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I.V. Paracetamol

БЕЗБЕДНА АНАЛГЕЗИЈА

менаџирање на болка кога сте загрижени за безбедноста

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

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

КЛИНИЧКА СТУДИЈА:
Ефект од **предоперативен i.v. paracetamol** за постоперативни аналгетски потреби кај пациенти кои се подлежни на оперативни зафати. A Sreenivasulu , R Prabhavathi, 2015
Цел: Да се утврди ефикасноста на **предоперативната употреба на 1000mg i.v. paracetamol** кај постоперативните болки и анелгетски потреби кај пациенти подлежни на хируршки зафати.
Метод: 60 пациенти беа поделени во две рандомизирани групи од по 30 пациенти.
На I. Група им беше администрирано **ампула од 1000mg i.v. paracetamol разредена 0,9%NaCl** р-ор 30 минути пред индукција **(ГРУПА П)**,
На II. Група им беше администрирано **i.v. 0,9% NaCl р-ор 100мл** 30 минути пред индукција **(ГРУПА НС)**
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

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- **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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CONTENT

WHAT WE TALK ABOUT WHEN WE TALK ABOUT GENDER EQUALITY AND EQUITY IN ANAESTHESIA AND CRITICAL CARE

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The 17 Sustainable Development Goals (SDGs), an urgent call for action by all countries is at the heart of the 2030 Agenda for Sustainable Development, adopted by all United Nations Member States in 2015 (1). Achieving gender equality and empowering all women and girls is placed fifth after ending poverty and hunger, ensuring good education and clean water, addressing climate change, and protecting life on earth (2). Unfortunately, according to the available indicators, the world is not on track to achieve gender equality by 2030. At the current rate of improvement, it will take 285 years to close gaps in legal protection and remove discriminatory laws and 140 years to achieve equal representation of women in leadership at the workplace (2).

In 2019, the World Health Organization published a gender and equity analysis of the global health and social workforce under a very indicative title: ***Delivered by Women, Led by Men*** (3). It has been predicted that by 2030 a shortfall of 18 million healthcare workers will be confronted. At the same time, both horizontal and vertical segregation by gender is present, often driven by stereotypes. Gender discrimination leads to lack of women in leadership positions, who held only 25% of them, despite consisting 70% of the healthcare workforce. A large percentage of women in healthcare encounter bias and harassment, lack of laws and social protection, as well as lower social status and gender pay gap. It has been concluded that gender inequality weakens the healthcare system and delivery of care. However, the most of data comes from high-income countries, with lots of gaps in research and methodology, meaning that no general conclusions can be made or efficacious measures for improvement proposed (3).

Anesthesia and intensive care are no different from other medical fields and mirror broader trends. In a recently published analysis of 30 published studies exploring women's place in anesthesia, their underrepresentation in academia and leadership has been confirmed (4). The increased number of women in medical schools and residency programs does not reflect in an increased number of women leaders. The leaky pipeline, earlier observed in STEM (science, technology, engineering and mathematics) is a metaphorical reference to the decrease in the number of women at every stage of the career progression and is declared in medicine, anesthesia included (4). Again, the research gap is present: the most of studies dealing with gender equality tend to focus on numbers and structure of women's underrepresentation, and almost none focus on the reasons behind it.

In recently published results of two different surveys including anesthesia professionals, it has been shown that women and men equally aspire to leadership positions and are dealing with the same obstacles, which seem to affect women more (5,6,7). One of the most prominent and most difficult to overcome is childbearing, which places a woman in the position of increased burden of work and challenged work-life balance. At the same time, the most intensive years of residency and training, or academic progression are also at the same age where many consider having children (8). A cross-sectional survey among women physicians, mostly mothers, showed that gender-based discrimination remains common and motherhood is an important reason, whether due to maternity leave (absence from work) or so-called "maternity penalty" (women with families compared to men are seen as "less experienced" and "less qualified") (8).

Obviously, there are other barriers that are often indirect and difficult to discern. Although macro inequities could be easy to recognize as obvious discrimination, they are rarely seen nowadays. Micro inequities, small events, often ephemeral and hard-to-prove, sometimes unintentionally are not easy to recognize or to address are those that create a culture of gender bias and inequity (9).
For example, in one Swedish study it has been shown that to have a comparable score on grant applications, women researchers need to have three times more first-author publications and to be 2.5 times more productive in a volume of publications or publishing in journals with a higher impact factor (8).
It has been recognized that the system needs changes, but somehow it is always expected that women will lean in, meaning that they should adjust and overcome with their efforts the existing frame of inequity (10).

Additionally, with gender, age, race, ethnicity, class, sexuality, religion, disability, weight and physical appearance, migration not only between different countries but within one, may intersect and create different modes of discrimination or privilege (11). Usually, it is not only gender that creates unfairness and discrimination. Further, unconscious bias is much more common and even incompatible with one's conscious values and because of that, it is difficult to be recognized and addressed. (8)

Aside from personal development and career progression, there is evidence, primarily from business and management sectors, that gender-diverse workplaces have improved productivity, innovation, decision-making, employee satisfaction and retention (8). Similar has been shown in the medical environment: more effective teamwork and higher collective intelligence have been linked with a more inclusive working environment. Also, gender-balanced clinical personnel can affect patients' outcomes: elderly patients have lower mortality if treated by female physicians (8). Women patients with acute myocardial infarction have higher mortality when treated by a male physician (12). When male physicians had more women colleagues and patients, this effect attenuated. Yet, not much about outcome and gender medicine is known in anesthesia and intensive care which opens a huge space for further research.

So, what is gender equality? The basic definition says that all individuals are free to develop their abilities and make choices without limitations imposed by gender rules. Equity would go a bit further: all individuals do not have the same starting point and adjustments to the imbalances should be made to fulfill personal abilities and choices. It is all about fairness, justice and basic human rights. In any working environment, the final goal is not to become the same; rights and opportunities should not depend on gender.

How can that be achieved?
Generally, the main focus goes in three directions (8):

- Raising awareness of the gender gap and existing gender bias,
- Identifying the reasons behind the underrepresentation of women and minorities and their challenged opportunity to advance on their career or academic tracks,
- Developing action plans to address these barriers objectively in a gender-neutral/ non-discriminative approach.

In public bodies, research organizations and higher education establishments, starting in 2022, it is required to have a gender equality plan (GEP) in place as a new eligibility criterion to get access to Horizon Europe funding (13). This is one of the strategies to ensure sustainable institutional change.

To meet the eligibility criterion, a GEP must fulfill 4 mandatory process-related requirements:

- Published a formal document on the institutional website,
- Dedicated resources to address the gender equality plan,
- Regular sex/ gender-disaggregated data on personnel and monitoring improvements or change,
- Awareness raising training on gender equality and unconscious bias for employees and decision-makers.

