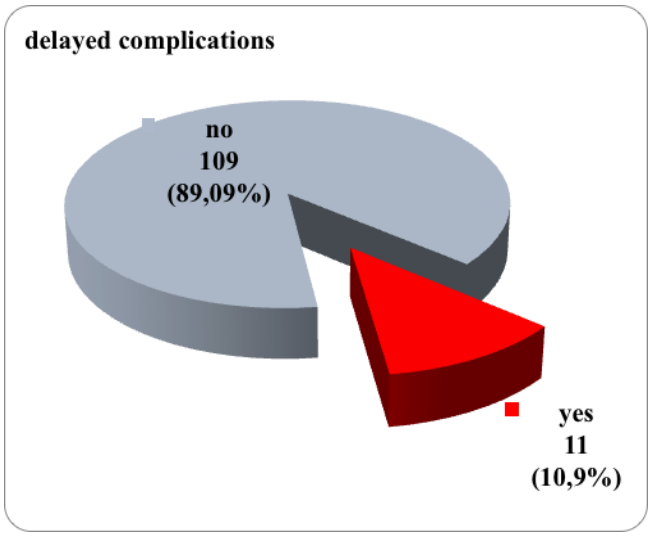
The results obtained by processing and analyzing data from 120 subjects, hemato-oncology pediatric patients who are to be administered chemotherapy using a long-term central venous catheter, are shown.

The gender structure of the respondents consisted of 68 male patients (56.67%) and 52 female patients (43.33%).

Patients ranged in age from 2 to 14 years, with a mean age of 6.1 ± 3.5 years. Half of the patients were older than 5 years (median=5 years).

Delayed complications after the application of a central venous catheter were registered in 14 patients, that is, the incidence of delayed complications was 11.67%. (Figure 1)

Figure 1. Graphic representation of frequency of delayed complications



Regarding the type of late complications, in 5 patients dislocation of the catheter was registered, in 2 catheter thrombosis, in 4 occlusion of the catheter. (table 1)

Delayed complications were manifested significantly more often by patients from the group with ETLCVC compared to patients from the group with TILCVC - 9 vs 2.

Table 1. Frequency of delayed complications in both groups

Delayed complications	**n**	group 1 n	group 2 n
Yes	11	9	2
No	109	51	58

Group 1 - ETLCVC (external tunneling long-term central venous catheter)

Group 2 - TILCVC (totally implanted long-term central venous catheter)

Catheter dislocation was recorded in 1 (1.67%) patients with TILCVC and 4 (6.67%) patients with ETLCVC. The higher prevalence of this complication in patients in whom ETLCVC was applied was not confirmed statistically as significant (p=0.17). (table 2)

Table 2. Frequency of catheter dislocation in both groups

Dislocation of the catheter	**n**	group 1 n (%)	group 2 n (%)	p - value
Yes	5	4 (6.67)	1 (1.67)	X^2=1.9
No	115	56 (93.33)	59 (98.33)	p=0.17

Group 1 - ETLCVC (external tunneling long-term central venous catheter)

Group 2 - TILCVC (totally implanted long-term central venous catheter)

X^2(Pearson Chi-square test)

Catheter thrombosis complication occurred insignificantly more often in patients with ETLCVC application, that is, in 2 (3.33%) patients from this group, and in no patient from the TILCVC group (p=0.15). (table 3)

Table 3. Frequency of catheter thrombosis in both groups

Thrombosis of the catheter	**n**	group 1 n (%)	group 2 n (%)	p - value
Yes	2	2 (3.33)	0	X^2=2.0
No	118	58 (96.67)	60 (100)	p=0.15

Group 1 - ETLCVC (external tunneling long-term central venous catheter)

Group 2 - TILCVC (totally implanted long-term central venous catheter)

X^2(Pearson Chi-square test)

Catheter occlusion was registered in 3(5%) patients with ETLCVC and 1(1.67%) patients with TILCVC, and without a statistically significant difference between the two groups (p=0.31). Catheter occlusion was insignificantly more common in patients with NTDCVK application. (table 4)

Table 4. Frequency of catheter occlusion in both groups

Catheter occlusion	**n**	group 1 n (%)	group 2 n (%)	p - value
Yes	4	3 (5)	1 (1.67)	X^2=1.0
No	116	57 (95)	59 (98.33)	p=0.31

Group 1 - ETLCVC (external tunneling long-term central venous catheter)

Group 2 - TILCVC (totally implanted long-term central venous catheter)

X^2(Pearson Chi-square test)

Discussion

Long-term central venous catheters are frequently utilized for various medical purposes such as blood sample collection, intravenous hydration, and the administration of medications to patients with diverse pathologies. The initial descriptions of these catheters were provided by Broviac in 1973 and later by Hickman in 1979 (28,29). These catheters were subcutaneously tunneled and featured a subcutaneous cuff. Totally implanted long-term central venous catheters (TILCVCs) offer several advantages, including the absence of external dressings, enhanced patient mobility, and the need for monthly injections of heparin solution for maintenance. Consequently, TILCVCs

are associated with fewer infections and complications compared to externally tunneled catheters (30). The overall complication rate for long-term central venous catheters is estimated to be between 10% and 15% (20,29). This paper focuses on delayed complications (such as catheter dislocation, catheter thrombosis and catheter occlusio) and their correlation with the type of catheter applied (23, 24, 26).

The study encompassed 120 pediatric oncology patients aged 2-14 years, with 90 patients diagnosed with leukemia (75%), 22 with solid tumors (18.3%), and 8 with lymphoma (6.7%). Acute lymphoblastic leukemia accounted for the majority of diagnoses (44%), followed by lymphoid leukemia (22.5%). The patients were categorized into two groups based on the type of long-term central venous catheter used for cytostatic therapy. Both groups exhibited homogeneity in terms of gender and age, with a predominant male gender in the first group (55%) and the second group (58%). The average age in both groups was 6.1 ± 3.5 years.

In this study, the overall rate of delayed complications was 10.9%. Long-term central venous catheters (CVCs) are indispensable tools in the management of pediatric oncology cases, providing reliable vascular access for the administration of chemotherapy, blood products, and other essential medications. However, these catheters are not without complications, and three significant issues warrant discussion: catheter dislocation, catheter thrombosis, and catheter occlusion.

Catheter dislocation, or unintended movement from its original placement site, poses a risk to the effective delivery of medical treatments. In pediatric oncology, the dynamic nature of a child's growth and development can contribute to catheter dislocation. Additionally, physical activity and inadvertent tugging on the catheter may further predispose pediatric patients to this complication. Preventive strategies, such as securement techniques, should be implemented to minimize the risk of dislocation. Routine assessments and vigilant monitoring play a crucial role in the early identification of dislocation, allowing for timely intervention and the prevention of treatment interruptions (12,16,22,29).

Catheter thrombosis, the formation of blood clots within the catheter lumen or the surrounding vasculature, is a frequent concern in long-term CVC use. Pediatric oncology patients, often undergoing aggressive chemotherapy regimens, are at an increased risk of thrombotic events. Thrombosis can impede blood flow, leading to catheter malfunction and potentially compromising the delivery of therapies. Prophylactic measures, including appropriate anticoagulation strategies and routine flushing protocols, are essential to minimize the risk of thrombosis. Regular monitoring for signs of thrombosis, such as sluggish blood return or resistance during flushing, enables prompt detection and intervention (16,27,29).

Catheter occlusion, the blockage of the catheter lumen, is another common complication in long-term CVC use. In pediatric oncology cases, occlusion may result from the accumulation of blood products, drug precipitates, or fibrin within the catheter. Routine flushing with appropriate solutions, maintaining adequate hydration, and employing proper catheter care practices can mitigate the risk of occlusion. Regular assessment of catheter patency and prompt intervention, such as catheter clearance protocols, are crucial in managing occlusive events and ensuring uninterrupted therapy delivery (26).

In addressing these complications collectively, a comprehensive and multidisciplinary approach is paramount. Healthcare providers in pediatric oncology must remain vigilant in adopting preventive measures, conducting routine assessments, and promptly addressing complications to optimize the safety and efficacy of long-term CVC placement. Moreover, continuous education for healthcare teams and caregivers is essential to enhance awareness

and promote adherence to best practices, ultimately improving the overall care and outcomes for pediatric oncology patients reliant on long-term central venous catheters.

Conclusion

The placement of long-term central venous catheters (CVCs) in pediatric oncology cases is a crucial component of comprehensive medical care, providing essential vascular access for the administration of critical therapies. Despite the undeniable benefits of CVCs in enhancing patient comfort and treatment efficacy, healthcare providers must navigate potential complications that may arise during their prolonged use.

Catheter dislocation, thrombosis, and occlusion emerge as notable challenges in the management of long-term CVCs in pediatric oncology. The dynamic nature of pediatric patients' growth and development, coupled with the intensive medical interventions they undergo, necessitates a nuanced and proactive approach to address these concerns.

Implementing preventive strategies, such as securement techniques to minimize dislocation risks, anticoagulation protocols to mitigate thrombotic events, and vigilant catheter care practices to prevent occlusions, is paramount. Regular assessments, monitoring, and prompt intervention are crucial components of a comprehensive care plan aimed at optimizing the safety and efficacy of long-term CVC placement.

Moreover, healthcare providers must engage in ongoing education and training to stay abreast of the latest advancements in catheter placement techniques, complication management, and evidence-based practices. Collaborative efforts involving multidisciplinary teams, including pediatric oncologists, nurses, and caregivers, are essential to ensure a holistic and patient-centered approach to long-term CVC care.

While challenges may arise, the benefits of long-term CVCs in pediatric oncology, including improved treatment delivery and reduced procedural stress, underscore their indispensable role in the continuum of care. As technology and medical knowledge advance, ongoing research and refinement of protocols will further enhance the safety and effectiveness of long-term CVC use in pediatric oncology cases.

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ORIGINAL ARTICLE

LUNG ULTRASOUND DERIVED INSIGHTS IN VENTILATOR ASSOCIATED PNEUMONIA

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Abstract

Lung Ultrasound (LUS) is widely used in diagnosis and monitoring of Ventilator Associated Pneumonia (VAP). The aim of our study is to evaluate and detect local lung events in mechanically ventilated patients, as well as to evaluate the usage of LUS in distinguishing VAP from Ventilator associated tracheobronchitis. We examined LUS finings in all patients who fulfilled the criteria for VAP, and stratified them according to the CLUE Protocol. We have examined the findings for VPLUS Score of each patient and tried to find a correlation between LUS Score and VPLUS Score. The average value of total LUSS of all patients examined was 11.05. LUS Score of the upper segments versus lower segments was 0.07 versus 2.1 respectively with 95% CI from 1.44 to 2.61, and significance level $p<0.0001$ suggesting the existence of statistically significant difference into distribution of pathological findings in between upper versus lower lung segments. Also, we found a LUS Scores difference of 3.46 with 95%CI of 0.95 to 5.96 and significance level of $p=0.0099$ which implies existence of statistically significant higher LUS Score values in patients with VPLUS >2 versus patients with VPLUS of 2. In conclusion, the pathological findings in patients with VAP were distributed in the dependent regions, while upper segments were spared. Also, only patients with VPLUS>2 instead of VPLUS≥2 should be considered as having VAP.

Key Words: *Lung Ultrasound, Ventilator Associated Pneumonia, Ventilator Associated Tracheobronchitis.*

Introduction

Lung ultrasound (LUS) is an attractive and repeatable point-of-care diagnostic tool that can provide significant data about the local lung parenchyma happenings in mechanically ventilated patients. As a feasible method with no irradiation power, nowadays it is widely used in diagnosis and monitoring of Ventilator Associated Pneumonia (VAP) (1,2).

Aim of Study

The aim of our observational study is to evaluate and detect local lung happenings in mechanically ventilated patients with positive microbiologic findings and abnormal laboratory values of the infective markers implicating possible presence of VAP, as well as to evaluate the usage of LUS in distinguishing VAP from Ventilator associated tracheobronchitis.

Material and Methods

We conducted a retrospective study in 18 patients hospitalized in the Intensive Care Unit at University Clinic for Neurosurgical Diseases in the period from 1st September 2019 to 1st of June 2020. In accordance with the Helsinki Declaration dated 1975 and revised in 2000, this study was conducted after obtaining an Ethical Approval given from the Institutional Ethical Committee under the number 5.1-2020/5.

The inclusion criteria for this study were: the patient must be ≥18 years old, must be mechanically ventilated more than 48 hours, must have abnormal laboratory findings for total White Blood Cells (WBC) count and/ or percentage of neutrophils and/ or elevated CRP. All patients must have positive microbiological findings of previously taken tracheobronchial aspirates and must have elevated body temperature. In other words, all patients that met the criteria for existing suspected VAP were included in our study. All patients that have fulfilled the inclusion criteria underwent LUS examination according to the BLUE protocol (1) obtained with Ultrasound Machine Mindray TP 2200 while curvilinear probe was used. We've examined bilaterally upper and lower, anterior, lateral and posterior in total 12 segments, and scored every segment with 0, 1, 2 or 3 when normal findings (A-lines and lung sliding) were present (Figure 1), when 3 well separated B-lines were present (Figure 2), more than 3 B-lines or coalescent B-lines were present and consolidations were noted, respectively. Total LUS Score (LUSS) was calculated for every patient and according to the CLUE protocol, the best result of LUSS could be 0 suggesting normal finding of well aerated lungs, and the worst seen result could be 36 including 12 zones of both lungs suggesting total lung de-aeration. According to the findings of the CLUE protocol, the degree of loss of aeration is graded as mild when the LUSS value is 1-5, moderate when LUSS value is ≥ 5 - 15 and severe when LUSS value is higher than 15. Average values of LUSS findings were calculated for every single segment examined, as well as for each lung separately and for total LUSS value. Comparison of two means as statistical method was used to calculate if there was any statistically significant difference of the findings in both lungs, as well as in upper versus lower lung segments. The findings of A/B patterns, B-patterns, consolidations, air bronchograms and pleural effusions were noted and evaluated with descriptive statistical methods. Also, we calculated the Ventilator-associated pneumonia lung ultrasound score (VPLUS) for each patient where purulent tracheal secretions were graded as 1 if present, existence of positive microbiological cultures were graded as 1 if present, existence of subpleural consolidations were graded as 1 if present, and finding of areas with bronchograms were graded with 2 if present. According to the literature, if VPLUS is ≥2 VAP could be identified with 71% sensitivity and 69% specificity (2).

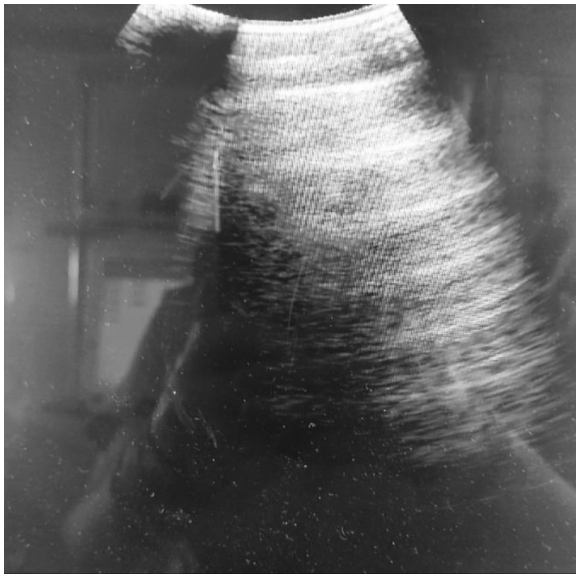

Figure 1. Normal ultrasonographic findings with presence of an A-lines suggest good lung aeration.

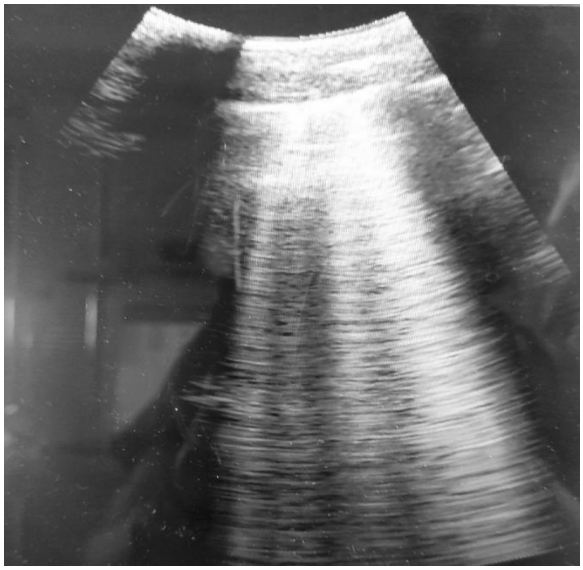

Figure 2. B-profile: well-shaped vertically positioned laser-like lines that show presence of an interstitial syndrome.

Results

We included 18 patients in our study which were in mean value 54.5 years old. Fifteen (83.3%) of the patients included were males. The average value for SpO_2 of the patients included was 94%, average WBC count was 11.7 $x10^9$/L, average percentage of neutrophils was 81.47%, the average value for CRP was 204.17mg/L, while mean body temperature was 38.3ºC. The average in hospital length of stay of all patients included in the study was 63.4 days.