Not all working environments are academic or will apply for funding and grants. However, developing plans for gender equality looks like a good strategy to address gender discrimination. The first step is to make a cross-section of the social environment and to recognize specific problems. Many women, particularly those who are working in predominantly women environments do not recognize problems in equality and equity. Additionally, countries have cultural, religious, social and economic differences, including everyday challenges in politics and disturbing environmental changes. The Corona-19 virus pandemic has just demonstrated the vulnerability of healthcare systems everywhere (8).

Gender equality and equity are not a technical thing, they are a highly political question (14). A high level of social consensus is necessary to move forward.

In anesthesiology and intensive care settings, reaching fairness, well-being and better standards of care is of utmost importance. Everybody can become an upstander and advocate for equal opportunities for all anesthesiologists. Professionals may have a diversity of professional interests and advancement toward education, research, or a variety of subspecialties, but fairness and equal opportunities should be a common goal and interest for all of us.

My professor of histology Vasilije Djordjević Čamba used to say: You can see (recognize) only what you already know.

Let us all learn and see inequality. Both professionals and patients deserve a fair healthcare environment.

Acknowledgements and potential conflicts of interest

The author declares no conflict of interest for this manuscript.

The author is former Chair of the Gender Equity Committee of the European Society of Anesthesiology and Intensive Care.

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ORIGINAL ARTICLE *UDK: 612.014.43-053.31:613.41-021.64*

INFLUENCE OF THE FIRST BATH ON BODY TEMPERATURE IN NEWBORNS

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Abstract

Introduction: Numerous factors cause temperature imbalance in newborns during the adaptation period. Hypothermia in a newborn is defined as a body temperature below 36.5°C. It is classified as mild, moderate and severe. It is often represented in the early neonatal period and has an impact on morbidity in newborns. One of the causes of hypothermia is the first bath in the maternity ward. According to WHO recommendations, the first bath of newborns in the maternity hospital should be delayed for at least 24 hours. The aim of the study is the influence of the first bath on the BT of the newborn.

Material and Methods: Measurement of body temperature was performed with a digital thermometer. The study included term, healthy newborns. Hypothermic newborns were warmed under a radiation heater until thermostabilizing, bathed with running water, with a temperature of 35-37 °C, for no more than 5 minutes in a period of 4-6 hours after birth. BT was measured hourly, 20 minutes after bathing and hourly until thermostabilizing under a radiant heater.

Results: In a study of 80 newborns examined, 52 met the criteria. Upon admission to the Basic Care Department, 61% of the examined newborns were hypothermic - 29 mildly hypothermic, 3 moderately hypothermic. 50% of newborns born with vaginal birth on admission to BCD were hypothermic, and 80% of those born by caesarean section. After 2 hours of admission to Basic Care Department, all neonates were thermostabilized except of 1 neonate (with borderline maturity). 20 minutes after bathing, 58% of newborns were hypothermic (29 mildly hypothermic, 1 with moderate hypothermia).

Conclusion: Thermal adaptation is faster in more mature newborns and in newborns born by vaginal delivery. Early first bath of term healthy newborns leads to mild hypothermia. Postponing of the first bath may be a good option to reduce hypothermia.

Key Words: *body temperature, first bath, newborn*

Introduction

Worldwide, 2.5 million children died in their first months of life, representing 47% of all deaths of children under five (1). The newborn, as the most vulnerable part of a population, has specific needs and is a sensitive marker for the quality of care. After birth, they begin with adaptation to breathing, adult type of circulation, as well as glucoregulation and thermoregulation - as part of metabolic adaptation.

Immediately after birth, in a transition period that lasts 6-10 hours, there are numerous factors that can interfere with the correct and smooth adjustment of body temperature (BT) and can lead

to hypothermia. Neonatal hypothermia is a progressive decrease in the axillary temperature of the newborn (BT < 36.5°C), and it is categorized as mild hypothermia (36°C-36.4°C), moderate hypothermia (32°C-35.9°C) and severe hypothermia (<32°C) (2). Immediately after birth, 0.3°C/ min. body temperature or 1-3°C/ 5 min is lost. With stool and urine, 3% of BT is lost, transepidermal - with evaporation 27% and 70% with convection, conduction and radiation. In optimal environmental conditions, loss of BT is 35W/m² maximum loss of temperature, of which the newborn can compensate 70W/m².

Although hypothermia is rarely a direct cause of death, it contributes to a significant proportion of neonatal mortality globally, mostly as a comorbidity (3). The temperature should be maintained between 36.5°C and 37.5°C (1,2).

One of the factors for hypothermia is the first bath in the maternity ward. Bathing can be a stressful procedure for an infant, and it is shown that early first bathing destabilizes vitals in healthy neonates, particularly temperature, glucose levels, and respiratory status (4,5). In many hospitals, the first bath is done immediately after birth. It means that the neonate is separated from the mother, skin to skin contact is either lost or reduced and the breastfeeding is postponed (6).

According to WHO recommendations, it should be postponed 24 hours after birth or if it cannot be realized during this period, for cultural reasons, after 6 hours from birth at the earliest.

There are no strict recommendations for the timing of the first bath in healthy neonates. The objective of this study was to determine the impact of a first early bath on thermal adaptation and hypothermia in term healthy newborns.

Material and Methods

This is a prospective study performed at the University Clinic for Gynecology and Obstetrics, at the Department of Basic Care (DBC) of the newborn in a period of 4 weeks.

The study included all late-term neonates ($37^{6/7}$-$41^{6/7}$gestational week) in the period between 01.02.2023 till 01.03.2023. Inclusion criteria for the study were late term neonates, healthy neonates. Exclusion criteria were all preterm infants, newborns that receive antibiotics, newborns transferred to neonatal ICU.

We evaluated mode of delivery (vaginal delivery or cesarean section), complications during labor and delivery, gestational age of the newborn, birth weight (BW), Apgar score, need for resuscitation and BT in different time points after birth. All newborns whose mother had complications during labor and delivery, as well as neonates that needed resuscitation were excluded from the study.

Ambient temperature in the DBC is 25°C. At the reception of the Department, admission of the newborn is carried out under a radiant heater (Drager, 400W - servo mode) and it consists in identification, measurement of BT and BW. The measurement of BT is carried out with a digital thermometer in a period of 5 minutes.

Newborn BT was monitored, depending on their condition on admission in DBC. Hypothermic newborns were warmed under a radiant heater until thermostabilizing, after which they were bathed with running water, with a temperature of 35-37°C, for no longer than 5 minutes. Newborns with normal BT upon admission were bathed in a time interval of 4-6 hours after birth. This is followed by care of the newborn, with drying in warm clean diapers, care of the umbilicus, urogenital region, immunization and antihemorrhagic prophylaxis.