All patients had a positive microbiological finding of the previously undertaken tracheobronchial aspirate. In half of the patients, which means 9 (50%), only one pathogen was isolated, and in the other half of the patients mixed, multiple pathogens were isolated. Gram positive bacteria were isolated only in 2 patients (11.1%), while gram

negative pathogens were found in 18 (100%) of the patients included in the study. Fungi (Candida albicans) were isolated in only 2 (11.1%) out of 18 patients. Acinetobacter species was found in 14 (77.7%) of the patients, as well as Pseudomonas aeruginosa was isolated in 14 (77.7%) of the examined specimens. Only in 2 patients, presence of Staphylococcus aureus was found.

According to the results of the LUS examination, presence of A/B pattern (Figure 3) and B pattern (Figure 2) were found in all examined patients (100%), distributed through the lungs and seen at different sites of examination. Lung consolidations (Figure 4) were seen in 14/18 patients (77.7%), while in 11/18 patients (61.1%) presence of air bronchogram was verified. Pleural effusion (Figure 5) was identified only in 7/18 patients (38.8%).

The average value of total LUSS of all patients examined was 11.05. If we score the severity of de-aeration according to the CLUE Protocol, 3/18 patients (16.6%) experienced severe aeration loss, while in the rest 15/18 patients (83.4%) we found moderate lung aeration loss. The mean LUSS for each of the lungs left and right were 1.17 and 1.06 respectively, showing absence of statistically significant difference in distribution of the pathological findings between both lungs. The average LUSS by segments in the left upper anterior, upper lateral, upper posterior and left lower anterior, lower lateral and lower posterior segment were: 0; 0.05; 0.22; 2.05; 2.05 and 2.7 respectively, while in the right upper anterior, upper lateral, upper posterior, right lower anterior, lower lateral and lower posterior segment were: 0; 0; 0.16; 1.66; 2.05; 2.5 respectively. According to the results for LUSS by segments we derived an average value for the LUSS of the upper segments versus lower segments which were 0.07 versus 2.1 respectively. We did a statistical analysis of the values for mean LUSS for upper versus lower segments with comparison of two means using www.scistat.com according which difference of 2.03 was calculated with 95% CI from 1.44 to 2.61 and significance level $p<0.0001$ suggesting existence of statistically significant difference into distribution of pathological findings in between upper versus lower lung segments, suggesting that pathological findings were predominant in the lower areas examined.

VPLUS was calculated for each patient after performing LUS examination. We found that only 4 patients with VPLUS equal of 2, while the other 14 patients were with VPLUS higher than 2. We've made a statistical analysis of comparison of two means using www.scistat.com where we've compared the mean LUSS of the patients with VPLUS equal of 2 versus the mean LUSS of the patients with VPLUS higher than 2. According to the analysis there was a difference of 3.46 with 95%CI of 0.95 to 5.96 and significance level of $p=0.0099$, which implies existence of statistically significant higher LUSS values in patients with VPLUS >2 versus patients with VPLUS of 2.

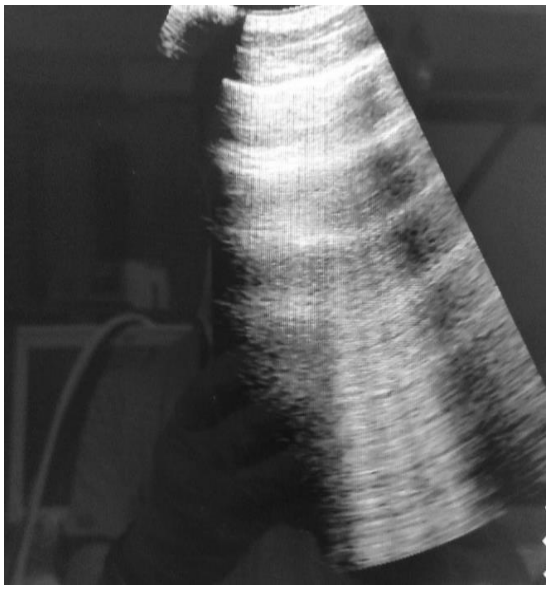

Figure 3. A/B profile: presence of A and B line showing mixed healthy lung parenchyma with parts of the lung with interstitial syndrome.

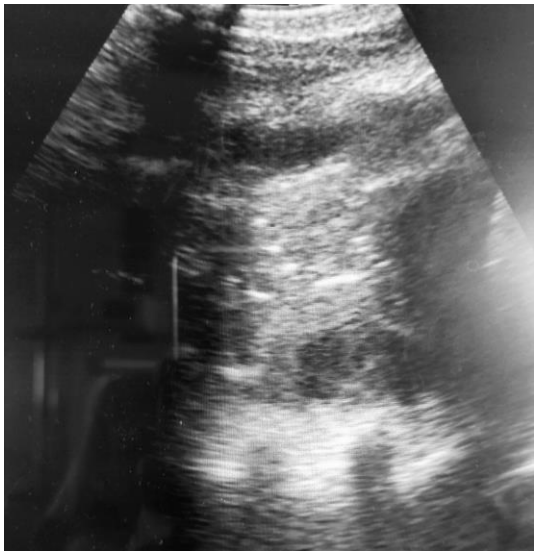

Figure 4. Lung consolidation (tissue like pattern).

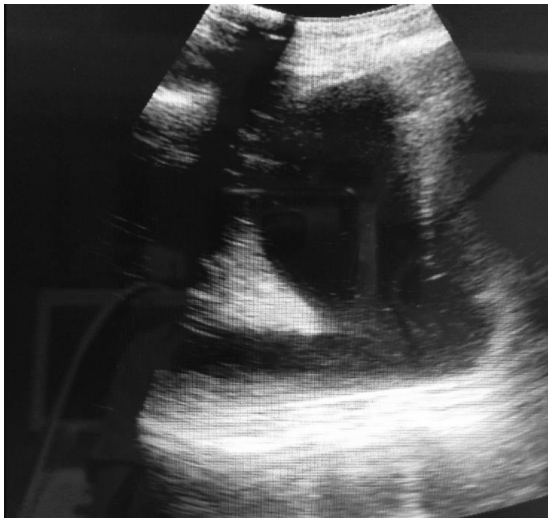

Figure 5. Pleural effusion surrounding the consolidated lung.

Discussion

The risk of developing VAP as nosocomial infection especially rises between 5th and 9th day of the mechanical ventilation, while the probability of VAP occurrence correlates with length of mechanical ventilation (3,4). According to the microbiological findings in our study the gram-negative bacteria were dominantly isolated in18/18 (100%) patients, as it is well described in the literature (5,6). The most frequently isolated gram-negative bacteria were Acinetobacter spp. and Pseudomonas aeruginosa, while the most frequently isolated gram-positive bacteria were Staphylococcus aureus which correlates with the statements found in the review made by Papazian L. et al (6).

According to our results derived by LUS, A/B pattern, as well as B pattern were detected at different segments at the same time in all patients examined. In other words, presence of A-lines as a sign of good aeration mixed with 2-3 B-lines as a sign of beginning of alveolo-interstitial syndrome, as well as finding of more than 3, well-shaped, multiple, separated or even coalescent B-lines were found at different areas of examination at the same time in the same patient which could explain the gradual VAP developing with many different pathological findings representing different stages of VAP in development in one patient at a time. In 77% of the patients, we noted presence of lung consolidations while in 61.1% of the patients the detected consolidations were accompanied with presence of air bronchogram suggesting VAP with 93% sensitivity and 81% specificity when both consolidation and air bronchogram were detected (2). Pleural effusions as a parapneumonic events were detected in 38.8% of the patients. Once more, detecting different type of findings in different segments examined in one patient at a time as above mentioned, probably suggests presence of different stages of VAP in development as it is discussed in the studies of Bouhemad B.et al as well as Mongodi S. et al (2,7). But the presence of subpleural consolidations or lobar consolidations with static or dynamic air bronchograms still are the mainstay of diagnosing VAP by using LUS, especially in patients without previously verified lung damage (8)(9)(10). According to Berlet T. et al the presence of punctiform or linear static either dynamic bronchogram with sensitivity of 100% and specificity of 60% confirms VAP existence (9).

Absence of statistically significant LUSS difference between each of both lungs found in our study, implies that according to distribution of the pathoanatomical changes, VAP is characterized as an infection that affects both lungs simultaneously. But we do find statistically significant difference in the LUSS of the upper segments versus lower examined segments which speaks about obvious difference in distribution of the pathological findings in between compared regions. In other words, pathological findings were predominantly distributed in the lower, posterolateral dependent lung regions, while the upper segments were mostly spared zones at the time of the examination. The statistically significant difference of the LUSS of the upper versus lower segments, did not show only difference in distribution of the LUS findings, but rather difference in their severity also.

We have calculated VPLUS for each patient included in the study, and all of them were fulfilling the criteria for diagnosis of VAP, which according to the literature is VPLUS ≥2 (2)(7). In 4 out of 18 patients we found VPLUS 2, meaning absence of LUS verified consolidation with bronchogram or subpleural consolidation. In the rest of 14 out of 18 patients which were graded as VPLUS 3 or 5, we found presence of subpleural consolidations or lobar consolidation with or without bronchogram. Therefore, we compared the mean LUSS of the group with VPLUS of 2 versus the group of patients where VPLUS >2, and we found existence of statistically significant difference which could imply that patients who have VPLUS of 2 still are not experiencing well defined VAP because of lacking clear presence of consolidations, but those patients rather have Ventilator associated Tracheobronchitis or maybe are in the very early stages when VAP is still in development. According to above discussed finding, we propose re-evaluation of the VPLUS usage as a VAP diagnostic criterion where all patients with VPLUS>2 should be treated as having VAP instead of VPLUS≥2, as mentioned in the literature. On the other hand, the patients with VPLUS 2 should be treated as VA Tracheobronchitis and should be re-evaluated with LUS later.

Conclusion

LUS in daily practice can provide significant data about real time lung events in mechanically ventilated patients, especially those where VAP is suspected. We have concluded that the pathological findings in patients with VAP are distributed in the dependent regions while upper lung segments were spared in both lungs Also, we propose that only patients with VPLUS>2 instead of VPLUS≥2 should be considered as having VAP.

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ORIGINAL ARTICLE

ANALYSIS OF FUNCTIONAL CONNECTOMES MEASURED WITH RS-FMRI IN PATIENTS WITH PARKINSON'S DISEASE WITH AND WITHOUT MILD COGNITIVE IMPAIRMENT

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Abstract

Introduction: Cognitive deficit is a common non-motor manifestation in patients with Parkinson's disease (PD). Over time, about 80% of PD patients develop dementia. The presence of a mild cognitive deficit, which does not interfere with daily activities, represents a high risk for conversion to dementia. There is a growing interest in the potential of neuroimaging techniques to develop non-invasive biomarkers in neurodegenerative disease, specifically in Parkinson's disease.
Objective: The main objective in this study is to find imaging biomarker that will differentiate patients with Parkinson's disease based on their cognitive status.
Methods: Thirty subjects participated in the current study and were grouped into 3 groups. The first group consisted of 10 healthy individuals, used as a control group. In the second group, 10 patients with Parkinson's disease and normal cognitive status were involved. Finally, the third group consisted of 10 patients with Parkinson's disease and mild cognitive deficit. The cognitive status of all subjects was evaluated using neuropsychological tests. Additionally, for all subject rs-fMRI was acquired to reconstruct the functional connectome. The edges from the reconstructed functional connectome were used as classification features to discriminate between the different groups.
Results: It was found that the global node degree of functional connectome is associated with decreased performance in some domains of cognitive function, like memory and executive functions.
Conclusion: The patterns of functional connectivity may be useful in discrimination patients with Parkinson's disease based on the presence of cognitive deficits.

Key Words: *Functional connectomes, mild cognitive impairment, rs-fMRI, Parkinson's disease.*

Introduction

Parkinson's disease (PD) is considered as an expression of diffuse neurodegeneration, which affects the peripheral and central nervous system. PD is a progressive alpha-synucleinopathy, which manifests characteristically with a wide range of appendicular, axial motor symptoms, accompanied in some cases by non-motor symptoms (1,2).

When talking of cognition in PD, the most frequently affected domains are executive function, attention, memory. The term "mild cognitive impairment" (MCI), in a patient with PD, refers to clinically evident cognitive impairment without functional decline (3,4), and therefore associated with a higher risk of developing dementia (5).

Pathologically in PD alpha-synucleinopathy with Lewy pathology develops in predictive stages. According to the leading hypothesis the process starts from the olfactory bulbs and dorsal motor nucleus of the vagus nerve (stage 1), then spreads to the rest of the brainstem nuclei and basal ganglia (stages 2 - 4) and finally to the neocortex (stages 5 and 6). The first signs of motor parkinsonism can be expected in stage 4 and/ or 5, when the loss of nigral dopaminergic cells exceeds the clinical threshold. With involvement of the neocortex, cognitive changes are expected (6,7).

However, during the new era, revision and update of diagnostic criteria for Parkinson's disease which include the cause of parkinsonism are published (8). This also emphasized that a clinical diagnosis of MCI in patients with Parkinson's disease, neuropsychological tests, which cover every domain of cognition, should be used. The most commonly neuropsychological tests that should be used are: Episodic memory - Rey-auditory test for remembering 15 words, with immediate recall and with delayed recall (9); Execution - Frontal Assessment Battery (FAB) (10) Stroop-color-word test (11); Attention- matrices for attention (12); Visuo-spatial domain- redrawing of the Rey-Osterrieth complex figure (13), the clock test (14) and for global cognition - Mini Mental State Examination (MMSE) (15).

On the other hand, finding an imaging biomarker that will differentiate patients with Parkinson's disease based on their cognitive status is still controversial. The functional magnetic resonance imaging (fMRI) is a technique that offers a non-invasive access to brain function, based on the changes of the blood-oxygen level dependent (BOLD) signals, that are indirectly associated with functional brain activity. In the human brain specific functions are localized to different parts of the brain and can be identified by fMRI and mapped at higher spatial resolution (16,17). Two fMRI techniques are used to study the brain function: resting state fMRI (rs-fMRI), and task-based fMRI, both determine different BOLD changes.

In recent years, graph theory has been used to understand the global topological organization of brain networks by applying this approach to rs-fMRI imaging. This study has shown the existence and properties of the *default mode network (DMN)*. It is a neural network of apparent resting brain states. Because DMN was first identified with the resting state, it has been appealing to many to associate DMN's function with the mental state that commonly accompanies a relaxed state, namely daydreaming, mind wandering or stimulus-independent thoughts (19). Furthermore, functional dysconnectivity detected before the occurrence of neuronal death and brain atrophy, has a potential to serve as a sensitive marker of pathological processes (20-22).

Therefore, for the patients with PD it is important to identify characteristic patterns of functional connectivity between specific brain regions with and without mild cognitive decline. So, the objective of this study is to find imaging biomarker (MRI)) that will differentiate patients with Parkinson's disease based on their cognitive status.

Methods and Material

This is a pilot study that was done after approval of the ethics committee of the Faculty of Medicine, University "Ss. Cyril and Methodius", Skopje. The pilot study included 30 patients divided into three groups. Group (PD-nonMCI)* included 10 patients with Parkinson's disease without mild cognitive impairment, group (PD-MCI)* included 10 patients with Parkinson's disease with mild cognitive impairment and control group consisted of 10 healthy individuals. All patients were recruited from the Neurology Clinic in Skopje, while the healthy individuals volunteered to participate in the study. All subjects have signed an informed consent to participate. To be included in the PD groups, patients had to had occurrence of Parkinson's disease starting after the age of 50, stage 1 and 2 of the disease according to the scale of Hoehn and Yahr (23), antiparkinsonian treatment** (24) started at least 4 weeks before entering the study. Patients with Parkinson's disease with diagnosed dementia, psychiatric diseases, medicines that potentially interfere with cognition, including psychotropic substances and anticholinergic drugs, and patients with serious cardiovascular or cerebrovascular diseases were excluded from the study.

Study protocol: all study's subjects underwent standardized study protocol (neuropsychological assessment and Magnetic Resonance Imaging MRI).

Neuropsychological assessment: The same psychological tests were administered to all subjects with Parkinson's disease. The neuropsychological tests were grouped according to cognitive function as follows: 1. Episodic memory - Rey auditory test for remembering 15 words, with immediate recall and with delayed recall; 2. Execution - Frontal Assessment Battery (FAB), Stroop-color-word test; 3. Attention-matrices for attention and 4. Visuo-spatial domain redrawing of the Rey–Osterrieth complex figure, the clock test. All participants were assessed with the Mini Mental State Examination (MMSE).

MRI protocol: All participants were scanned with a 3T SIEMENS Prisma Scanner, using the following multimodal protocol: 1. DTI sequence (TR=12.5ms, TE=89ms, voxel size=2x2x2mm3, gradient direction=30, maximum b value=1000s/mm2), 2. MPRAGE sequence (TR=2200ms, TE=2.26ms, flip angle= 8 degrees, TI=950ms, FOV=256x256mm, voxel size=1x1x1mm3), 3. Rs-fMRI sequence (TR=2550ms, TE=25ms,flip angles=90 degrees, time points=220, voxel size=2.8x2.8x2.8mm3).