We measured BT on admission in DBC on every hour until bath, 20 minutes after bathing and until thermostabilizing under a radiant heater.

Results

80 newborns were examined, only 52 met the criteria and were included in the study. 8 newborns were in 37th gestational week (gw), 6 were 38th gw, 12 were 39th gw, 24 neonates were in 40th gw and 2 were in 41st gw. By type of birth, 32 were born with vaginal delivery, 20 with caesarean section.

On admission to DBC, 61% of the newborns were hypothermic – 29 were mildly hypothermic, 3 moderately hypothermic. 50% of those born with vaginal delivery were hypothermic and 80% of those born by caesarean section.

1 hour after admission to the DBC, 22 newborns were thermostabilized, 10 were still mildly hypothermic.

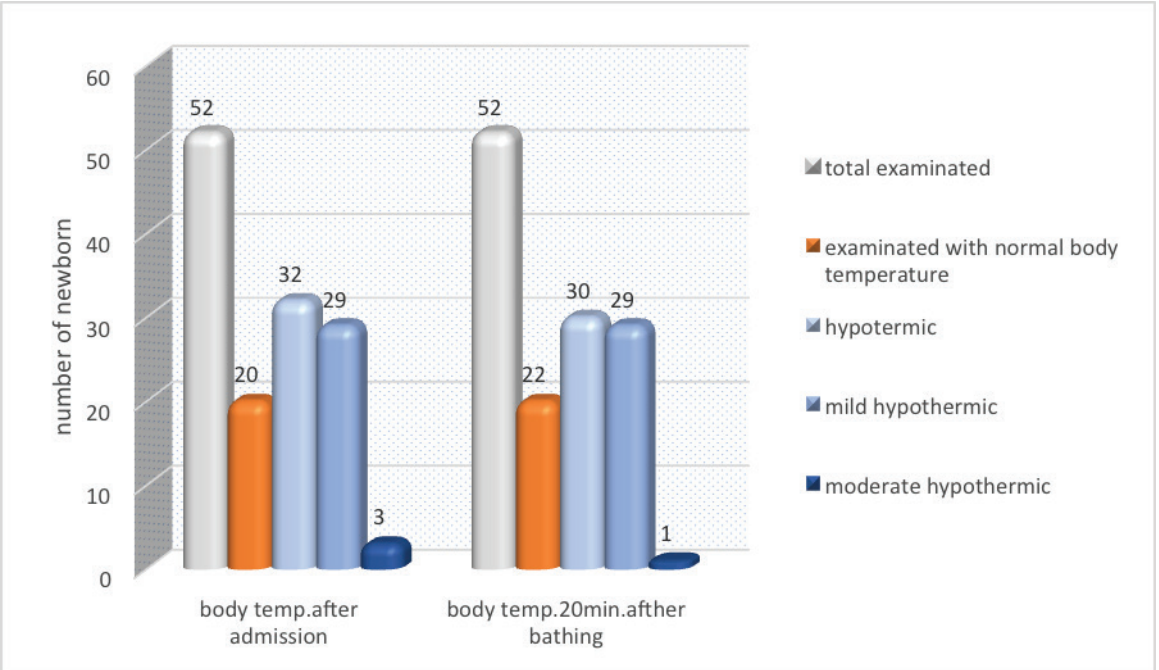
2 hours after admission to the DBC, all newborns were thermostabilized, except 1 newborn (with borderline maturity).

3 hours after admission to the DBC, all newborns were thermostabilized.

20 min after bathing 58% of the newborns were hypothermic - mildly hypothermic 29, 1 with moderate hypothermia. Newborns with normal BT at admission had 50% drop in temperature (1-2 °C) after bathing, while newborns that were hypothermic on admission to the DBC had 80% drop in BT (2-3 °C) after bathing.

6 hours after admission to the DBC, and 2 hours after the first bath all newborns were thermostabilized.

Table 1. Hypothermia in early first bath of newborns



Discussion

In a big systematic review by Priyadarshi and al from 2022, that included 16 studies and 39,020 healthy term newborns, regarding the time period of the first bath and thermal adaptation, they came to the conclusion that bathing the newborn within 24 hours of birth may reduce the risk of neonatal mortality and neonatal hypothermia compared to bathing in the first 24 hours, although these conclusions are limited by low-certainty evidence (7).

Bayih et al in their study in 2019, that included 403 newborns in Eastern Ethiopia, indicate a high prevalence of neonatal hypothermia in the adaptation period as a result of the absence of skin-to-skin contact with the mother, use of a cap, warm transport intra department and prematurity (8).

Kelly et al in their study in 2018, after monitoring BT of healthy term newborns with the first bath 3, 6, 9 hours after birth, indicate an insignificant difference in BT and normothermia after 2 hours of bathing in all three groups (9).

Compared to the large studies showing effects of early bathing versus delayed bathing on mortality of newborns, thermoregulation, glycemia, BW, breastfeeding, the aim of our study was to show the effect of early bathing on BT in the newborns in our maternity hospital and to compare the obtained results. This is a small segment of the temperature chain in which there is always room for correction and improvement.

Given that it is a small number of respondents, in a time interval of 4 weeks, the percentage value of the obtained results for hypothermia of newborns after bathing, in our study is higher. Differences are detected in the acceptance of the term delayed bathing. From a review of the literature and published results, in some maternity hospitals, delayed bathing is accepted 9 hours after the birth, in some 12 hours after birth, in others 24 hours after (10-12). Given the dynamics of work, the first bath of the newborn in our maternity hospital is 4-6 hours after birth, but in accordance to the adaptation and stability of vital parameters and BT of the newborn. Thermal adaptation is shorter in more mature newborns, than in newborns with borderline maturity. Newborns born with vaginal delivery have better thermal adaptation, compared to the newborns born with sectio ceasarea. In our study, we detect hypothermia of a mild degree after early bathing, which coincides with the published results of other authors (9). If, on admission to the DBC, newborns have a normal BT, after taking a bath, there is a smaller drop in BT, compared to the newborns who are hypothermic on admission to the department.

According to all available evidences, it is desirable to postpone the first bath 24 hours after birth. It is necessary to introduce a protocol for the first bath of a newborn in every maternity hospital, as well as to provide constant monitoring for its implementation, in accordance to the efforts to reduce the neonatal morbidity and improve the quality of work.

Conclusion

Thermal adaptation is faster in more mature newborns and in newborns born with vaginal delivery. Early first bath of term healthy newborns leads to mild hypothermia. Postponing of the first bath can be a good option to reduce hypothermia. A protocol for the first bath of a newborn and its implementation is needed in the efforts of reducing the neonatal morbidity and improving the quality of work.

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SUBJECTIVE METHODS FOR ASSESSMENT OF DEEP MYOMETRIAL AND CERVICAL INVASION IN PATIENTS WITH ENDOMETRIAL CANCER WITH TRANSVAGINAL ULTRASOUND

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Abstract

Introduction: Endometrial cancer is the most common gynecological malignancy. In this study, the diagnostic accuracy of subjective methods with transvaginal ultrasonography for the assessment of deep myometrial and cervical invasion in patients with endometrial cancer was analyzed in order to choose the optimal surgical treatment.

Material and Methods: It represents a prospective cohort study in which 45 patients with a histological diagnosis of endometrial cancer were analyzed. They are examined with transvaginal ultrasound to assess deep myometrial and cervical invasion with subjective methods based on IETA (International Endometrial Tumor Analysis) terminology.

Results: Subjective assessment of deep myometrial invasion based on the International Endometrial Tumor Analysis (IETA) endometrial cancer terminology yielded a sensitivity of 88% and a specificity of 65%. Subjective assessment of deep myometrial invasion includes tumor echogenicity, endometrial-myometrial junction, color Doppler result and vascular pattern. Subjective assessment of cervical invasion includes loss of clear demarcation of tumor tissue from the cervical stroma and in the presence of stronger perfusion. Our subjective assessment of cervical invasion had a sensitivity of 76% and a specificity of 92%.

The obtained results are comparable with relevant works on this issue.

Conclusion: Transvaginal ultrasonography is similarly effective to nuclear magnetic resonance for assessing deep myometrial and cervical invasion; therefore, it can be used as a preoperative triage diagnostic tool to choose a surgical modality from which the mostly poor surgical candidate patients would benefit.

***Key Words**: cervical invasion, myometrial invasion, subjective methods, transvaginal ultrasound.*

Introduction

Endometrial carcinoma is the most prevalent gynecological cancer in developed nations and the second most common in developing ones. The predominant histological type is endometrioid endometrial carcinoma, associated with a favorable prognosis, often presenting early with abnormal uterine bleeding. Conversely, other histologic types, such as serous, clear cell, carcinosarcoma, and various mixed uterine carcinomas, tend to have a poorer prognosis (1).

This cancer affects 1-2% of women in developed countries, with a peak incidence between ages 60 and 70, although a notable percentage occurs before age of 40. Chronic elevation of estrogen, without sufficient counteraction by progestin, is a primary risk factor, encompassing factors like tamoxifen use, clomiphene use, chronic anovulation, obesity, estrogen-secreting tumors and hormonal factors (1-7).

Less common type 2 neoplasms, characterized by nuclear grade 3 endometrioid histology and non-endometrioid histology, are not estrogen-sensitive, arise from atrophic endometrium, and have a less understood etiology(8). Lynch syndrome, Cowden syndrome, a family history of endometrial cancer and potentially BRCA mutations are hereditary factors which increase the risk (9-12).

Clinical presentation typically involves abnormal uterine bleeding in 75-90% of cases. However, bleeding quantity alone does not strongly correlate with the risk; factors like age and other risk factors should be considered. Diagnosis often occurs over the age of 55, through abnormal cervical cytology, incidental findings from various imaging modalities or during hysterectomy for other reasons.

Pelvic examination is less informative, and ultrasound in postmenopausal patients becomes suspicious when endometrial thickness approaches 20mm. An endometrial thickness below 4mm in premenopausal patients correlates with low risk. Diagnosis is established through dilatation and curettage, hysteroscopy or endometrial biopsy.

Endometrial cancers are traditionally divided into two types: type 1, representing 80% of the cases, is estrogen-driven, originating from endometrial hyperplasia, and has a good prognosis(13,14). Lack of exposure to progesterone is considered equally important in its pathogenesis. Type 2, clinically aggressive with histology like serous and clear cell, responds poorly to progesterone treatment and has a less favorable prognosis (13-15).

The newer molecular classification offers more consistent categorization with better predictive and prognostic information through genomic and proteomic analyses (16).

Prognostically, endometrial cancers are categorized into low-risk and high-risk. High-risk factors include poor differentiation, non-endometrioid histology, deep myometrial invasion, and tumors larger than 20mm on preoperative imaging. Treatment for high-risk cases involves radical surgery with lymph node evaluation. The low-risk endometrioid cancers with grades 1 and 2 and myometrial invasion <50% are treated with extrafascial hysterectomy without lymph node evaluation (17).

Objective

Utilizing transvaginal ultrasonography before surgery serves as a preoperative screening tool for patients diagnosed with endometrial cancer. The objective is to identify individuals at a heightened risk of deep myometrial and cervical invasion, aiding in the selection of appropriate treatment strategies. For those deemed at high risk, radical interventions involving parametrectomy and lymphadenectomy are necessary, ensuring optimal treatment. Conversely, patients identified as low risk through preoperative ultrasound would undergo extrafascial hysterectomy, avoiding the potential hazards associated with more extensive surgical procedures. This approach is particularly advantageous for elderly individuals, those with obesity, hypertension, diabetes and other comorbidities, where extensive surgical treatments could negatively impact overall prognosis and recovery. Ultrasound, serving as an alternative to nuclear magnetic resonance,

offers comparable sensitivity and specificity, making it an ideal, cost-effective and easily applicable tool in routine clinical practice.

Material and Methods

A prospective cohort clinical study involved 45 patients diagnosed with endometrial cancer through procedures such as dilatation and curettage, hysteroscopy or endometrial biopsy. The study conducted at the University Clinic for Gynecology and Obstetrics included patients meeting the criteria and providing informed consent.

Each patient diagnosed with endometrial carcinoma underwent preoperative transvaginal ultrasound without prior knowledge of the histological subtype or nuclear grade. Patients' selection adhered to specific inclusion and exclusion criteria.

Ultrasound examination was done by Voluson S6 General Electronics (GE), 2021.

Table 1. Demographic variables of 45 patients presented in numbers and percentage (n/%)

Variables	The number and percentages of 45 patients
BMI kg/m2 of 45 patients	Normal weight 5/11%, Undernourished1/2%, Overweight15/33%, Obesity class 116/35%, Obesity class 21/2%, Obesity class 37/15%
Menopausal status of 45 patients	Reproductive period 9/20%, Menopause 36/80%
Current use of high/medium potential hormone therapy, 45 patients	Yes 43/95% No 2/4%
FIGO stage	45 patients
IA	20/44%
IB	7/15%
II	14/31%
IIIA	0
IIIB	1/2%
IIIC1	3/6%
IIIC2	0
IVA	0
IVB	0
Histological subtype and grade	45 patients
Endometrioid adenocarcinoma G1 NG1	3/6%
Endometrioid adenocarcinoma G2 NG2	27/60%
Endometrioid adenocarcinoma G3 NG3	5/11%
Serous	4/9%
Mixed	4/9%
Carcinosarcoma	2/4%

Inclusion criteria:

- All patients with a diagnosis of endometrial cancer and atypical hyperplasia.