Once the images for all subjects were acquired, a quality check was performed by a trained neuroscientist, and only the images that have passed the QC were analyzed. After the QC, the images were preprocessed. The T1w image was processed with freesurfer (ref) to parcellate the brain into 68 cortical and 14 subcortical cerebral gray matter regions using the Desikan-Killiany Atlas (26). Additionally, the rs-fMRI images were also preprocessed to correct for some of the most common artifacts slice timing, motion, and susceptibility-based artifact. The fmriprep (ref) pipeline was used to perform the preprocessing on the rs-fMRI images.

After correcting for the bias in the fMRI images caused by artifacts, both preprocessed T1w and rs-fMRI images were registered to standard MNI (Montreal Neurological Institute) space using a non-linear transformation as implemented in ANTs (27). Then, the average time series of all voxels included in each region were extracted and the partial correlation was computed between the time series of each pair of regions. The individual brain network was defined with 68 cortical and 14 subcortical brain regions as

nodes and 3,362 unique interconnection links. In order to obtain characterization of connectome differences between groups, we looked at the topological organization of the brain network (28, 29).

** Patients were evaluated according to diagnostic criteria for PD (MDS-PD), as well as with neuropsychological assessment for their cognitive status, using multiple neuropsychological tests for different domains of cognition.*

*** For antiparkinsonian treatment was considered antiparkinsonian drugs, various combinations of levodopa, dopamine agonists, catechol-O-methyl transferase inhibitors, monoamine oxidase inhibitors, amantadine. Levodopa equivalent daily dose (LEDD) was estimated in a way suggested by Tomlison et al (24).*

Results

Demographic and Neurocognitive Characteristic

The subjects were evaluated using the MDS-UPDRS. Also, the subjects were assessed for their cognitive abilities using the already named neuropsychological tests. By using the Kruskal-Wallis nonparametric test, we compared the demographic and the clinical scores (Table 1). With a $\chi 2$ test, the gender was compared.

In all three groups, there was no significant difference in demographic characteristics ($p>0.05$). However, there was observed a significant difference between the groups for the MMSE, the tests of episodic memory, executive function and visuospatial abilities, whereas the group with PD and with mild cognitive decline had significant lower scores (Table 1).

Table 1. Demographic and cognitive outcomes.

	Control group (n=10)	PD-nonMCI (n=10)	PD-MCI (n=10)	p-value
Age	63.3 (10.3)	63.6 (9.5)	66.5 (11.1)	0.404
Gender (female)	7	9	9	0.796
Hand dominance (right)	10	10	10	0.495
MDS-UPDRS	-	14.6 (7.2)	16.8 (11.0)	0.358
LEDD	-	5.9 (4.0)	10.1 (7.2)	0.013
MMSE	29.7 (0.5)	29.4 (0.7)	28.6 (1.5)	0.001
Episode memory	-0.01 (0.56)	-0.06 (1.04)	-0.91 (0.86)	<0.001
Execitive function	0.04 (0.64)	-0.02 (0.65)	-1.69 (1.80)	<0.001
Attention	0.06 (0.75)	0.13 (0.68)	0.31 (0.75)	0.366
Visuospatial score	-0.02 (0.8)	-0.23 (0.62)	-1.53 (1.05)	<0.001

MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; LEDD, Levodopa equivalent daily dose; MMSE, Mini-Mental State Examination; PD-nonMCI, Parkinson's disease-non-Mild Cognitive Impairment; PD-MCI, Parkinson's disease-Mild Cognitive Impairment.

Imagining and fMRI Data

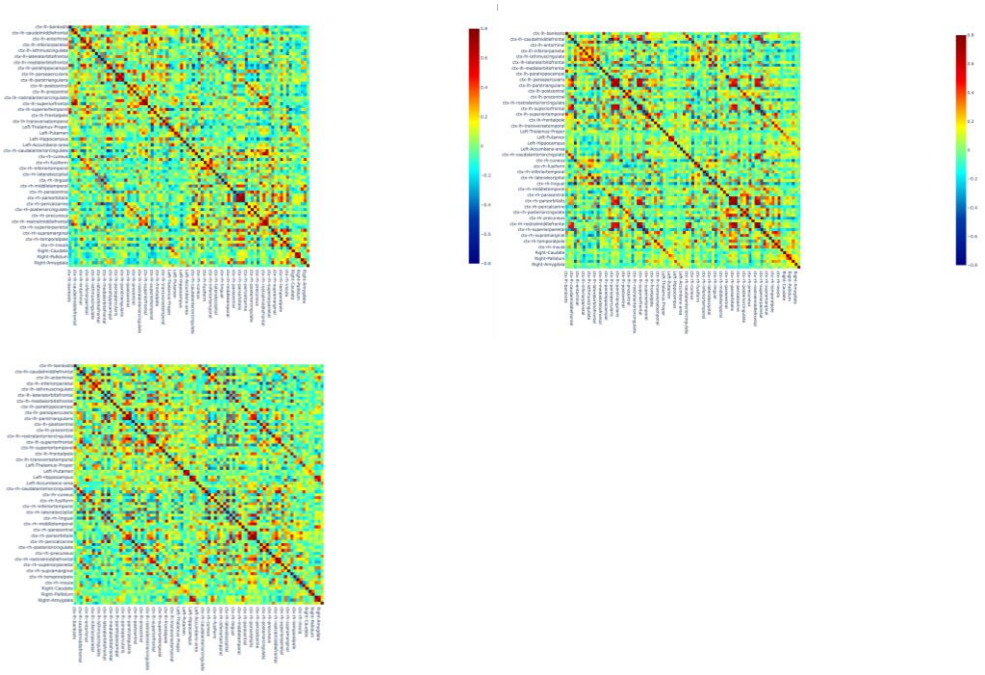

Figure 1. Global metrics and intersubject correlation among different scans at different connectivity densities. Functional connectivity networks at different connectivity densities. For each scan and each individual, three essential properties of the voxel-based functional networks were calculated at different connectivity densities, including the mean functional connectivity strength (FCS), the largest component size (LCS) and the number of isolated nodes.

The comparison of connectomes between the groups was done by looking at the average nodal strength. We found a significant reduction of the average connection strength in patients with PD-MCI versus the control group ($p<0.01$) and in patients with PD without MCI versus the control group. No significant difference between PD without MCI with MCI (Pearson's correlation coefficient).

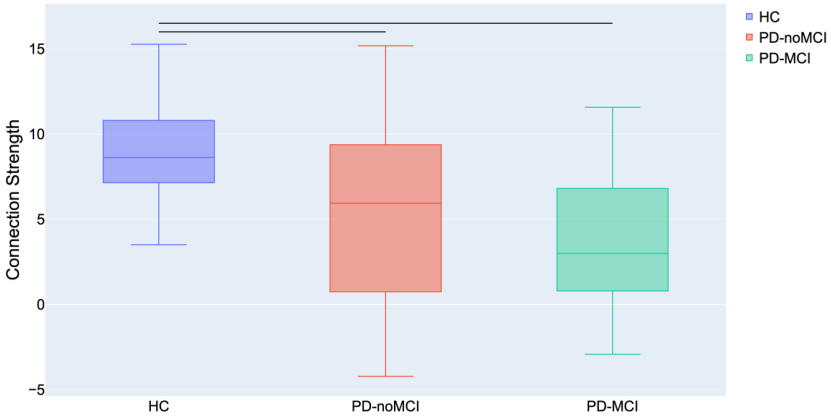

Figure2. The Pearson correlation coefficients between any pairs of the scans across subjects on each metric.

Discussion

Using functional connectomes, we achieved high accuracy in classifying Parkinson's disease patients with and without mild cognitive deficit. Even though our study included small number of patients, the results suggest that functional connectivity patterns can be used to determinate and differentiate Parkinson's disease patients based on their cognitive status. In this study, significant changes in connectivity were observed in patients with Parkinson's disease especially in the mild cognitive deficit (PD-MCI) group. This is consistent with findings from previous studies even though different numbers of patients are used in both studies (30,31).

With new neuroimaging biomarkers sensitive to cognitive impairment in neurodegenerative disease, scientists may have the ability to predict cognitive decline, to identify at-risk patients who could benefit from potential early treatment (32).

Neuroimaging techniques such as fMRI have traditionally been used to study the pathophysiology of brain disorders by comparing patient groups with healthy groups (33,34). A growing number of studies have attempted to develop prognostic/ diagnostic tool through neuroimaging techniques. To become clinically useful, findings from such studies need to demonstrate reproducibility and generalizability (35,36).

However, many fMRI studies have failed to be replicated. The use of non-standardized sequences (37), the lack of standardization of the steps in image preprocessing (38), as well as flexibility in data collection, analysis and reporting of results (39), are some potential culprits for this problem in replication.

In our study, we assessed the generalizability of our findings using an independent validation sample. The validation dataset was obtained using identical fMRI acquisition parameters, image preprocessing protocol and analytical methods.

Study has limitations. This is a small sample of subject size, so the results even though were elaborated and corrected adequately from statistic expert, we must consider that Parkinson disease is not the most frequent disease and additionally in this study diagnostic tools are not completely standardized, and this is the first study from the Republic of North Macedonia that functionally encopresis so many variables. This study needs and opens a door for larger randomized study to determine the early recognition of patients with PD and functional brain deficit, to have better treatment outcome in these patients.

Conclusion

From the analysis, it was shown that multivariate resting-state functional connectivity models can be used to differentiate Parkinson's disease patients according to their cognitive status, using a fMRI. The resulting data obtained from functional connectomes, have the potential of sensitive biomarkers for the extent of cognitive impairment in patients with Parkinson's disease. Still larger studies are needed.

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REVIEW ARTICLE

MANAGEMENT OF SEVERE TRAUMATIC BRAIN INJURY IN PEDIATRIC PATIENTS

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Abstract

Traumatic brain injury is the leading cause of death and disability in children. Pediatric TBI is associated with several specific characteristics for the pediatric population that differ from adults. These differences are due to anatomical and physiological differences related to age, the mechanism of injury and difficulties in neurological evaluation. The specific pathological response to TBI results in distinctive accompanying neurological symptoms. Advances in technology and diagnostic methods have made diagnosis, treatment and prevention of complications easier. Better knowledge of the pathophysiology of traumatic brain injuries in childhood will provide a better basis for clinical management and treatment. This effort summarizes the results of recent relevant studies on this topic. Additionally, a clinical algorithm for the management and treatment of TBI in the pediatric population will be presented in accordance with the latest published data.

Key words: *Algorithm, clinical management, pathophysiology, pediatric population, traumatic brain injury.*

Definition

Traumatic brain injury (TBI) is defined as an injury to the head and brain caused by an external force that leads to impairment of brain function.

Epidemiology

According to the Centre for Disease Control and Prevention (CDC), nearly half a million children aged 0 to 14 admitted to emergency centers are due to TBI; 10% of the injuries are with a severe clinical picture (1). Mortality is higher in children under 4 years of age compared to those of 5 to 14 years of age. Head injuries are more common in male children and there is a 4 times higher risk of death compared to female children (2). The mechanism of injury depends on gender and age. According to the CDC, the most common cause of TBI is a fall from a height, then blunt force trauma, motorcycle accidents including bicycle accidents, fights, self-harm and sports injuries (3).

Anatomical and Physiological Characteristics of TBI in Pediatric Population

Children are more susceptible to TBI due to a larger head in relation to the body and weaker cranial bones, which provide less protection to intracranial structures. Additionally, they have a smaller subarachnoid space compared to adults, so a small increase in volume will lead to a large increase in intracranial pressure and incarceration. Less myelination in children leads to increased sensitivity to inflammatory mediators (4).

The cerebral metabolic rate of oxygen consumption is higher in children (5.2mL/100 gr/min of brain tissue) compared to adults, which makes them less tolerant to hypoxia (5). Autoregulation in neonates is maintained within a narrow mean arterial pressure (MAP) in range of 20–60mmHg. Beyond those limits, the relationship between Cerebral blood flow and systemic blood pressure is parallel. As a result, neonates are susceptible to brain ischemia and intraventricular hemorrhage (6).

Pathophysiology

The consequences of neurotrauma depend not only on the primary, but also secondary injuries. Primary injuries are the result of the effect of direct force on intracranial structures and happen at the moment of impact. They lead to disruption of cell membranes and disturbance of the electrolyte balance. Elevation of intracellular calcium leads to activation of N-methyl-D-aspartate (NMDA) receptors, cell depolarization and accumulation of oxygen radicals that cause cell death. Secondary injuries, on the other hand, occur over minutes or days after the primary injury and are the result of chains of vascular, cellular and biochemical changes which lead to more pronounced inflammatory changes, edema, ischemia and necrosis (7).

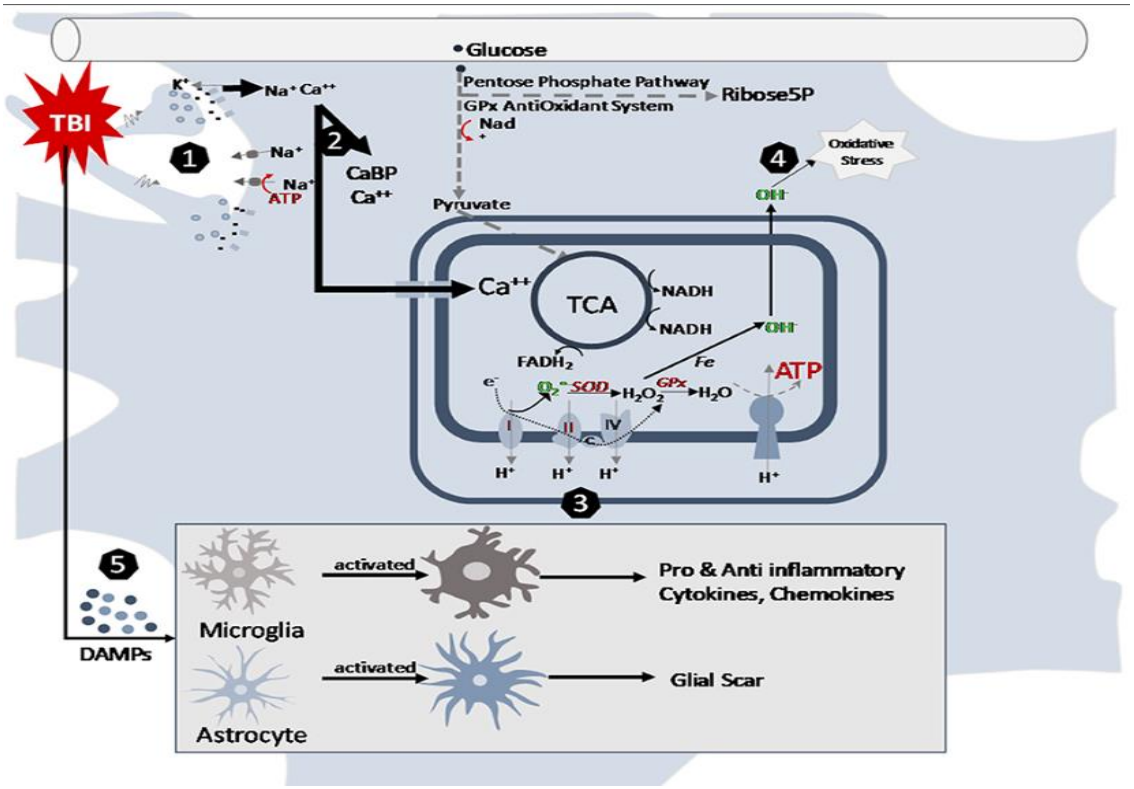

Figure 1. Cellular pathways altered by traumatic brain injury in the juvenile brain (7).

Classification

Multiple classifications of head trauma in children can be found in the literature. This is the result of diverse causes and pathophysiologic mechanisms of different TBI that are not fully understood. Classification of TBI can be made according to severity and mechanism of injury. According to physical mechanism TBI can be classified as blunt and penetrating, and also as primary (when a direct hit or indirect-acceleration deceleration forces make the damage), and secondary which is the result of cellular and molecular damage, vasogenic and cytogenic edema (8). Another method of classification is through pathoanatomic characteristics. TBI can be divided into focal which is commonly the result of direct hit, and diffuse, which is due to acceleration deceleration forces. Focal injury can be contusion, hemorrhage, subarachnoid hemorrhage, subdural and epidural hematoma. Based on severity TBI can be classified according to the Glasgow Comma Scale score. GCS from 13 – 15 is classified as mild TBI, 9 - 12 as moderate TBI and 3-8 as a severe TBI (9). Classification of TBI can also be based on the duration of loss of consciousness. Children with 0 - 30 minutes of loss of consciousness can be classified as mild TBI, those between 30 minutes and 24 hours as moderate TBI, children with loss of consciousness more than 24 hours as having severe TBI.