Exclusion criteria:

- Patients without hysterectomy or with a hysterectomy performed more than 120 days after ultrasound assessment.
- Final diagnosis other than endometrial cancer.
- Presence of tumor duplication or another synchronous gynecological malignancy.
- Incomplete ultrasound assessment.
- Refusal of signed consent to participate in the study.

Ultrasonography was conducted in a lithotomy position with an empty bladder. The ultrasound device initially zoomed in on the uterus in a mid-sagittal section for clearer visualization, evaluating the uterus from horn to horn (lateral to lateral wall) and in transverse cross-section from cranial to caudal. The subjective 2D assessment of myometrial and cervical invasion followed the International Endometrial Tumor Analysis IETA Terminology, considering tumor echogenicity, endometrial-myometrial junction, color Doppler result, and vascular pattern (Figure1).

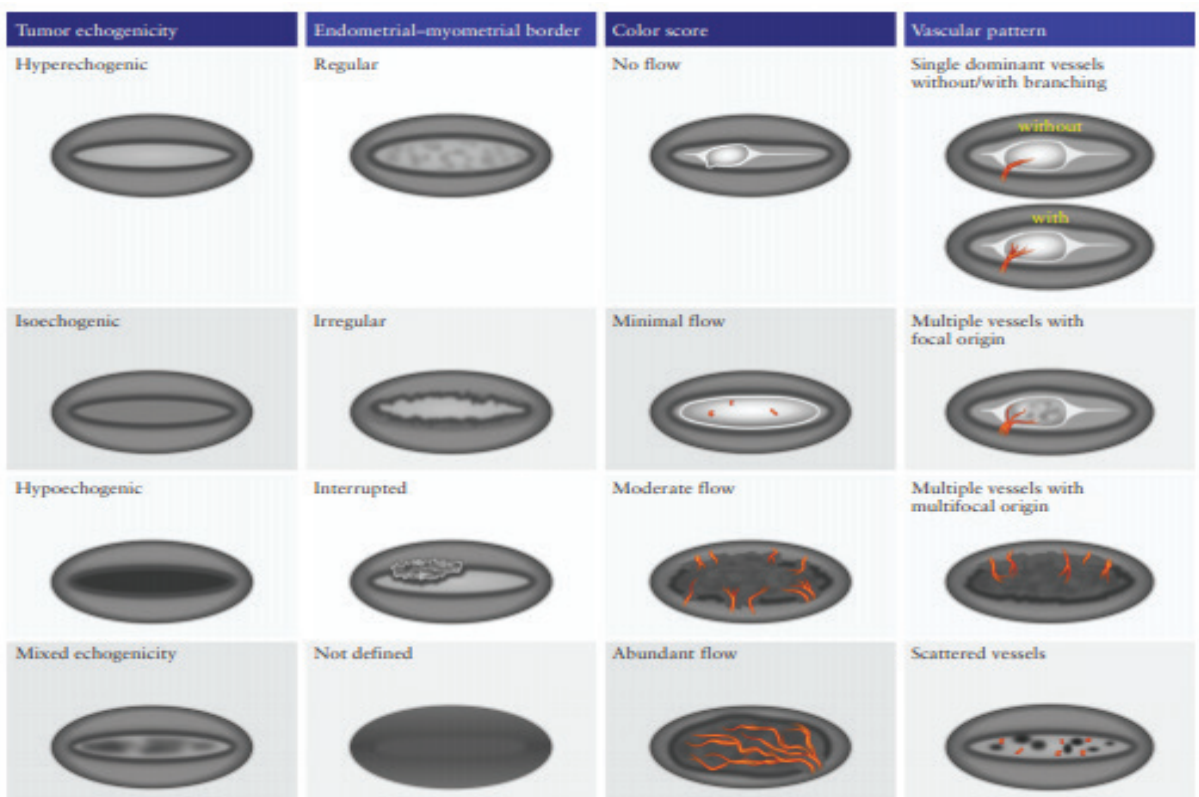
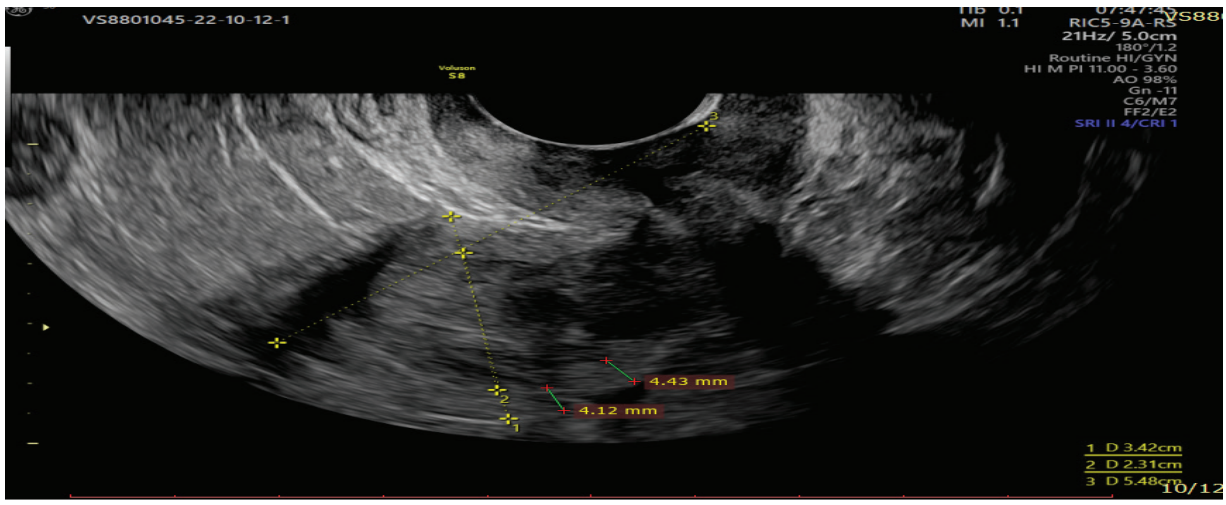