Primary head injuries can be extra-axial, intra-axial and vascular. Examples of extra-axial head injuries are epidural and subdural hematoma, subarachnoid hemorrhage and intraventricular hemorrhage. Intra-axial injuries are contusion and cerebral hematoma and diffuse axonal injury. Vascular injuries can be pseudo aneurysm, dissection and different types of fistulas.

Secondary head injuries can be subdivided into acute and chronic. Acute injuries are brain edema, herniation, infarction and infection. Chronic injuries are for example hydrocephalus, cerebral tissue destruction and cerebrospinal fistula.

Diagnostics

The gold standard in the diagnosis of acute brain injury is Computed Tomography. But CT is also associated with radiation. Cancer incidence is significantly higher in children and adolescents who are exposed to CT (10). The physician needs to decide which child needs the CT scan of the brain. Several clinical decision-making tools (CHALICE, PECARN and CATCH) have been proposed and validated to help the decision-making process (11). Observation studies have shown that PECARN has the best sensitivity[ii]. Another limitation of the CT scan consists in its low sensitivity in diagnosing Diffuse axonal injury (DAI). The patients with a Diffuse axonal injury, initially have normal CT scan. The findings of the initial CT scan do not correlate with the clinical picture where significant neurological symptoms and signs of elevated intracranial pressure are present. The subsequent CT scan is often positive and shows the secondary injury. On the other hand, MRI has greater sensitivity and specificity for DAI (12).

Clinical Picture

In the pediatric population multidisciplinary team approach is needed for effective clinical management. The management is through primary and secondary assessment. The primary assessment is conducted according to the A, B, C, D, E approach followed by a secondary assessment. During the secondary assessment, a history of comorbidities and diseases that are of interest to the patient is also taken. The Glasgow Coma Score is a commonly used tool for assessing consciousness. A modified version of the GCS for assessing consciousness in infants and children is shown in Table 1 (4).

Table 1. Modified Glasgow Coma Scale for infants and children.

	Child	Infant	Score
Eye opening	Spontaneous To speech To pain only No response	Spontaneous To speech To pain only No response	4 3 2 1
Best verbal response	Oriented, appropriate Confused Inappropriate words Incomprehensible sounds No response	Coos and babbles Irritable cries Cries to pain Moans to pain No response	5 4 3 2 1
Best motor response*	Obeys commands Localizes painful stimulus Withdraws in response to pain Flexion in response to pain Extension in response to pain No response	Moves spontaneously and purposefully Withdraws to touch Withdraws to response in pain Abnormal flexion posture to pain Abnormal extension posture to pain No response	6 5 4 3 2 1

In children with severe TBI, neurological deficit is also present initially. Symptoms are divided into early and late. Early symptoms (vomiting, headache, change of consciousness, neurological deficit, respiratory irregularities and convulsions) and late symptoms (Cushing reflex, paralysis of the III and IV cranial nerves, decerebrations and decortications and visual disturbances).

Factors that are associated with poor prognosis of pediatric patients with TBI are shown in Table 2 (11).

Table 2. Predictors of outcome in pediatric TBI are shown in the following table (11).

Predictors
Age
High Injury Severity Score (ISS)
GCS ≤7
Hypoxia (PaO2<60 mmHg)
Hypotension
Hyperventilation (PaCO2<35 mmHg)
Hyperglycemia (glucose >250 mg/dL)
Hyperthermia (>38°C)
Requirement for blood transfusion (≥20mL/kg)
Intracranial hypertension (ICP >20mmHg)
Cerebral perfusion pressure <40mmHg

Airway Management Oxygenation Sedation and Ventilation Strategies

GCS≤8 is an indication for immediate endotracheal intubation and ventilation for airway protection, and management of elevated ICP. But the pediatric airway management represents a particular challenge. This is because of the anatomical and physiological differences compared to the adult airway. Younger children have a prominent occiput, so a pad placed under the thoracic spine provides neutral alignment of the spine. In this way, excessive flexion that may occur in the supine position is avoided. Additionally, because of uncertainty in the presence of concomitant craniospinal injury (CSI), cervical immobilization is necessary until it is excluded by clinical and radiological investigations to avoid compression of the spinal cord and worsening of neurological injury. It is best to use a combination of several techniques to stabilize the cervical spine, such as a spine board, forehead strap, sandbags. For children over 6 months of age, a rigid cervical collar can be used. The presence of blood and regurgitated masses in the mouth, injuries of the larynx and pharynx and intracranial hypertension, can also cause complications in airway management. Inadequate assessment of respiratory status can lead to inadequate resuscitation, deterioration and subsequent hypoxia. All patients with TBI who require endotracheal intubation are assumed to have a full stomach and thus undergo rapid sequence induction. Extreme care should be taken during laryngoscopy and intubation in order to avoid neck displacement. A video laryngoscope can also be used to prevent hemodynamic instability and ICP elevation. Nasotracheal intubation should be avoided if there are basilar skull fractures. Hypoxemia (PaO2<60mmHg) has deleterious effects in children with TBI because of the linearly increase of cerebral blood flow, cerebral blood volume and intracranial pressure. It was previously shown that it is an independent predictor of mortality. Therefore, all available measures should be taken to prevent it and correct it. Although in adults positive end-expiratory pressure (PEEP) has been shown to increase intracranial pressure (ICP), in children the optimal PEEP is not established. Hyperventilation can be used to decrease ICP and delay possible herniation, but only as a temporary measure until definitive management because it leads to cerebral vasoconstriction, reduced cerebral blood flow CBF and cerebral hypoxia (13). If clinicians decide to hyperventilate the pediatric patient, advanced neuromonitoring should be used to monitor for possible cerebral ischemia. The patients with TBI are at risk for lung injury, which leads to the use of lung protective ventilation.[iii] Studies do not show reduction in mortality or length of mechanical ventilation in these patients. The cornerstone is still to maintain normocapnia and prevent hypoxia (14).

When managing the airway of child with the appropriate sedative agent and its dose should be carefully considered in order to facilitate airway intervention, while maintaining both mean arterial pressure (MAP) and cerebral perfusion pressure (CPP) (15). Benzodiazepines, propofol etomidate, ketamine, have all been used and studied in patients with TBI. Their advantages and disadvantages are well documented. No single sedative agent has been shown to be better for adult patients with severe TBI, when compared to functional recovery, management of increased ICP or mortality (16). Therefore, in children with known adrenal insufficiency, etomidate may the preferred agent. For hemodynamically unstable patients, ketamine can be used, and in patients where benzodiazepines and propofol are used, care must be taken to prevent and correct hypotension.

Circulatory Support Coagulation and Transfusion

TBI in children is often accompanied by hypotension and anemia, which as hypoxia, is also associated with poor outcome because of reduced oxygen delivery. There are several mechanisms for hypotension such as acute traumatic coagulopathy (ATC), internal and external hemorrhage and neurogenic hypotension. Acute traumatic coagulopathy is the direct effect of trauma and can be exaggerated with hemodilution with fluid resuscitation, hypoperfusion, hypothermia, acidosis and hypocalcemia. Risk factors for ATC in children include GCS ≤8,

increasing age, higher disease severity and brain contusion/laceration (17). If ICP monitoring is not used and there is a suspicion of its elevation, it is recommended to maintain slightly elevated blood pressure in order to sustain adequate cerebral perfusion pressure (CPP) (18). For that purpose, Isotonic crystalloid solutions are used the most often for resuscitation. Hypertonic saline has the advantage of increasing arterial pressure with a small volume in patients where fluid overload is a concern. A transfusion of red blood cells is recommended if hemoglobin level is below 8.0g/dl in children with TBI (19). In cases where adequate mean arterial pressure cannot be achieved with fluids, only concomitant intravenous vasopressors like noradrenaline and phenylephrine should be initiated (20).

Glycemic Control, Nutrition and Steroids

Hyperglycemia is another predictor for poor outcome in pediatric TBI. Recent studies show that the presence of hyperglycemia in the first 24 hours after admission is associated with increased length of stay in intensive care, increased duration of mechanical ventilation and increased mortality (21). Causes of hyperglycemia after TBI include increased gluconeogenesis and glycogenolysis, activation of the autonomic nervous system, activation of inflammatory cytokine pathways, pituitary and adrenal disfunction. Therefore, Dextrose as a solution for resuscitation should be avoided, except in established hypoglycemia. Hyperglycemia should be treated with caution because of the potential for hypoglycemia and neurologic sequelae if not recognized and treated. Given the possible negative effects of both hypo and hyperglycemia, Intermittent monitoring of blood glucose intraoperatively is recommended (21). Caloric expenditure in these patients may be double the expected resting energy expenditure. Increased caloric needs are result of increased temperature, muscle tone, GCS and measurement time associated with the injury. There is a significantly higher mortality rate as a result of undernourishment in the two-weeks' post-injury period compared to receiving full nutrition for 7 days. The patients with adequate nutritional support have been shown to have less infections and complications. There for nutritional support should start slowly during the first 48 hours with the aim to achieve full nutritional support by day seven from trauma (22). Use of steroids is accompanied by complications like hyperglycemia, infection, bleeding from the gastrointestinal tract. A large multicenter study showed no benefit of their use (23).

Temperature Control

Recent studies have shown no benefit from moderate hypothermia (32–33°C) versus normothermia in children with severe TBI (24,25). According to the recommendations, moderate hypothermia begins within a time frame of 8 hours after severe TBI lasting 48 hours, and can serve as a neuroprotective measure, as well as for refractory intracranial hypertension. A warming rate greater than 0.5°C should be avoided because it is complicated with cardiovascular instability, increased ICP, coagulopathy and sepsis. Hyperthermia, on the other hand, worsens the prognosis after TBI by increased metabolic demand, lipid peroxidation, inflammation and seizure reduction (26).

Intracranial Pressure and Neuromonitoring

Normal intracranial pressure in children and newborns ranges from 3-7mmHg and 1.5-6 respectively (27). Elevation of ICP can be the result of traumatic intracranial process, vascular swelling and/ or cerebral edema. The recommendations state that immediate intervention is needed at intracranial pressure (ICP) >20mmHg. Values of cerebral perfusion pressure above 43, 54 and 58mmHg in children aged 2-6, 7-10, 11-16, are associated with a better outcome (28). Intracranial pressure monitoring may be considered for children with abnormal KTM and initial GCS <8. Despite the recommendations, ICP monitoring is used only in 7.7 to 55% of children with severe craniocerebral injury with GCS 3. In those cases, an improvement in the outcome was also observed, but with a significantly longer stay in the hospital, more days on a respirator. Common measures that are used to reduce ICP

are placing the head in a position of 30°, sedation and analgesia, intubation and controlled mechanical ventilation, CSF-drainage, diuretics, osmotherapy (mannitol, HS), controlled hyperventilation. In refractory cases, barbiturate coma and moderate hypothermia, surgical decompression may be helpful (29).

Prophylaxis of Convulsions

Post-traumatic convulsions in childhood occur in 19% of the cases. Most often in the first 24 hours after the injury. Their consequences are multiple such as deepening and prolongation of hypoxia, increased release of excitotoxic neurotransmitters, increase in oxygen consumption rate and ICP and fluctuations in systemic blood pressure. Age under 2 years, nonaccidental trauma, GCS<8, skull fracture, subdural hematoma, are associated with occurrence of seizures in the first 7 days after injury. The use of phenytoin is recommended for the prevention of early post-traumatic convulsions (30).

Conclusion

Neurotrauma continues to be a leading cause of mortality in pediatric patients worldwide. More and more children are at risk of traffic accidents as passengers, pedestrians and cyclists. Children have a unique pattern of injury and response to it. It is necessary to move towards a more sophisticated algorithm in the care of such patients based on the unique pathophysiology of each individual.

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REVIEW ARTICLE

NATURAL KILLER CELLS A PRIMARY NATURAL DEFENCE AGAINST TUMOR SPREAD: CAN WE HELP WITH THE CHOICE OF ANESTHESIOLOGY TECHNIQUE?

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Abstract

Natural killer (NK) cells are a part of the innate immune system and were named after their ability to kill tumor cells without prior stimulation. They are presenting a frequency of around 5% in the blood, and even in such small numbers they are able to recognize and lyse virally infected cells and tumor cells. Morphologically, NK cells belong to the family of granular lymphocytes, while the phenotypic formula of these large cells is CD3−CD56+. CD16 is the most important surface receptor of the NK cells in the phase of the initiation of immune response and increased cell activity. Also, as a part of granular lymphocytes family, the NK cells contain multiple granular structures with either perforin or granzymes, that exhibit
cytotoxic characteristics. The effect on different anesthetic techniques on the immune response to infection or the presence of tumor cells, is attracting increasing attention of the science. The results of some animal studies have identified some anesthetic techniques and/or anesthetic drugs that can reduce the incidence of metastasis during breast cancer surgery. Propofol and local anesthetics are the most emphasized in this manner. Regional anesthesia techniques are well known for their ability to attenuate the stress response to surgical trauma and to prevent negative effects on the immune function in the perioperative period. Fentanyl on the other hand has negative both short- and long-term effects on the activity of NK cells, while in some animal model's tramadol was shown to have protective effect with decreased incidence of metastasis during carcinoma surgery.

Key words: *Natural killer cells, tumor dissemination, anesthetic techniques.*

Introduction

The perioperative period is considered the critical period in cancer surgery because various factors can influence whether disseminated tumor cells will lead to metastases formation or they will be eliminated by the immune system. Several factors that can influence the perioperative immune function either in the direction of immunosuppression or preservation of innate immunity are of ongoing research interest. The association between the anesthetic technique and cancer recurrence was investigated in a population of patients with both breast and prostate cancer, but the results are still not conclusive enough. The results of some animal studies have identified some anesthetic techniques and/ or anesthetic drugs that reduce the

incidence of metastasis during breast cancer surgery. Propofol and local anesthetics are the most emphasized in this manner. As it is not yet clear what is the exact mechanism how these techniques are successfully preserving the innate immune function, the main hypothesis is that local anesthetic techniques have the effect of reducing the inflammatory reaction of the host to the stress caused by operative procedure (1).

When they were first discovered in 1960's it was believed that **the natural killer (NK) cells** are just an annoying artefact in the background activity of the cytotoxicity assays. These cells came into spotlight as the literature gained increasing knowledge of their role in the defensive actions against viral infections and malignant processes. Recently some clinical studies started to investigate the success of including the NK cells in immune based therapies in the treatment of malignancy. These lymphocytes are a part of the innate immune system and were named after their ability to kill tumor cells without prior stimulation, but they are also playing an important role in the immune defense against various threats. In terms of their vast potential to defend against different infections and against dissemination of tumor cells, NK cells are currently defined as founding members of innate lymphoid cell family (ILC) (2). They are presenting a frequency of around 5% in the blood, and even in such small numbers they are a part of the first line defense, able to recognize and lyse virally infected cells and tumor cells (3). Morphologically NK cells belong to the family of granular lymphocytes, while the phenotypic formula of these large cells is **CD3−CD56+**. NK cells can be subdivided into 2 groups: **CD16+CD56^{dim}** subgroup that consists of biggest number in circulation and the relatively immature **CD16−CD56^{bright}** subgroup. Mature NK cells have an array of known receptors that can trigger their effector functions when they are stimulated either alone or in combination (2). As with most of the immune active cells, the activity of NK cells and their potential is controlled by the interplay of signals provided by the receptors on their surface. The states of either full activation or the state of inhibition are both achieved by complex balance of signals on the cell surface. This is providing the necessary tight control in order to avoid self-induced damage by NK cells to normal cells (3). Using these immune receptors, NK cells can identify and attack enemy cells without previous memory, which is providing the first line defense against tumors and microbial agents. **CD16 is** the most important receptor of NK cells in the phase of the initiation of immune response and increased cell activity**. NKG2D** is another well-studied and important receptor, with numerous referrals in the literature. The presence of abnormal cells is momentarily triggering the NK cells effector functions, including cytotoxicity, cytokine production and proliferation. Contrary to other immune cells that require time for the activation and initiation of cytolysis, the response of NK cells is prompt and quick. This is offering new perspective in the area of development of new modalities of immune therapy (4). As part of granular lymphocytes family, the NK cells contain multiple granular structures with either perforin or granzymes, that exhibit cytotoxic characteristics. Upon the contact with the target cell, NK cells are creating synapse like contact with the stressed cell by which the specific granules are excreted, and the final kill is achieved. Additionally, NK cells are able to kill tumor cells by using molecules in the tumor necrosis factor (TNF) family, whose main role is the creation of cell connections that will result in lysis of the target cell. Recently, the secretory function of NK cells has come to the attention of the researchers. The secretion of cytokines or other chemokines is part of the activation process of the NK cells and has the role of controlling the further immune actions. NK cells are the best known for the secretion of IFN-γ

and TNF, as well as for production of IL10 and other growth factors and chemokines. The main purpose of this secretory activity of NK cells is the deepening and enhancing of the immune response by proliferation of other immune cells and their aggravation on the site of inflammation (5). Tumor cells, on the other hand, have developed various adaptive mechanisms to disturb the actions of the NK cells and to escape elimination. Moreover, tumor cells have the ability to locally secrete various factors that are altering NK cells and can decrease their cytotoxic potential.

Originally when they were first discovered, it was thought that NK cells were solely effector cells without memory. Current knowledge gained from clinical studies, on the other hand, implies that NK cells during the process of maturation can undergo some form of training in order to establish certain memory and to further increase their cytotoxicity (4). The data from in-vitro studies are showing that after the initial reaction to infection or tumor, NK cells are able to produce prolonged immune function simultaneously with the adaptive part of the immune system. The improved functional capacity of mature NK cells is the "consequence" of their initial process of initiation and activation. The term "immune training" in the case of NK cells refers to the acquisition of memory like properties after being sensitized with cytokines. Additionally, NK cells are enhancing their production of interferon (IFN-γ) upon restimulation, resulting in increased cytotoxicity towards target tumor cells. This is the base for development of specific cancer immunotherapy that is currently in phase 2 clinical trials for the treatment of leukemias, but also some solid malignant tumors (4).

This is also mirrored during acute virus infection, when naive NK cells undergo rapid metabolic reprogramming into potent effector NK cells (3). Several cytokines, including **IL-2, -10, -12, -15, -18 and -21 and type I IFNs,** are involved in the enhanced NK cell proliferation and effector functions during infection and inflammation. After being released by phagocytic cells and B lymphocytes, Il12 plays an important role in enhanced cascade production of other cytokines, in the first place the release of IFN-γ and TNF by NK cells. When released early during inflammation, IL12 is the activator of NK cells but also of the other T lymphocytes with the effect of increasing their activity and proliferation (6). The enhanced production of IFN-γ has central role in the differentiation of Th1 lymphocytes that will be vital in the defense against the dissemination of tumor cells. The initial reports regarding the role of NK cells in tumor elimination were in the context of the cellular infiltration and exerting direct cytotoxicity of primary tumors. However, the later reports showed that this action comprises only a minor population, raising questions about their true importance. Also, the results from some in-vitro studies have shown that NK cells are mostly present in the circulation and in smaller numbers within solid tumors, which can indicate that they are more important in the elimination of the misplaced tumor cells and the prevention of the development of metastasis (2). NK cells were first implicated in **tumor immunosurveillance** in the 1980s, when a higher incidence of cancers was reported in human population with defective NK cell function caused by certain genetic disorders (2). Some authors reported that in patients with malignancy the measurements showed reduced activity and smaller number of the NK cells compared to healthy population (3).

The effect of different **anesthetic techniques** on the immune response to infection, inflammation or the presence of tumor cells, is attracting increasing attention of the science. Considering that surgery is

"golden standard" in the treatment of the early-stage malignant disease, anesthesiology techniques are coming into spotlight regarding their potential to shape immune defense against tumor cells dissemination. Opioids are the most used analgetic agents during surgery, but with conflicting effects on the immunomodulation. Fentanyl has negative both short- and long-term effects on the activity of NK cells, while on the other hand, in animal models tramadol showed protective effect with decreased incidence of metastasis during carcinoma surgery. However, we need to emphasize that inadequate perioperative pain treatment strategy results in a stress reaction in the host's environment which suppresses cell-mediated immunity (1). Other anesthetic drugs were proven to have negative impact on the activity of NK cells in the perioperative period during breast cancer surgery which can result in dissemination of the malignancy. Ketamine and volatile anesthetics are in this group of anesthetics. Propofol is the most popular anesthetic agent in cancer surgery, mostly due to its positive pharmacodynamic properties, but also because of the reports that doesn't produce negative impact on the activity of NK cells. In a mouse model, the administration of propofol caused reduced spread of the tumor and increased defensive role of the T lymphocytes. Another positive effect is the decreased levels of PGE2 which is of clinical significance if we know that prostaglandins have receptor mediated effect of down regulation of NK cells activity. Regional anesthesia techniques are well known for their ability to attenuate the stress response to surgical trauma, and to prevent negative effects on the immune function in the perioperative period. The main benefit of spinal anesthesia and the regional nerve blocking techniques is the avoidance of the volatile anesthetic and either elimination or significant decrease in the required dose of fentanyl. Indirectly we can expect a positive effect on the Th1/Th2 ratio and an increase in the NK cells cytotoxicity. In-vitro studies confirmed that regional regimen of anesthesia treatment results in significant decrease in the incidence of metastasis after operation due to malignancy (1).

Conclusion

At the end, we need to emphasize the importance of the immune defense against spread of the tumor cells in the perioperative settings. The role of NK cells in the direct elimination of the displaced tumor cells is confirmed, however the signaling pathways and the factors that are either enhancing or disturbing NK cells cytotoxicity are yet to be investigated and understood. The influence of different anesthetic techniques on the balance of the immune system during operation offers new fields of interest for clinical studies and investigation.

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CASE REPORT

THE ROLE OF INTRAOPERATIVE ECHOCARDIOGRAPHY IN ANESTHETIC MANAGEMENT OF A COMPLEX ABDOMINAL AORTIC ANEURYSM REPAIR

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Abstract

This case presents highlights of the role of intraoperative echocardiography in the successful management of a 65-years-old male scheduled for abdominal aortic aneurysm (AAA) repair. The patient was presented with an abdominal aortic aneurysm with multiple comorbidities and recent myocardial infarction with post stenting hemopericardium, making the anesthetic management for the surgical intervention challenging. Intraoperative echocardiography played a crucial role in establishing decisions about the treatment and guiding therapy for ensuring a favorable outcome. This report emphasizes the significance of intraoperative echocardiography as a real time monitor of hemodynamics in enhancing patient's safety and favorable clinical outcomes during high-risk surgical procedures.

Key Words: *Abdominal Aortic Aneurism Repair, Intraoperative echocardiography. Point of care, Ultrasound.*

Introduction

Abdominal aortic aneurysm (AAA) is a serious vascular condition characterized by the aortic wall weakening and dilation of the abdominal aorta greater than 3cm (1). AAA frequently demands surgical repair which timing depends on aneurism dimensions and symptomatology. If the AAA is left untreated, it poses a high risk of rupture, leading to life-threatening hemorrhage with possible death. AAA is related

to significant cardiovascular morbidity and mortality, while most of the patients could be asymptomatic until rupture occurs when the overall mortality is up to 80% (2,3). Surgical intervention is often required to prevent rupture and maintain patient's well-being. Some studies have shown that perioperative mortality for AAA surgical repair is 4-8%, while developing a major perioperative adverse event including myocardial infarction, pneumonia, cerebrovascular ischemia, kidney injury, deep vein thrombosis and colonic ischemia could be met in stunning 15-30% of the cases (4) making this intervention not only surgical, but rather a bigger challenge for the anesthesiologist. Therefore, AAA repair in complex cases demands careful anesthetic evaluation and vicious perioperative management, particularly when patients present with concurrent cardiovascular issues.

Case Presentation

A 65-years-old male with a significant medical history of hypertension, a heavy smoking habit (2 packs per day) and a recent diagnosis of acute coronary infarction was scheduled for AAA repair. Preoperative imaging revealed an infrarenal abdominal aortic aneurysm measuring 11cm in length and 4.5cm in diameter, with circumferential mural thrombosis and peripheral hyperdensity, indicating a high risk of rupture. Fourteen days before surgery, the patient complained of chest pain and breathing difficulties, prompting an electrocardiogram revealing occurrence of an acute myocardial infarction demanding coronary angiography and subsequent stenting. The angiography revealed severe stenosis in the left anterior descending artery (95%) and left main (99%), which necessitated the placement of two stents. Unfortunately, a coronary artery rupture occurred during the stenting, and the patient has developed a subsequent hemopericardium. Echocardiography has demonstrated pericardial effusion and presence of fresh coagulum inside pericardial sac, warranting further evaluation. A second coronary angiography the next day showed no extravasation of contrast, but the pericardium was observed to be thickened and filled with blood without any influence of the cardiac filling and contractility. The patient was treated with Clopidogrel 75mg and Aspirin 100mg due to coronary artery stenting, but because of the present abdominal pain and CT findings showing a high risk of AAA rupture, he was scheduled for a AAA surgical repair. High-risk informed consent due to possible anesthetic and surgery related complications was obtained from the patient prior to intervention. Due to the risk of stent thrombosis dual antiaggregating therapy was sustained even at the day of surgery. The anesthetic management of this complex case was made under standard noninvasive and invasive measurement of arterial blood pressure after right radial arterial line placement, which was inserted after a successful Allen's test, as well as central venous pressure measurement after right jugular central line insertion using ultrasound. Vital signs before surgery showed hemodynamic instability with hypotension (90/50mmHg), a heart rate of 120bpm and oxygen saturation of 93%. The patient was started on a noradrenaline infusion (8mg/50ml) at a rate of 0.1mcg/kg/min to address the hypotension. Induction in anesthesia was made with a careful titrating of anesthetic medications using Midazolam 1mg, Ketamine 100mg, Propofol 20mg, Fentanyl 50mcg and muscle relaxation was provided by Cisatracurium 10mg. After induction and successful placement of an

endotracheal tube with No. 8.5, the patient was ventilated using a pressure-control volume-guaranteed mode. Intraoperatively, anesthesia was maintained with sevoflurane (1% with MAC 0.5-0.7) while analgesia was provided by continuous infusion of remifentanil (2mg/50ml) at 0.05mcg/kg/min, Metamizole Sodium 2.5g and Acetaminophen 1g. Because of sustained hemodynamic instability with hypotension and tachycardia with heart rate of 120-130 beats per minute and requirement of escalating doses of continuous Norepinephrine infusion, we have made an intraoperative transthoracic echocardiography. Due to surgical isolation just below the fourth rib transthoracic examination was difficult and incomplete, but it has provided significant data for the hemodynamics of the patient leading us to a substantial change in intraoperative treatment. Actually, the echocardiographic findings have shown persistence of a pericardial effusion mentioned before without influence of right ventricular filling nor systolic function which ruled out the diagnosis of pericardial tamponade as a cause of hemodynamic instability (Figure 1). Echocardiographic examination has shown presence of atrial fibrillation with inappropriate left ventricular contraction seen by eyeballing and confirmed in M-mode tracing of the left ventricle. Also, absence of the atrial kick on transmitral doppler was confirmed which is considered as a pathognomonic sign for AFF. Left atrial enlargement was met without any thrombotic masses in the left heart. After the echocardiographic examination, the patient has received Metoprolol 5mg in slow i.v. bolus which resulted in pharmacological cardioversion leading to converting the patient into sinus rhythm with HR of 65 and hemodynamic stabilization with SBP of >120mmHg and DBP >70 and MAP greater than 65mmHg, in order to maintain adequate perfusion. Another quick point of care – echocardiographic evaluation was made later on which has confirmed conversion of atrial fibrillation into sinus rhythm with clear distinction of systole and diastole on the left ventricular M-mode tracing, and significant improvement of the cardiac output due to establishment of left ventricular competence (Figure 2). After pharmacological rhythm conversion into sinus rhythm, improvement of hemodynamics was met, and we have lowered the intraoperative doses of norepinephrine to 0.02mcg/kg/min. During the surgery we have used cell salvage in order to minimize blood loss and maintain hemodynamic stability. The surgery has lasted for 5 hours, with an aortic clamping time of approximately one hour and 10 minutes. After successful performance of surgical technique and fulfillment of extubation criteria, the patient was safely extubated in the operating room and transferred to the Post Anesthesia Care Unit for further monitoring. Prior to transport I PACU, he was completely hemodynamically stable without need of any vasopressors nor inotropes. Postoperatively the patient has received metoprolol once daily with no adverse events until hospital discharge.

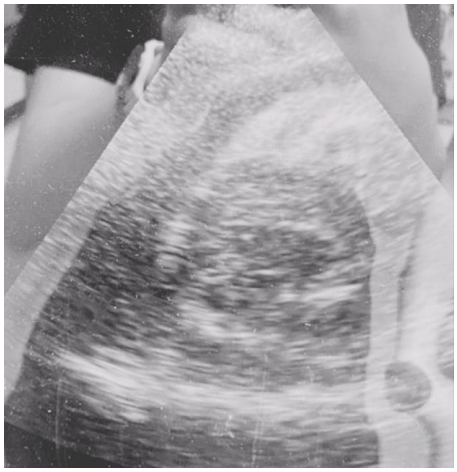

Figure 1. Pericardial effusion without impairment of ventricular filling.

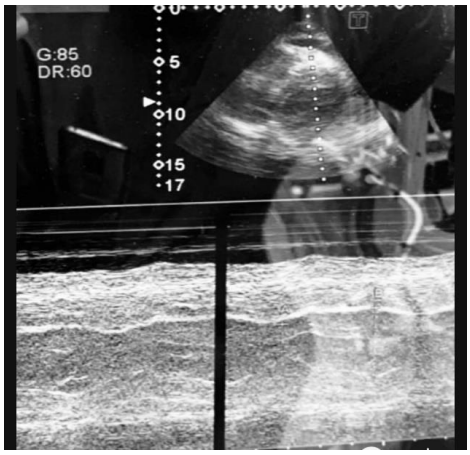

Figure 2. M-mode tracing of left ventricle with visible systolic and diastolic movement of the myocardium after cardioversion.

Discussion

Anesthetic management of patients with AAA with cardiovascular comorbidities, especially in semi-elective or in an emergent case could be a real challenge for the anesthesiologist. We report such a case with a recent acute cardiovascular accident making the case even more complicated. Because of the case complexity, as well as because of the risk of well-known possible intraoperative complications, we have used standard noninvasive and invasive monitoring due to picturing hemodynamics in a real time. It was well recognized before, that operative blood loss, metabolic and hemodynamic changes, induction of anesthesia, aortic clumping as well as declamping could cause substantial myocardial stress and lead to cardiac injury causing adverse events intraoperatively or in the early postoperative period (5). The

negative effect over myocardial contractility provoked with aortic clamping during open aortic repair was described by Kalman et al. in their study implying that this crucial event of the surgery could influence myocardial performance by lowering cardiac contractility, which was proven to be returned to its baseline values after declamping (6). Diastolic compliance decrease related to aortic declamping was described also in the same study relaying to the echocardiographic measurements suggesting possible myocardial ischemic injury and ventricular dysfunction during the surgery (6). As it was mentioned in the previous study, Cuypers PW et al. have also identified that open aneurismatic repair by itself is a serious risk factor for developing intraoperative and perioperative ischemia (7). Using echocardiography, they have identified that aortic clamping and declamping are two critical events precipitating significant hemodynamic changes that could lead to myocardial injury and disfunction. Aortic declamping was identified as a critical event that could lead to Cardiac Index increasement due to lowering the SVR and elevating the preload with possibly deleterious effect in patients with previously established diagnosis of Coronary Artery Disease (CAD), due to higher myocardial metabolic activity and elevated oxygen demand (7). The presence of a multivessel CAD and the left main artery occlusion involvement were identified as risk factors for developing intraoperative myocardial ischemia, as well as postoperative myocardial ischemia in patients who underwent open AAA repair (8). Another study has highlighted the importance of CAD regarding mortality in patients undergoing open AAA repair, as well as the fact that correction of the severe CAD before surgery is beneficial in preventing perioperative mortality (9). Keeping in mind all above mentioned facts about the complexity of the surgical procedure regarding its hemodynamic effects and already present multivessel CAD, the occurrence of intraoperative and perioperative adverse cardiac events was more than likely. Despite the recent percutaneous intervention and correction of the severe CAD in our patient, which was previously stated as a beneficial in such a case, we have continued to be vigilant because of the acute myocardial infarction recentness and its influence over still not-healed cardiomyocytes. Because of all above mentioned risk factors, expected intraoperative complications, as well as well-known intraoperative hemodynamic changes, we have used transthoracic echocardiography as a real time, point of care monitor intraoperatively during diagnosis and treatment of hemodynamic instability. Most of the knowledge gained about the hemodynamic changes and myocardial performance during open AAA repair were gained by using transesophageal and transthoracic echocardiography (5-7). In our case due to lack of transesophageal echocardiography machine, we were forced to use transthoracic echocardiography in a very limited window due to surgical isolation. Nowadays, evaluation of cardiac function, competence and hemodynamics with a point of care echocardiography is strongly recommended by the European Society of Intensive Care Medicine. According to the recommendations, the evaluation of the left ventricular systolic, diastolic function and pericardial bed in cases of shock and hemodynamic instability is strongly advised and recommended to be done bedside (10) as in our case. In our case presentation, the usage of Transthoracic echocardiography (TTE) led to point of care diagnosis of cause of hemodynamic instability, leaving all presumptive differential diagnosis behind and has provided suitable guidance of therapy inside intraoperative period. Performing echocardiography and its benefits regarding atrial fibrillation was recommended by Shakya S et al. and Troughton RW et al. (11,12). Despite non-invasive and invasive monitoring during open AAA

repair as a standard procedure, we have added TTE as a real time window in order to guide, maintain and correct hemodynamics, due to safely managing such a high-risk patient.