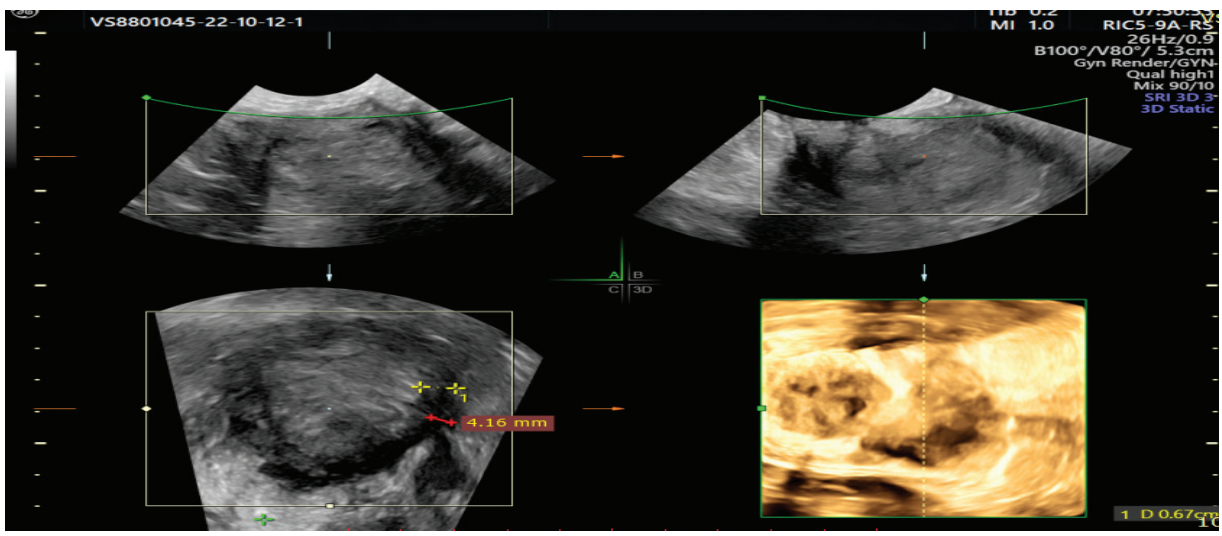
Figure 1. Schematic diagram summarizing morphological and Doppler features according to IETA terminology (18).

Tumor echogenicity can be isoechoic, hypoechoic, heterogeneous and hyperechoic. Endometrial myometrial junction can be regular, irregular, interrupted or undefined. Color Doppler: no flow, minimal flow, moderate flow, abundant flow.

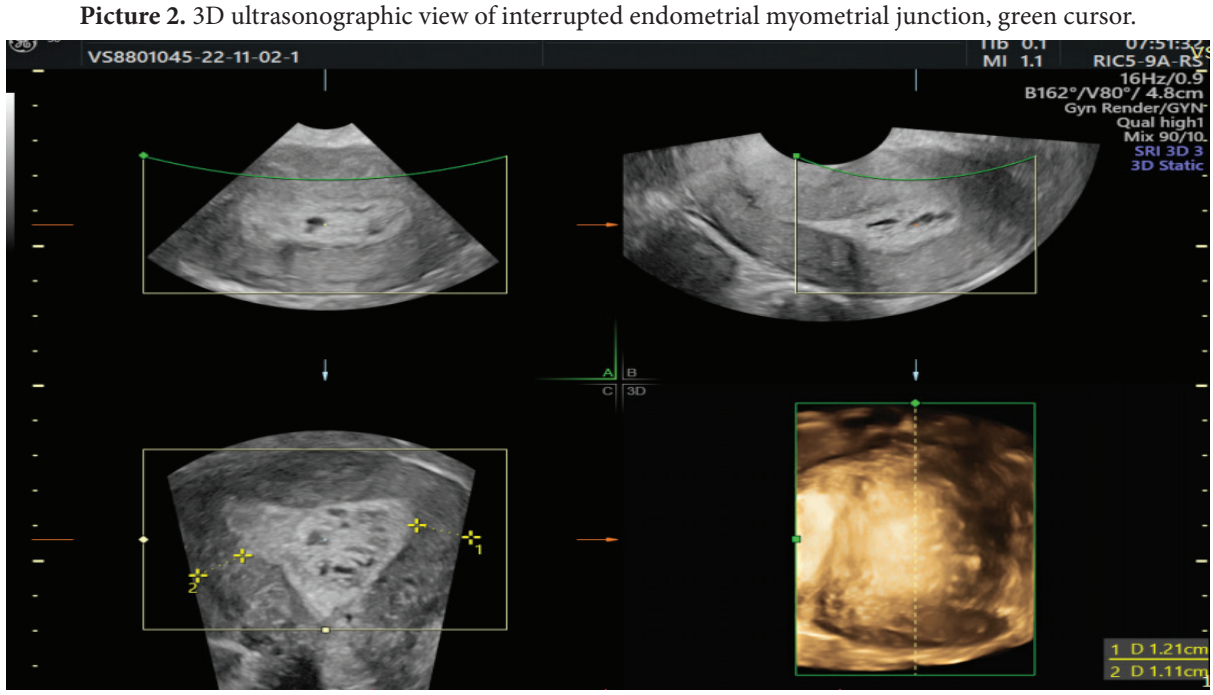
Vascular pattern: single blood vessel with or without laceration, multiple blood vessels of focal origin, multiple blood vessels of multifocal origin, scattered blood vessels(Pictures 1-6).



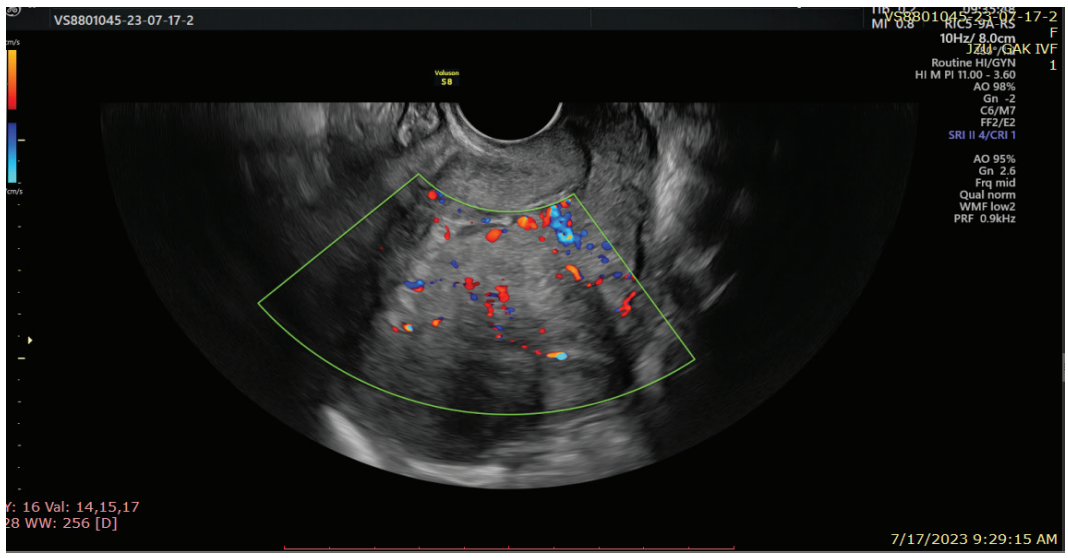
Picture1. Interrupted endometrial myometrial junction- green cursors.