Conclusion

In this case presentation, we emphasize the crucial role of intraoperative echocardiography in guiding interventions and ensuring a favorable outcome for patients undergoing complex open abdominal aortic aneurysm repair. Performing a TTE has allowed prompt identification of the cause of hemodynamic instability and management of cardiac complications during surgery, contributing to greater safety and improved clinical outcomes. In absence of TEE equipment, even limited window TTE could provide significant real time data about hemodynamical happenings essential for maintaining hemodynamic stability. In high-risk surgeries, we recommend integrating intraoperative echocardiography as part of standard care protocol due to significant enhancement of patient's care and optimizing surgical outcomes.

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OPIOID FREE ANESTHESIA IN LAPAROSCOPIC RIGHT HEMICOLECTOMY WITH ILEO-TRANSVERSAL EXTRACORPOREAL ANASTOMOSIS

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Abstract

Lately, anesthesiologists tend to reduce the use of opioids due to their side effects whether it is during surgery or in post-surgery period. This case shows that the use of opioid free anesthesia consisting of a combination of magnesium sulfate, ketamine and lidocaine in a patient undergoing laparoscopic abdominal surgery, also reduces the post operative use of opioids.

Key Words: *magnesium, multimodal approach, laparoscopic surgery, lidocaine, ketamine, opioid free anesthesia.*

Introduction

Laparoscopy is a type of surgical procedure that allows a surgeon to access the inside of the abdomen and pelvis without making large incisions in the skin. This procedure is also known as minimally invasive surgery. The advantages of this technique versus open surgery include: a shorter hospital stay and faster recovery time, less pain and bleeding after the operation and reduced scarring. Though laparoscopic surgeries are considered relatively painless and are associated with early recovery and lesser duration of hospital stay, they can cause severe pain, especially in the first 4 hours of the immediate post-operative period due to carbon dioxide intraperitoneal inflation resulting in abdominal distension and increased abdominal pressure (1).

Laparoscopic surgeries are usually performed in general anesthesia. It is up to the anesthesiologist to decide whether it will be a combination of inhaled anesthetics with intravenous anesthetics or only TIVA. Intravenous opioids are commonly used to provide analgesia and supplement sedation during general anesthesia or monitored anesthesia care. Even though they provide analgesia, opioids have been associated with significant side effects such as dizziness, sedation, nausea, constipation, vomiting, physical dependence, muscle rigidity, tolerance, respiratory depression and addiction (2). Acute surgical pain in the immediate post-operative period is a significant risk factor for the development of chronic pain and its controlling is crucial for reducing the risk of chronic post-operative pain (3). Anesthesiologists play an important role in identifying at-risk patients for long-term opioid use, and that is why it is important to reduce perioperative opioid administration and decrease related side effects (4).

In this case we would like to provide multimodal analgesia with drugs other than opioids such as lidocaine, magnesium sulfate and ketamine for perioperative analgesia with an aim to reduce opioid requirement and its associated adverse effects.

Case Report

A 76-years-old woman underwent a cecum polypectomy several years ago. On a scheduled total colonoscopy, for the second time there had been a polyp with a diameter of 2cm present on the cecum. Another polyp with 1cm diameter was presented on the right flexure, and along the large intestine several diverticula predominantly in the left colon were present. Hemorrhoids piles of I-II grade were present in the anus. After the exam, the given diagnose was polyp on the coecum perpendicular polyp, hemorrhoids grade I-IV, st after polypectomy aa V. The patient was scheduled for elective colonoscopy polypectomy the next day. Since it was not successful, the patient was submitted for elective laparoscopic surgery. As with all standard elective surgeries, the patient came into the anesthesiology pre-operation checkup. The patient was ASA 4 classification with history of hypertension, COPD and heavy smoker, gallstones, renal cyst, glaucoma, DM type II with a long list of allergies on different medications, such as acetylsalicylic acid, diclofenac and grass. The patient had a normal ECG with no abnormalities, TA 160/60, HR 60 beats/min, $Sa0_2$ 98%, body weight 70 kilograms, vesicular auscultation on both lungs during the exam. Blood work analysis preoperatively showed Hbg 123, RBC 3.84, HCT 0.360, WBC 7.5, PLT 328, CRP 1.9, normal serum protein status, normal electrolytes status, normal AST and ALT levels and normal urea and creatinine levels, Glu 9.8. Patient was advised to fast from 18h in the afternoon until the time of the surgery. On the day of the surgery, the patient was given a sedative (diazepam 5mg) preoperatively and was submitted in the OR a couple of hours later. After the standard monitoring of vital parameters, the anesthesiologist proceeded with preoxygenation with 100% oxygen with high flow of 10l/min for several minutes while induction in anesthesia. For induction it was used a multimodal approach: diazepam 2.5mg; opioid (fentanyl 0.15mcg/kg = 100mcg); ketamine 35mg; lidocaine (1mg/kg = 70mg); dexamethasone 4mg; propofol (2mg/kg=140mg): long lasting muscle relaxant pancuronium 1mg, succinylcholine 100mg and after intubation with endotracheal tube number 7.5, another dose of long-lasting muscle relaxant pancuronium 5mg. Inhaled anesthetic sevoflurane was administrated with 2%. Since the goal was opioid free perioperative anesthesia, in a 50ml syringe were combined magnesium sulfate 3g (25-50mg/kg), lidocaine 2% 140mg (2mg/kg) and ketamine 42mg (0.2mg/kg/h) for continuous infusion for maintenance of anesthesia combined with sevoflurane 3%. During the surgery, the patient was hemodynamically stable with BP 100-150 systolic and steady HR of 60 beats/min and $Sa0_2$ of 100% with MAC 0.9-1.1. No extra opioids were required. Intravenous continuous crystalloid fluids 3000ml were administrated and diuresis was normal with 900ml urine at the end of the 5 hours long surgery.

After extubation, the patient was sent in PACU. Pain scores, vital signs and monitoring were done at 0, 2, 4, 6, 12, 24 hours postoperatively and rescue non-opioid analgesic paracetamol of 1g was given if pain score was >5 and if pain score was >8 tramadol 100mg was given.

Discussion

The purpose of this abstract is to show the beneficial side of opioid free perioperative anesthesia. Opioids as a group of drugs are used in perioperative pain management and acute postoperative pain. They act as blockers on the sympathetic nervous system in order to block the pathway of nociceptive signals. Many studies have shown that patients who underwent opioid perioperative pain management seem to require up to 25-30% more opioids in the postoperative period. Even though opioids offer fast onset of action, and they are great for analgesia, they also have side effects. One of them is acute tolerance, postoperative nausea and vomiting, sleep deprivation, euphoria, urinary retention, pupillary constriction and respiratory depression. In order to bypass all these side effect, but still manage to secure adequate pain control, a new approach has been suggested not long ago called multimodal general anesthesia. It represents a combination of inhaled anesthetics with non-opioid drugs which block the nociceptive signal pathways such as ketamine, lidocaine, magnesium sulfate, dexmedetomidine. In this specific case, ketamine (0.2mg/kg/h), lidocaine (2% - 2mg/kg), magnesium sulfate (25-20mg/kg) were placed in a 50ml syringe for continuous infusion for anesthesia maintenance combined with 2% sevoflurane in perioperative pain management as opposed to opioids.

Lidocaine is a local anesthetic which has found its place in general anesthesia due to its effects: reversable blockage of impulse transfer through nerve fibers important for regional anesthesia, antiarrhythmic, anti-inflammatory and antibacterial action. Lidocaine's the most important action is the anti-nociceptive one with blocking the sodium and potassium channels in the medulla spinalis. With its fast onset of action and lesser toxicity, it has become a drug of choice for opioid-free anesthesia. The second drug used is ketamine. It is a dissociative anesthetic used for induction and maintenance of anesthesia, a hypnotic drug but in contrary to opioids it does not cause respiratory depression, but it causes involuntary movement and amnesia. Positive effects and actions of ketamine are analgesia, antidepressant and bronchodilator. Ketamine is proven useful in postoperative nausea and vomiting, but only if administered in sub anesthetic doses. Magnesium sulfate took its place in perioperative use not long ago. It has a wide specter of use, the most commonly in pregnancy regarding preeclampsia. Magnesium sulfate has also antiarrhythmic, anti-inflammatory, neuroprotective role, and it was proven to be useful in treatment of asthma and postoperative tremor and hypercoagulability. By itself, magnesium sulfate is not a potent analgetic, however it does enhance the time of action of the non-depolarizing muscle relaxants, and also blocks the nociceptive signal pathways.

Conclusion

Continuous infusion of this solution during perioperative period, combined with sevoflurane 2% and single dose of steroid dexamethasone achieve co-analgesia, without the use of opioids (5,6) resulting in opioid free acute postoperative pain management within the first 24 hours and no postoperative nausea and vomiting.

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CASE REPORT

MANAGEMENT OF INTOXICATION WITH THE CA-CHANNEL BLOCKER – LERCANIDIPINE

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Abstract

Lercanidipine is a dihydropyridine calcium channel blocker that works by relaxing and opening the blood vessels, allowing the blood to circulate more freely around the body. This lowers the blood pressure and allows the heart to work more efficiently. An overdose of calcium channel blockers results in toxicity along with profound hypotension and shock. We present a case of a 27-years-old woman who was admittedto the ICU, after the intentional ingestion of large amounts of the calcium channel blocker, Lercanidipine. She was presented with refractory hypotension and non-cardiogenic pulmonary edema, which was treated successfully with the guidance of invasive hemodynamic parameters. The treatment included high-dose insulin infusions in combination with dextrose (10%), calcium, norepinephrine and dobutamine infusions. When supportive and specific pharmacological measures fail to adequately reverse refractory conditions in a calcium channel blocker overdose, the use of extracorporeal life support should be considered. The efficacy of these pharmacological and non-pharmacological interventions generally advocated in calcium channel blocker poisoning that needs further in-depth mechanistic foundation, in order to improve individualized treatment of calcium channel blocker overdosed patients.

Key Words: *Calcium-channel blocker, Intoxication, Lercanidipine, Overdose.*

Introduction

Calcium channel blockers are widely prescribed for the management of hypertension, arrhythmias and angina pectoris (1-2). They can be divided into dihydropyridines and non-dihydropyridines based on expected physiologic effects. The dihydropyridines are potent vasodilators but have a minimal effect on myocardium contractility and conduction pathways, whereas the non-dihydropyridines have a greater effect on myocardium contractility and conduction pathways, but a minimal effect on vasodilatation. However, at the higher doses seen, especially in massive overdose cases, such selectivity is usually lost (3).

Lercanidipine, a dihydropyridine (CCB), is commonly used as an antihypertensive drug. He works by relaxing and opening the blood vessels allowing the blood to circulate more freely around the body.This mechanism lowers the blood pressure and allows the heart to work more efficiently. It is completely metabolized in the liver. The elimination half-life is 8 to 10 hours, and the drug does not accumulate. Because of the depot effect, the antihypertensive action lasts for at least 24 hours and 50% is excreted via the urine. In the case of severe toxicity, good outcomes can be achieved through aggressive treatment and the provision of circulatory support (4). American Poison Control Centers (APCC) have reported cardiovascular drugs as the third fastest-growing category of substance exposures. According to a 2021 report, by APCC there are 6,162 exposures to CCBs, resulting in 37 deaths and 1,228 exposures occurred in children younger than 6 years old(5).

Case Report

A 27-years-old woman who had been hospitalized to the Department of Toxicology was moved to the Intensive Care Unit. She was conscious, contactable, and oriented in time, place, and people at the time of admission. She acknowledged taking all CCBs, including lercanidipine, at the same time. She was tachycardic and hypotensive and on oxygen mask. The patient's vital signs upon arrival were 100% peripheral oxygen saturation (SaO2), 115/min heart rate, and 53/23mmHg blood pressure. Antibiotic, antiemetic, gastroprotective, anticoagulant, diuretic, catecholamine support and hyperinsulinemiceuglycemic therapy were all started right away. In order to test for the blood type, full blood counts, electrolytes, liver and kidney function, blood glycose, C-reactive protein, and coagulation, we collected samples. We also obtained lung X-rays, implanted a nasogastric tube, and coordinated the monitoring of the acid-base state. Potassium was 3.02mmol/L, glucose was 22.8mmol/L, lactate was 12.82mmol/L, and BE was 20.3mmol/L in her initial serum electrolyte panel. A tachycardia of 160 beats per minute was detected on her ECG.

The patient was initially admitted to the Department of Toxicology, where she was treated with 3.5 liters of IV fluids, including 60ml of calcium glutamate injection, a titrated insulin drip, an uptitrated dopamine drip, 30ml of KCL 7.4% injection, and 250ml of lipofundin injection.

However, noradrenaline (0.04mcg/kg/min) and dobutamine (2mcg/kg/min) infusions were started in the ICU due to persistently low blood pressure, as well as vasogenic and cardiogenic shock. Actrapid 1–10 I.U./kg/hr. hyperinsulinemia euglycemia therapy was started at the same time. Abruptly, the patient's condition began to worsen, exhibiting non-cardiogenic pulmonary edema and mental disintegration. It was decided to place the patient on mechanical ventilation and intubate her. On day two, we administered an infusion of amiocordin (600mg/50ml; 2.2ml/h) and glyceryltrinitrate (0.1mcg/kg/hr). Blood pressure was consistently low, and we were attempting to keep it within a moderate range of at least 60mmHg MAP. A low dose of nitroglycerin (0.025 micrograms/kg/min) was started for coronary dilatation due to the patient's continuous tachycardia. On the third day, amiocordin was used to manage the tachycardia and GTN was discontinued. We also closely monitored the arterial blood gas analyses (ABG) and we had linear decline of the lactates by the third day (7.25mmol/L after 24h; 4.03mmol/L after 48h; 1.75mmol/L after 72 hours). After the glucose level returned to normal on the fourth post-admission day, the glyceryl trinitrate infusion was stopped. Following a week, the amiocordin infusion was discontinued, and weaning off catecholamines was initiated, with a gradual reduction, based on hemodynamic stability. By the time the patient's ABG returned to normal on nineth day (lactates-0.70 mmol/L), they met the requirements to

be weaned off from mechanical ventilation. After the choice to wean was made, the sedation was discontinued. After a whole day, she was successfully and painlessly extubated the following day. On the fourteenth day of stay, the patient was released from the Department of Toxicology, exhibiting no neurological deficits.

Discussion

Cardiac arrhythmias, angina pectoris, hypertension and other conditions are treated using CCBs. There are two forms of these drugs available: immediate-release and extended-release. Conventionally used CCBs fall into one of three primary chemical classes: dihydropyridines (i.e. lercanidipine), benzothiazepines (i.e. diltiazem), or phenylalkylamines (i.e. verapamil). Each subclass has a different affinity for cardiac tissue and vascular smooth muscle.

The majority of experts' consensus recommendations for therapies for CCB toxicity are based on poor levels of evidence. Hemodialysis and hemofiltration fail to remove CCBs due to their large distribution volume (2-6). In the example we've given, hemofiltration wasnot started.

Every CCB subclass suppresses the synthesis of pancreatic insulin and results in end-organ insulin resistance, which raises blood sugar levels. One clinical sign of the severity of poisoning is hyperglycemia. In our instance, hyperinsulinemiaeuglycemic medication was used to treat glycemia (9). Moreover, CCBs prevent glucose catabolism and calcium-stimulated mitochondrial activity, which leads to the production of lactate and ATP hydrolysis and ultimately, metabolic acidosis (8). In the situation we presented, bicarbonates were administered when blood pressure returned to normal and satisfactory urine production was maintained.

Severe hypoperfusion and end-organ ischemia resulting from a severe dosage can cause seizures, myocardial infarction, ARDS, renal failure, intestinal infarction and stroke (8). Many methods can be used to treat CCB poisoning: Within one to two hours of consumption, gastric lavage or 1g/kg of activated charcoal may be administered for intestinal purification. Calcium administration is justified by the fact that raising the extracellular calcium concentration promotes calcium influx through open L-type calcium channels. However, reactions to severe poisoning are inconsistent and subpar. Severe CCB poisoning can be effectively treated with hyperinsulinemiaeuglycemia. Monitoring of potassium and blood glucose levels is necessary prior to starting withinsulin therapy. The current recommendation for insulin dosage is 1 I.U./kg for a regular intravenous bolus followed by 1–10 I.U./kg/hr for continuous infusion, which we successfully used in our case (10-13).

In severe cases of CCB poisoning, patients may experience profound cardiovascular collapse due to the loss of peripheral vascular resistance and cardiac depression. This refractory hypotension requires aggressive intervention, often involving the use of vasopressors such as dopamine, noradrenaline, epinephrine or dobutamine. However, selecting the most appropriate agent can be challenging and requires careful consideration of the patient's hemodynamic status and underlying cardiac function. Our situation was well treated with dobutamin and norepinephrine (10).

Furthermore, the management of CCB poisoning extends beyond pharmacological interventions. Patients may require supportive measures such as mechanical ventilation to address respiratory failure secondary to severe hypoperfusion or metabolic acidosis (10). On admission our patient was not intubated and placed on mechanical ventilation, but after situation deteriorated mechanical ventilation was started for 10 days. Additionally, close monitoring of electrolyte levels, particularly potassium, is essential as hypokalemia can exacerbate cardiovascular instability and arrhythmias.