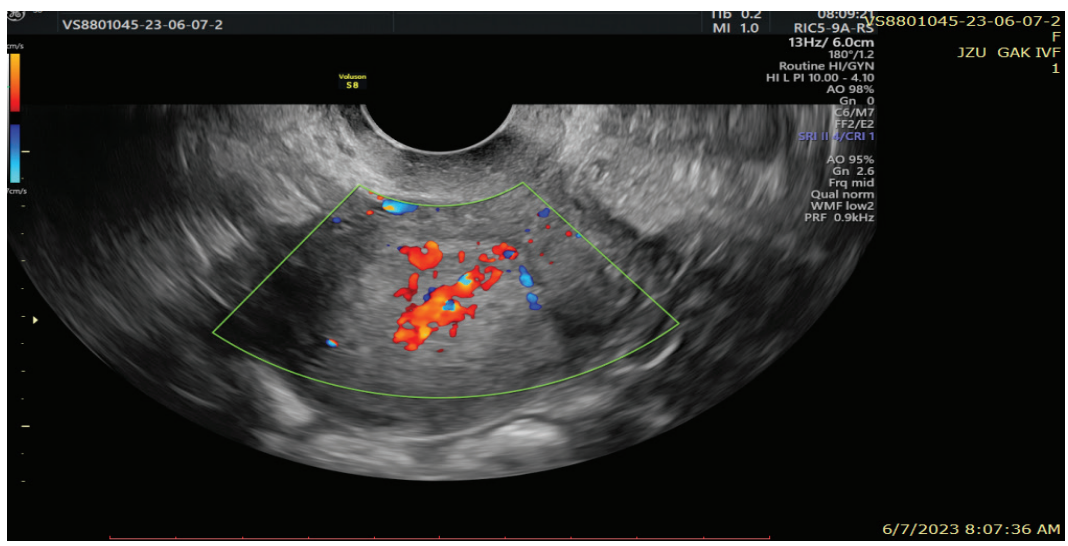
Picture 2. 3D ultrasonographic view of interrupted endometrial myometrial junction, green cursor.



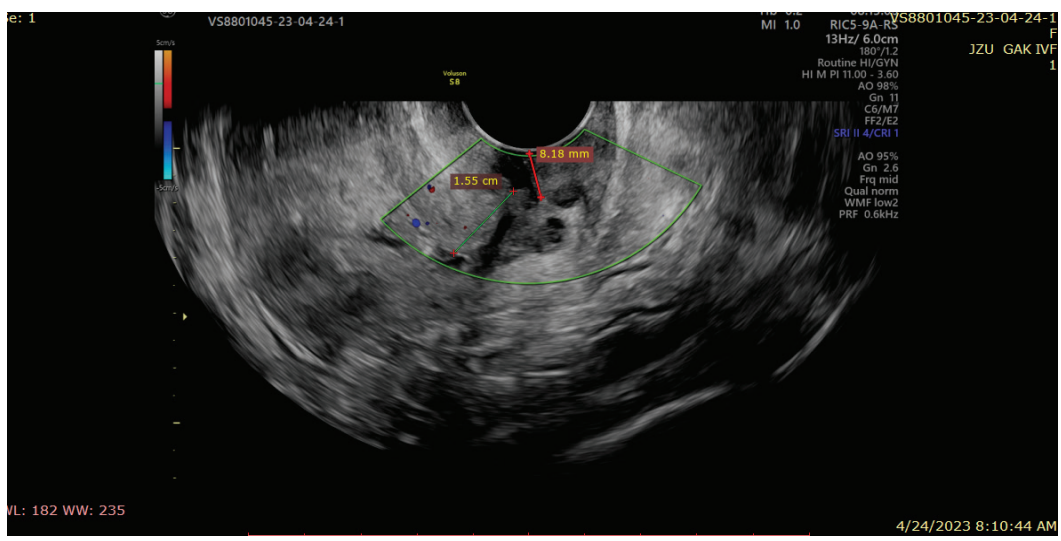
Picture 3. 2D and 3D ultrasonographic images with heterogeneous endometrium.



Picture 4. Doppler view of heterogeneous endometrium with interrupted endometrial myometrial junction and scattered blood vessels.



Picture 5. Prominent Doppler flow diagram.



Picture 6.Showing tumor invasion into the cervical stroma, visualizes clear demarcation of tumor echogenicity from the cervical stroma.

Results

A total of 45 patients were included in this study, for which statistical data on sensitivity, specificity, positive predictive value, negative predictive value, prevalence of disease, positive likelihood ratio, negative likelihood ratio and accuracy were calculated for the subjective methods not listed above. All of them are comparedto the definitive postoperative pathohistology.

Table 2. Subjective deep myometrial invasion.

Statistics	Value	95% CI
Sensitivity	88.00%	68.78% to 97.45%
Specificity	65.00%	40.78% to 84.61%
Positive Likelihood Ratio	2.51	1.36 to 4.65
Negative Likelihood Ratio	0.18	0.06 to 0.56
Disease prevalence (*)	55.56%	40.00% to 70.36%
Positive Predictive Value (*)	75.86%	62.96% to 85.32%
Negative Predictive Value (*)	81.25%	58.84% to 92.93%
Accuracy (*)	77.78%	62.91% to 88.80%

Table 3. Subjective cervical invasion.

Statistics	Value	95% CI
Sensitivity	76.47%	50.10% to 93.19%
Specificity	92.86%	76.50% to 99.12%
Positive Likelihood Ratio	10.71	2.74 to 41.77
Negative Likelihood Ratio	0.25	0.11 to 0.60
Disease prevalence (*)	37.78%	23.77% to 53.46%
Positive Predictive Value (*)	86.67%	62.49% to 96.21%
Negative Predictive Value (*)	86.67%	73.28% to 93.91%
Accuracy (*)	86.67%	73.21% to 94.95%

Discussion

The staging process for endometrial cancer differs from that of cervical cancer, where clinical staging is employed. As the most prevalent gynecological neoplasm, endometrial cancer staging is donesurgically. The most patients diagnosed with endometrial cancer undergo a hysterectomy with bilateral salpingo-oophorectomy and retroperitoneal lymphatic dissection to determine the extent of the disease. Lymph node involvement rates increase with nuclear-grade progression and myometrial invasion. Therefore, lymph node evaluation is crucial, especially for patients meeting Mayo criteria, indicating type 2 endometrial carcinomas, nuclear grade 3 endometrioid endometrial carcinomas, neoplasms invading over half of the myometrium, or neoplasms exceeding 20mm on imaging or intraoperative assessment (17).

Patients not meeting Mayo criteria have a lymph node involvement risk of less than 5%, making lymph node dissection unnecessary reducing complications such as lymphedema, cellulitis

and thrombotic events. This approach particularly benefits patients with advanced age, obesity, hypertension, diabetes and comorbidities, minimizingthe postoperative complications and improving long-term recovery and survival.