In cases where conventional therapies fail to adequately manage CCB toxicity, extracorporeal life support (ECLS) may be considered as a rescue therapy. ECLS techniques, such as veno-arterial extracorporeal membrane oxygenation (VA-ECMO), can provide circulatory and respiratory support while allowing for the removal of toxins from the bloodstream. Due to limited resources in our center unfortunately ECMO is not available (14-16).

Despite advancements in treatment modalities, the prognosis of severe CCB poisoning remains guarded, particularly in cases of delayed presentation or profound cardiovascular collapse. Early recognition of toxicity, prompt initiation of appropriate therapies, and close monitoring of the patient's response are crucial for optimizing outcomes in these challenging cases (14).

Overall, the management of severe CCB poisoning requires a multidisciplinary approach involving emergency physicians, toxicologists, intensivists, and pharmacists working collaboratively to provide comprehensive care to affected patients. Continued research and education in this field are essential to further refine treatment strategies and improve patients'outcomes (14). In our presented case, colleagues were not able to stabilize the patient, and she was transferred to the ICU, where profound treatment was taken with mechanical ventilation and intensive therapy guided by invasive hemodynamic monitoring and repeated arterial blood gas analysis, laboratory investigation and a coagulation test.

Conclusion

CCBs overdoses are challenging to treat, and the usual management can fail in cases with significant overdoses. It is important to havetaken a careful history, to do a physical examination, and to do close invasive hemodynamic monitoring, to anticipate complications and treat them as they occur. Urgent administration of fluids, calcium, vasopressors and hyperinsulinemiceuglycemic therapy seem to be the most validated initial approaches to treatment. Our successful management strategy should serve as a good learning experience for how to manage this kind of patient.

Abbreviations

CCBs: Calcium channel blockers; MAP: Mean arterial pressure; GTN: glyceryltrinitrate.

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CASE REPORT

ABDUCENS NERVE PALSY AFTER SPINAL ANESTHESIA

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Abstract

We present a case of a 22-years-old patient who was hospitalized in order to plan an operative treatment of a rupture of the anterior cruciate ligament of the left knee and a lesion of the medial meniscus. The patient was injured during football training. Preoperative analyses (laboratory, transfusion analysis, EKG) were normal. The patient was not taking pharmacological therapy. He gave information about a COVID-19 infection 3 months ago with mild clinical manifestations.

The intervention was performed under spinal anesthesia with mild intravenous sedation. Vital parameters were as follows: tension 120/80mmHg, HR 76, and SpO2 98%. We administered 3.4ml of 0.5% Bupivacaine and 0.1mcg of Fentanyl. The puncture was performed with a 26-gauge cutting spinal needle. Three days after the operation, the patient complained of nausea, inability to handle the light, cephalea and seeing double images, as well as inability to move the right eyeball to the right.

Key Words: *cranial nerve palsy; diplopia; spinal anesthesia.*

Introduction

This case highlights the importance of vigilance for atypical postoperative presentations and the need for prompt neurological evaluation and management. The motivation for reporting this case stems from its rarity and the potential implications for perioperative care. By sharing this clinical encounter, we aim to contribute to the medical literature and raise awareness among clinicians regarding the possibility of neurological complications following spinal anesthesia.

Spinal anesthesia was the first regional anesthetic technique (1) The first operation under spinal anesthesia was performed in Germany in 1898. It was performed by August Bier. Spinal anesthesia is a technique in

which the local anesthetic is injected directly in the subarachnoid space. It is used for procedures that involve the pelvis, lower extremities, and lower abdomen.

Complications of spinal anesthesia are of very low incidence. Severe complications are infrequent (1). Spinal anesthesia is an extremely safe technique especially when it is done by an experienced anesthesiologist (2). Some of the complications of spinal anesthesia are nausea, vomiting, neurological manifestations, spinal hematoma, arachnoiditis, post-dural puncture headache, and hypotension.

Case presentation

We present a case of a 22-year-old patient who was hospitalized in order to plan an operative treatment of a rupture of the anterior cruciate ligament of the left knee and a lesion of the medial meniscus. The patient was injured during football training. Preoperative analyses (laboratory, transfusion analysis, EKG) were normal. The patient was not taking pharmacological therapy. He gave information about a COVID-19 infection three months ago with mild clinical manifestations. He doesn't smoke. The intervention was performed under spinal anesthesia with mild intravenous sedation. Vital parameters were as follows: tension 120/80 mmHg, HR 76, and SpO2 98%. We administrated 3.4ml of 0.5% Bupivacaine and 0.1 mcg of Fentanyl. The puncture was performed with a 26-gauge spinal needle. The postoperative course was normal and the patient was mobilized on the same day.

Three days after the operation, the patient complained of nausea, inability to handle the light, cephalea and seeing double images, and inability to move the right eyeball to the right. A neurologist was consulted. During the examination, the patient was aware and oriented in all directions. His speech was intact. The eyeballs were centrally positioned in the orbits, and pupils were isochoric, with an orderly reaction to direct exposure to light. Diplopia was reported when looking to the right. Nystagmus was not observed during the examination. No facial muscle asymmetry was noted. Speech function was normal without any deviations. Symmetrical elevation of palatal arches during phonation. Coordination tests were performed without any dysmetria. Plantar reflex examination revealed bilateral plantar flexion responses.

An urgent contrast-enhanced CT scan was performed, revealing normal luminal views of the arteries in the circle of Willis, with no evidence of stenosis or aneurysmal dilatation. The patient was transferred to the neurology department. An examination by an ophthalmologist was also done in consultation. Ophthalmologist also confirmed paresis of n. abducens.

After two days, magnetic resonance (MRI) of the brain (native and post-contrast series) was performed with the following result: . In the parenchyma of the cerebrum, cerebellum, and brainstem, no MRI signs of focal lesions or expansive changes were registered. Pathological accumulation of contrast was not detected. Ventricular system and subarachnoid spaces were presented as wide and free.

The arrangement of the bulbs and spaces behind the eyes was normal.

During the patient's hospitalization, laboratory analyses were within reference values. The patient was treated with an anticoagulant, corticosteroid, antibiotic, gastroprotective, and vitamin therapy. The patient was discharged after 12 days in an improved general condition and scheduled a follow-up examination

with a neurologist in three weeks. During the patient's control examination, the pupil of the right eye was properly reactive, and abduction of the sixth cranial nerve was possible.

The patient was treated with corticosteroid and vitamin therapy for 14 days. Complete recovery of the patient was observed after one month.

Discussion

Cranial nerve (CN) palsy is a rare complication after spinal anesthesia (3). The incidence varies between 1:300 and 1:8000. All cranial nerves except cranial nerve 1, 9, and 10 can be involved. Cranial nerve 6 is the most commonly involved because of its long intracranial course. Isolated abducens palsy is more frequent in elderly patients, especially in persons with hypertension and diabetes (4). This complication is rarely observed in younger and healthy people. Differential diagnoses of this condition are tumors, leukemia, vascular lesions, sarcoidosis, infections, and hemorrhages.

Patients experiencing diplopia may also exhibit complete paralysis of the lateral rectus muscle.. This usually occurs between one day and three weeks after spinal anesthesia. In 2/3 of the patients, the symptoms subside within a week. In 25% of the patients, symptoms may persist for more than a month, while in about 10% of the patients, symptoms persist for more than 3 months (3).

Cranial nerve 6 palsy caused by low spinal fluid pressure is very rare. It is associated with a spinal fluid leak (5). During the performance of spinal anesthesia excessive leakage of cerebrospinal fluid may occur through the injection site. If excessive leakage of cerebrospinal fluid occurs, this could result in an intracranial hypotension. During intracranial hypotension, the leakage of cerebrospinal fluid is greater than its production (6). Intracranial hypotension that occurs after spinal anesthesia could cause traction of abducens. Stretching the nerve could lead into local ischemia. It is also associated with certain symptoms, such as nausea, vomiting, and vertigo (3). When the dural puncture is performed with 26- or 27-gauge needle complications like this are rare, but could occur (7). M. rectus superior is innervated by the sixth cranial nerve. That’s an explanation why cranial nerve 6 palsy causes diplopia. (8).

It’s better to use a pencil-point spinal needle than a cutting spinal needle. The frequency of post-dural puncture headache (PDPH) is lower when a pencil-point spinal needle is used instead of a cutting spinal needle (9).

The number of reported cases with this complication is very low. That’s the reason why there is no much information about the mechanism of injury and treatment of this condition. Recovery is usually spontaneous. It usually lasts from 3 weeks to 8 months .

Conclusion

Although the complications from spinal anesthesia cannot be avoided it's recommended to use a smaller needle. Opting for a pencil-point spinal needle is preferred over a cutting spinal needle, as it reduces the likelihood of post-dural puncture headaches. It causes less trauma to the tissue. Intraoperative and postoperative hydration of patients is very important as well. In our case, the puncture was made with a 26-gauge needle, but the complication still occurred.

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SURVEY

ANESTHESIOLOGY CHALLENGES DURING TAVI PROCEDURE

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Abstract

Transfemoral transcatheter aortic valve implantation (TAVI) is nowadays a routine procedure for elderly patients with severe aortic stenosis and high perioperative risk. With growing experience, further device development, and the expansion of "intermediate risk" patients, there is increasing interest in performing this procedure under conscious sedation (TAVI-S) instead of the previously favored general anesthesia approach (TAVI-GA). The benefits of TAVI-S include reduced procedure time, shorter length of stay in the intensive care unit (ICU), reduced need for intraprocedural vasopressor support, and the potential to perform the procedure without the direct presence of an anesthesiologist for cost savings. To date, there are no data from randomized trials. Only non-randomized studies were reviewed. Patients' selection, study methods and endpoints varied significantly between published studies. Factors related to the procedure, including hypotension, may add to existing age-specific renal impairment, and increase the risk of acute kidney injury. Hypotonia of the hypopharyngeal muscles in elderly patients, intraprocedural hypercarbia and certain anesthetic drugs may increase the risk of aspiration in sedated patients. General anesthesia and conscious sedation have been successfully used to treat patients with severe AS undergoing TAVI with similar reported short-term and long-term mortality outcomes. It is believed that the significant incidence of complications and unplanned conversion to general anesthesia during TAVI-S mandates the presence from start to finish of an experienced cardiologist and anesthesiologist in order to optimize patients' outcomes. Good quality randomized data are needed to determine the optimal anesthetic regimen for patients undergoing TAVI.

Key words: *Anesthesia, aortic stenosis, transfemoral transcatheter aortic valve implantation.*

Introduction

Aortic stenosis, a progressive narrowing of the aortic valve, is one of the most common valve problems in developed countries. In developing countries, the main cause is attributed to rheumatic heart disease. It can be asymptomatic for a long time, and it is present in 25% of adults over the age of 61. Transfemoral aortic valve implantation (TAVI) and balloon aortic valvuloplasty (BAV) are less invasive techniques for the treatment of severe aortic stenosis with long-term and short-term benefits respectively. The first BAV was produced in 1983. Unfortunately, registries have shown high rates of restenosis. In 2002, at the University of Rouen in France, Dr. Alain Cribier performed the first case of percutaneous aortic valve replacement on a 57-years-old patient with inoperable aortic stenosis. Patients are selected for TAVI based on clinical judgment and risk assessed by a multidisciplinary team

of cardiologists, cardiothoracic surgeons and anesthesiologists. Statements by the European Association for Cardiothoracic Surgery (EACTS) and the European Society of Cardiology (ESC) currently limit TAVI to high-risk patients or those with contraindications to surgery. European Society of Anesthesiology (ESA) and ESC guidelines state that TAVI can be considered in patients with severe aortic stenosis, unsuitable for open surgery, but requiring an emergency life-sustaining valve.

Material and Method

As person ages, calcium can build up on the valve, making it harder and thicker. As a result, the aortic valve cannot open properly, forcing the heart to work harder to pump blood through the narrowed valve. This is a condition called aortic stenosis. The gold standard in the diagnosis of aortic stenosis, as well as all valvular heart diseases, is echocardiography, i.e. ultrasound of the heart. Modern echocardiographic devices allow excellent visualization of the heart, its cavities and valves provide the opportunity for dynamic measurements and assessment of the parameters that indicate the degree of valvular dysfunction. Aortic stenosis can lead to shortness of breath, chest pain, fatigue and dizziness. Aortic stenosis is a disease that gradually develops over a long period of time, progressing from mild to severe form. It often does not give warning symptoms and is therefore more difficult to diagnose. Aortic stenosis is often detected during a routine examination when a murmur is heard on auscultation. Usually, this noise appears long before other symptoms appear. Aortic stenosis can cause electrocardiogram (ECG) changes as well as low blood pressure. Due to the gradual development and compensatory ability of the heart, patients with aortic stenosis are usually asymptomatic for a long period, while the appearance of symptoms usually reflects an advanced stage of the disease. The causes of this disease can be rheumatic fever, calcific degeneration and bicuspid valve. About 45 TAVI procedures have been performed at the University Clinic of Cardiology in the last two years, and it can boast of a small number of complications and good outcome for patients who were followed up in the intensive care unit.

Results

Although there are no randomized data on this type of procedure, the European PARTNER trial in 2011/12 showed that TAVI is at least as good as SAVR (surgical aortic valve replacement) for high-risk patients, perhaps better, and should be the standard for care of an inoperable patient. Over the last few years, trans-thoracic catheter techniques have emerged as the primary treatment options for aortic stenosis for the inoperable and high-risk patient. Over 200,000 aortic implants have been performed worldwide with good results compared to SAVR. Procedural results report success rates of 98%, with a 30-day mortality of less than 5%. Improvement in symptoms and reduction in hospitalization also occur in the immediate future.

Discussion

TAVI is aortic valve implantation without removal of the diseased valve, performed under local anesthesia and general anesthesia. The TAVI approach is X-ray guided and provides full expansion of the replacement valve to the valve site via a catheter. After the new valve expands, it pushes the old valve

leaflets out of the way, and the tissue in the replacement valve takes over the valve's normal function. All this is performed under conscious sedation and local anesthesia.
TAVI is usually completed within 1 to 2 hours. The groin and wrist will be cleaned with an antiseptic solution, and then the patient will be covered with a large sterile compress. The groin (and sometimes the wrist) will be completely numb from the local anesthetic and may sting for about 30 seconds. Pressure may be felt, but no pain should be felt during the procedure. If at any time the patient feels pain or discomfort, the doctor should be notified, and more local anesthetic or pain relief may be given. At least three small hollow tubes (introducers) will be inserted into the groin vein and arteries, and sometimes into the wrist artery. These are places for access to the valve and for catheters (thin flexible long tubes) that are used to take pictures or make aortograms and measure the pressure of the heart.
In preparation for the new valve, balloon aortic valvuloplasty (BAV) may be performed to stretch and widen the aortic valve and make room for the new one. The heart will be stimulated to beat very fast during each balloon inflation with the help of the pacing cable, i.e. with a temporary pacemaker (PPM) which will be previously inserted through the groin, i.e. through the v.femoralis. Pressure measurements with the new valve operating will be recorded. Another BAV can be performed to ensure that the new valve is seated properly and there are no leaks. Final x-rays and safety checks will be done before the catheters and sheaths are removed. At this stage, the sedation will begin to wear off and the patient will feel more alert.

Conclusion

Nowadays, the most preferred treatment is the minimally invasive approach, which is the TAVI procedure. The length of time, the advancement of technology, as well as the recovery in intensive care makes this procedure advisable in the elderly population. Clinical and echocardiographic follow-up of the valves over 5 years would be well documented. Only time will tell if the valve's durability matches that of surgical prostheses. This is especially important if TAVI is offered to younger patients' groups in the future. Transthoracic aortic valve implantation is now a well-established technique for the treatment of aortic stenosis in high-risk patients. Experiences in TAVI and valve technology are advancing rapidly. When it comes to general anesthesia and conscious sedation, they are successfully used to treat patients with severe aortic stenosis undergoing TAVI. However, the anesthetic regimen itself remains only one part of a complex procedure for complex patients and the lack of randomized data to guide practice has resulted in wide variation in the management of patients undergoing TAVI. Experienced high-volume TAVI centers continue to report very positive outcomes for patients treated with both sedation and general anesthesia. Complications and unplanned conversion to general anesthesia during TAVI, mandate the presence from start to finish of the procedure with an experienced anesthesiologist and cardiologist in order to optimize patients' outcomes.

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HISTORY

30 YEARS ASSOCIATION OF DOCTORS IN ANESTHESIOLOGY, REANIMATION AND INTENSIVE TREATMENT (ZLARIL) IN THE REPUBLIC OF NORTH MACEDONIA

How we started...

Nojkov J

The disintegration of the SFRY occurred after a series of violent conflicts and military actions, primarily in the territories of Slovenia and Croatia and especially in Bosnia, followed by numerous civilian casualties. Slovenia and Croatia declared independence in 1991, followed by Bosnia and Herzegovina and Macedonia. The formation of the independent Republic of Macedonia took place in 1991 and passed without military action, but with accentuated inter-ethnic tensions.

The beginnings of the new state were followed by enthusiasm and numerous efforts for international recognition. Also important were the efforts to include the numerous professional organizations that emerged from the former state in the international associations. It was the same with the organization of physician anesthesiologists. In the Yugoslav federation, there was a so-called JUARIL (Yugoslav Association for Anesthesiology, Reanimation and Intensive Care) at the federal level, and in all republics there was a section of anesthesiologists as part of the Medical Associations. Congresses were held every 3 years, while intersectional meetings were held in different republics every year. Among the last activities of the Macedonian section of anesthesiologists was the organization of intersectional meetings in Skopje (Prof. Nikola Andonov 1979), as well as the 4th JUARIL Congress in Ohrid (Prof. Nikola Andonov 1980) and intersectional meeting in Bitola (Dr. Dimitar Sekulovski, 1988). The last activities of JUARIL were the last 5th Congress in Belgrade in 1989, where, according to the system of rotation, the management was taken over by colleagues from Croatia, as well as the intersectional meeting a year later in Neum (BiH), which passed with only half the participation of anesthesiologists, and when already the atmosphere of war was felt it was obvious that the state was falling apart.

Macedonia declared its independence on September 17, 1991, when the Declaration of Independence was signed. Independence and Sovereignty were adopted based on the successfully completed referendum held on September 8 of the same year. This was followed by the formation of the Macedonian army and the national institutions in accordance to the new changes. The holding organizations also changed their names afterwards. First, the former Association of Doctors of Macedonia (ZLM) changed its name to the Macedonian Medical Association (MLD), and then its specialists' sections became associations of doctors of certain specialties. Thus, the Section of Anesthesiologists of Macedonia became the Association of Physicians for Anesthesia, Resuscitation and Intensive Care (ZLARIL) with a decision brought on June 19, 1993, at the meeting held in Kriva Palanka. Then a decision was made on renaming, the new work regulations were accepted, and the management board was supplemented. The first management board of ZLARIL consisted of: Nojkov Jordan, president; Shuplinovski Zlatko, secretary; Krstevski Zvonko, treasurer, and members Sholjakova Marija, Miloshevska Violeta, Zlatko Petrov and Stojchevski Velcho. Zvonko Krstevski created the graphic solution for the logo of the association, which is still in use today.

In the following years, there was a struggle for admission of our Association to the professional international organizations WFSA, WFSICCM, ESA, EA and ESRA. First of all, it was important for us to be admitted to the world anesthesiology organization (WFSA), i.e. to its European section (European Regional Section - ERS), which was renamed in CENSA and later in ESA (European Society of Anesthesiologists) in 1994. The procedure started after the letter from the last president and secretary of JUARIL from Croatia Dr. Perushko and Dr. Shchap in which they informed us that the organization no longer exists or exists only as an organization of anesthesiologists from

Serbia and Montenegro, but that they do not have any information about it because all connections between them and Belgrade have been severed. They also wrote in the letter that they have submitted their irrevocable resignation from their positions and recommend us to seek admission to WFSA as an independent association. Attached they sent an application form, which we filled in, and sent it to the WFSA secretary Dr. Saywan Lim on 1st of July 1992. The first contact with the president of the WFSA, Dr. John Zorab, was made by me together with Dr. Lazar Shendov in the fall of the same year in Hague, Holland, during the 10th WFSA congress. In the conversation we expressed our desire for membership as an Association from an independent state, we informed that our association had 137 members and that we agreed to fulfill all WFSA obligations. Dr. Z. Zorab admired our initiative and promised to put us in touch with the secretary of the organization. On January 13, 1993, a letter arrived from the new secretary of the WFSA, Dr. M.D. Vickers. In the letter, he welcomed our initiative, but stated that the problem was that we were not yet a member of the United Nations and were not recognized by the UK Foreign Office as an independent country. He also wrote that they had no evidence that JUARIL no longer existed and that it would be good if an official member of the leadership from Belgrade "liberated" us from membership in the former organization. One of the ideas he proposed was to establish some "correspondence form" of cooperation through which we would have complete information about the work at WFSA. In that sense, Dr. Wetchler, the president of the WFSA Executive Committee, would forward this proposal to the next meeting of the Committee, from where he, as secretary, would be entitled to take further actions. The problem was solved with the admission of our country as a member of the United Nations on April 8, 1993. Then followed a letter from the secretary of WFSA Vickers to the secretary of our Association Dr. Zlatko Shuplinovski that the WFSA Executive Committee approved conditional full membership of our Association until the holding of the General Assembly in 1996. Thus, during the holding of the 11th WFSA Congress in the period April 14-20, 1996 in Sydney, Australia in the presence of numerous anesthesiologists from Macedonia, at the General Assembly ZLARIL was accepted as a full member of the WFSA.

The benefit of admission to the World Organization of Anesthesiologists was manifold. We received notices of all professional events through letters, and the newsletters “World Anesthesia” and “Update in Anesthesia” in the coming years reached about 50 copies to our members. At the request of the editor in this journal in 1999, I wrote a "profile" of our association in which the history of our country, the historical development of anesthesiology, the method and program of specialization, the most common used anesthesiology techniques, as well as the prevalence of surgical health network were noted. A slightly modified text with similar content was published the following year in the newsletter of the European Academy of Anesthesiology. These were small but significant steps in the struggle for the international emancipation of our country. Also, in those years we received regular invitations to the meetings of the presidents of the European anesthesiology societies which were usually held in conjunction with the annual meetings of the German Society of Anesthesiology (AGAI). Our members regularly participated with their papers in all major scientific meetings (World congresses in Sydney 1996, Montreal 2000, Paris 2004, Cape Town 2008, European congresses in Jerusalem, Frankfurt, Lisbon, Florence, Bermingen, etc.)

Admission to the WFSICCM (World Federation of Societies of Intensive and Critical Care Medicine) went easier, but the cooperation was not so intense. It all started with our request for admission on April 6, 1993, and the admission itself was carried out in Madrid on June 15 of the same year at the meeting of the General Assembly. The participation of our colleagues in the professional meetings of WFSICCM was modest, but the members of ZLARIL benefited the most from the distribution of the magazines of this organization” Intensive Care World” and “Intensive & Critical Care Digest”, which for several years came to our home addresses free of charge. I would like to mention here that in the previous two organizations we were members as an association and we provided the membership fee through sponsorships, which was often a problem. The third international organization we collaborated with was the European Society of Regional Anesthesia (ESRA). The relationship started with my

contact with its president A. Van Steenberge who then invited me as a lecturer at their annual meeting in Brussels. The following year (May 23-24, 1997) in Ohrid, together with Zoran Guchev, we organized the Zonal ESRA Meeting, in which they participated or taught alongside their own colleagues and colleagues from neighboring countries, Bulgaria, Serbia, Belgium and Italy. It is important to note that in the coming years we have also established a relationship with the UEMS (Union Europeenne des Medicins Specialistes, Section Anaesthesiology, Reanimation and Intensive Care), which is a specialized body of the European Union for coordinating and harmonizing programs and regimes for the education of staff from our specialty. Since we were not members of the EU, our representatives (Maria Sholyakova, Jordan Nojkov) had the status of associate members with the right to participate, but without the right to make decisions. As head of the Department, Maria Sholyakova was the most active in this field, and as a result of her advocacy, we were among the first in the Balkans to start organizing cycles of FAEPA courses for the European diploma. The cooperation with this body also resulted in changes in the program and the length of the specialization in anesthesiology and intensive care, which we aligned with European recommendations.

In the first years after independence, we worked with great enthusiasm. The state was visited by many officials from Western countries, among whom many were from the field of health. Aid in equipment and medicines also arrived through several countries and organizations. Our Association was active in the field of professional development of the membership through the organization of numerous meetings, symposiums and seminars. In the first four years alone, 20 meetings were held, as well as the 1st Congress of Anesthesiologists of Macedonia. Most of these meetings were intended for our members, but there were also joint meetings with transfusiologists and hematologists, with microbiologists, and with surgeons on interdisciplinary topics (therapy with blood and blood substitutes, thromboprophylaxis, interhospital infections and rational use of antibiotics, preparation of patients for surgery, etc.). Among the larger gatherings were two symposia, one on pain treatment and the second on cardiopulmonary resuscitation intended for a wider group of doctors and held within the framework of the "Medicine" fair event. I would like to mention here that the anesthesiologists were the leading educators for CPR (cardiopulmonary resuscitation) of the doctors in our country, starting from the eighties of the last century until today. Among the meetings there were also two of a solemn nature. One was in the occasion of the ceremonial commissioning of the new department for intensive treatment at KARIL, and the second in the occasion of the 30-years existence of the anesthesiology service in Bitola. The crown of our professional activity was the organization of the 1st Congress of Anesthesiologists of Macedonia, which was held in May 1995 at the "Desaret" hotel in Ohrid. Organizing such an event with international participation was a big test that we successfully passed, at least according to the echoes that could be heard among the participants and the medical public. At that time, 160 anesthesiologists worked in Macedonia, and the Congress received as many as 130 papers from domestic authors and about sixty from foreign participants from Bulgaria, S.R. Yugoslavia, Slovenia, Denmark, Germany, France and Japan. At the Congress, there were also 5 accompanying symposia and a very rich social and entertaining life. Even seen from today's point of view, it can be said that the Congress was oversized because the previous Yugoslav congresses served us as a benchmark, but it can be said with certainty that it served as a standard for many professional congresses long after. After this Congress, six more congresses followed (in 1999, 2005, 2010, 2014, 2019, and the presidents of the congress committees were Violeta Milosheva, Mirjana Sosholceva, Jasmina Nanceva, Biljana Shirgovska and Maja Mojsova, subsequently. All of them were at an enviable professional level.

The events in the professional field were also accompanied by significant social activities. The frequent meetings of the Association contributed to the development of the feeling of togetherness among colleagues and to the improvement of personal contacts. The meetings were held in almost all cities and tourist places in Macedonia, and colleagues from the interior presented their professional papers much more than today. There were many trips by

organized bus transport, and the attendance was high. At the meetings, members also received information about personal events, such as completion of specializations, masters' or doctorate degrees, or retirements. Also, the meetings served as a place where information was shared about upcoming international professional events, which was a replacement for today's Internet. The meetings always ended with a joint lunch and many times with a music program.

Published Works of Importance for the History of Macedonian Anesthesiology

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10. Book of proceeding. 5th Congress of of Macedonian Anesthesiologists. 2-5 October 2014 Simposium: History of anesthesia in Skopje, Shtip, Veles, Strumica, and Kavadarci. (Abstrakts, in Macedonian) Autors: Andonov V, Martinovska K, Josimovska V, Eftimova B, Nojkov J, Leova M, Baldzieva A. and Karovska-Pavlova M. p. 151-160.

LETTER TO THE EDITOR

SUBJECT: ADHD AND ANESTHESIA: CONCERNS TO A CHILD PSYCHIATRIST

Dear Editor,

I am writing to express my concern regarding the use of anesthesia in children with Attention Deficit Hyperactivity Disorder (ADHD) during medical procedures. As a child and adolescent psychiatrist, I believe it is crucial to raise awareness about the potential risks and considerations associated with this practice.

While anesthesia is commonly used to sedate children during medical procedures to ensure their comfort and safety, recent studies have highlighted potential concerns regarding its use in children with ADHD. A study by Sprung et al. (2012) found that children with ADHD may have increased anesthesia requirements and higher rates of postoperative agitation compared to children without ADHD. This suggests that children with ADHD may be more vulnerable to adverse events during anesthesia.

Additionally, the first prospective study examining perioperative behaviors in children with ADHD done by Tait et al. (2010) suggests that children with ADHD are more uncooperative on induction of anesthesia and are more likely to exhibit exaggerated postoperative maladaptive behavioral changes compared to children without these disorders. These findings underscore the importance of carefully assessing and managing anesthesia in children with ADHD to minimize potential complications and ensure optimal outcomes.

As healthcare professionals, it is essential to consider alternative approaches to anesthesia and sedation in children with ADHD. Non-pharmacological interventions, such as distraction techniques, preoperative preparation and parental presence, have been shown to reduce anxiety and improve cooperation in children with ADHD during medical procedures (Kain et al., 2015). Additionally, individualized anesthesia protocols tailored to the specific needs of children with ADHD may help optimize safety and effectiveness.

Furthermore, I urge policymakers and healthcare institutions to prioritize research and education on the use of anesthesia in children with ADHD. Evidence-based guidelines and protocols should be developed to guide clinical practice and ensure the safety and well-being of children with ADHD undergoing medical procedures.

In conclusion, the use of anesthesia in children with ADHD requires careful consideration and management to minimize risks and optimize outcomes. By raising awareness about this important issue and advocating for evidence-based approaches to anesthesia care, we can better support the needs of children with ADHD and promote optimal outcomes for all patients.

Thank you for considering my perspective on this matter.

Sincerely,

Dr. Biljana Gagachovska
Sub-specialist in Child and Adolescent Psychiatry
University Clinic of Psychiatry Skopje, Republic of North Macedonia

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GUIDELINES FOR AUTHORS

Macedonian Journal of Anaesthesia (MJA) is a scientific journal of the Macedonian Society of Anaesthesia (MSA) and Macedonian Society of Critical Care Medicine (MSCCM). The aim of this specialized medical journal is to speed and promote scientific achievements, novelties', clinical experience's, reviews, controversial topics in anesthesia, reanimation and intensive care, as well as other correlated medical branches.

The Journal is published four times a year (April, June, October and December), but additional supplements might be published when needed. MJA publishes original articles in basic and applied research, review articles, case studies, therapeutic and technological innovation, discussions, critics, surveys, impressions from meetings, information for international conferences and reviews of new books or variate.

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

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

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Manuscript should be sent together with the accompanying letter from the corresponding authors where declaration that the text has not been published previously is signed. Additional conflict of interests and confirmation by all the authors should be declared in this letter (example: Annex no. 1).

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Language and style of the manuscripts should be clear, simple to according the language, anesthesiological and medical taxonomy.

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

The inline space should be 2. Do not use Bold or Italic letters for the whole text (only for parts that have to be emphasized). Manuscript should not exceed 10 pages (without the references).

Abbreviations and correct medical terms should be used according to the International Committee of Editors of Medical Journals (http://www.icmje.org). Use only standard abbreviations; use of nonstandard abbreviations can be confusing to readers. Avoid abbreviations in the title of the manuscript. The spelled-out abbreviation followed by the abbreviation in parenthesis should be used on first mention unless the abbreviation is a standard unit of measurement.

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

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

Acknowledgment and Author contributions sections are displayed after the conclusion and before the reference section.

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This sections include only the citied references. **The references** are listed in order of appearance in the paper and the citation is standard numbers enclosed in small brackets in the same line with the text ( ).

For each reference if more than three authors appear provide the names of the first three authors and followed by **et al.**

1. Examples:

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2. Journal supplements:

AzmanJ, Frkovic V, Bilic L, et al. Korelacija I regresija. Acta Med Croat 2006;60 (suppl I):81-89.| 70 |

3. Books

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

4. Doctoral or master thesis

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

5. Electronic reference

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

Webster NR. The anaesthetist as peri-operative physician. Anaesthesia. http://dx.doi.org/10.1046/j.1365-2044.2000.01722.x

References used from abstracts are marked as (abstr)., and from letters with (letter)

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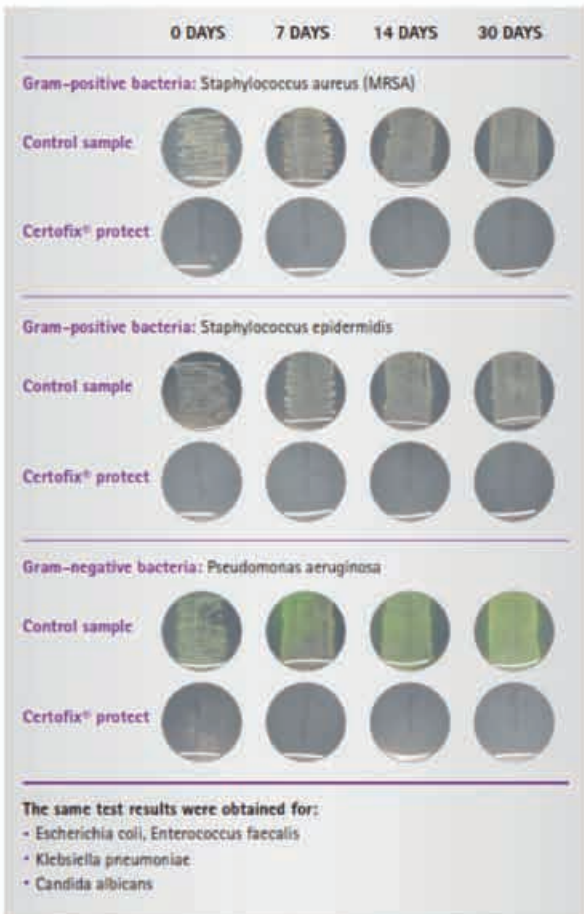

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