Subjective assessment using IETA terminology aids in distinguishing high-risk from low-risk endometrial cancers and is crucial in the prediction of myometrial and cervical invasion. Morphological differences between well, moderately, and poorly differentiated endometrioid carcinomas become apparent, with tumor size proving to be the only ultrasound predictor of high-risk cancer (18).

Studies comparing subjective and objective methods for myometrial and cervical invasion detection suggest that subjective assessments, particularly when utilizing IETA terminology, can be as effective as or even superior to objective measurements, such as that of F. MASCILINI, according to which subjective assessment of cervical and myometrial invasion is as good or better than any objective measurement technique (19).

The one of J. L. Alcázar reveals that the diagnostic potential of transvaginal ultrasonography in detecting deep myometrial invasions in women with endometrial cancer, gives a cumulative sensitivity of 82% and a cumulative specificity of 81%. Comparing subjective with objective measurement techniques,it has been observed that all methods are similar (20).

Filip Frühauf concluded that the sensitivity of the subjective assessment of myometrial invasion was superior to the investigated objective models (21).

In our subjective assessment of deep myometrial invasion based on the IETA terminology, the sensitivity and specificity are 88% and 65%, respectively (Table 2).

Various variables from the subjective and objective techniques for assessing myometrial and cervical invasion affect the accuracy of the results, leading to overestimation or underestimation. The accuracy of subjective assessment of myometrial and cervical invasion by ultrasound was significantly influenced by tumor size, tumor vascularization density, tumor vessel architecture and histological appearance. However, it was not significantly affected by BMI, uterine position and picture quality (22).

Subjective methods can also assess cervical invasion. Subjective assessment of cervical invasion may be more successful because dynamic ultrasonographic assessment can differentiate bulging or protrusion into an endocervical canal from actual cervical stromal invasion. Cervical stromal invasion is characterized by a loss of clear demarcation of the endometrial lesion from the cervical stroma and by increased tumor perfusion.

Our subjective assessment of cervical invasion had a sensitivity of 76% and a specificity of 92% (Table 3).

Regarding 3D Ultrasonography, there are different data regarding its effectiveness in predicting deep myometrial and cervical stromal invasion. Its advantages are that it can provide significant information about myometrial invasion of the uterine angles in a coronary section (23).

However, 2D ultrasonography is less effective than 2D ultrasonography for assessing myometrial invasion (23). Subjective assessment of myometrial invasion has a sensitivity of 92.6% and a specificity of 82.3% (24).

The possibilities of 3D ultrasonography, such as volume computerized imaging, computerizedultrasonographic tomography and rendering, can help assess myometrial and cervical invasion (Picture 3) (24).

Conclusion

Subjective assessment of deep myometrial and cervical invasion based on the IETA terminology is of great help; its sensitivity and specificity are close to, even better than, the previously known objective parameters for assessment of deep myometrial and cervical invasion. Our results are similar to other relevant publications in this field. Transvaginal ultrasonographyalso has accuracy similar to that of nuclear magnetic resonance.Subjective evaluation methods can significantly benefit patients' selection of the optimal surgical modality, especially poor surgical candidates.

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WHAT DID WE LEARN DURING CLASSIFICATIONS TO SEVERE AND NON-SEVERE COVID-19 PATIENTS IN AN EMERGENCY UNIT ON THE ADMISSION DAY?

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Abstract

Introduction: We aim with this study to present the lessons we've learned during the pandemic time and to demonstrate the methods that we used for the classification of the severity of the patient's condition. The most studies focus on derangement in vital signs including oxygen saturation when an infection like COVID-19 affects the body or before any clinical deterioration. On contrary, it has been found that low oxygen saturation can be monitored even if the patient is feeling well, and symptoms are absent in the phenomenon named silent hypoxemia. Many studies highlight the beneficial use of screening tools like NEWS 2 when silent hypoxemia is recognized.

Material and Methods: This is a retrospective study of 117 patients with confirmed COVID-19 disease from January 2021 and January 2022. Assessment of patients was performed at the Emergency Unit of City General Hospital "8th of September", Skopje, Macedonia, transformed into the main COVID-19 Center during the pandemic. We measured vital signs and NEWS 2 score in each patient on the admission day. Patients were classified according to Chinese diagnosis and treatment protocol for COVID-19 into two groups: severe and non-severe. We compared demographic factors (age, gender), comorbidities, shortness of breath, radiological findings, length of hospital, and homestay between the groups.

Results: 117 patients met the criteria for the study. 40% of the patients reported severe type. NEWS2, age, shortness of breath, severe general condition and radiological findings were significantly greater in the severe group, but the level of mean O2 saturation, length of hospital stay and incidence of comorbidities were higher in the non-severe group. The author concludes that a high percentage of comorbidities in the severe group can be a cause for severity in younger patients.

Conclusion : The lesson we learned with this triage is that patient's feelings are not always related to his/ her medical condition. Besides he / she felled well, there might be a beginning of a storm of clinical deterioration. Therefore, using screening methods such as NEWS 2 score can be beneficial during practicing triage on admission day.

Key Words: *COVID-19, emergency admission, triage.*

Introduction

Beyond COVID-19, the lessons we learned during the pandemic time, motivated us to present the methods that we used for classification of the severity of the patient's condition in order to optimize his/her outcome. Once the patient arrives in the emergency unit, and later on during hospitalization, monitoring of vital signs such as blood pressure, heart rate, temperature, respiratory rate and oxygen saturation are commonly used for estimating patients' medical condition (1). Derangement in oxygen saturation is set in among these vital signs when an infection like COVID-19 affects the body or prior to any clinical deterioration (2). The strong linking of the coronavirus to respiratory cells is one of the reasons for impaired oxygen supply and derangement in oxygen saturation as a consequence of that (3). Thus, several studies have hallmarked the main manifestation of low oxygen saturation in patients with COVID-19 (4,5).

Additionally, changes in other vital signs: heart rate and breathing rate, followed by symptoms such as shortness of breath, blush coloring in face and lips, and chest pain was observed in patients when hypoxemia with low oxygen saturation developed (6).

Contrary, it has been found that low oxygen saturation could be monitored even if the patient was feeling well and didn't show any signs of disease (7). The explored phenomenon was named silent hypoxemia (8). Therefore, it is important to perform measurements of oxygen saturation in all patients with COVID-19 pneumonia regardless of the type of disease.

The World Health Organization recommends noninvasive measurement of oxygen saturation of COVID-19 patients with an electronic device such as pulse oximetry (9). In patients with silent hypoxemia, when symptoms are absent, screening tools like NEWS 2 can be beneficial in order to predict early clinical deterioration and risk for severity (10). We applied NEWS 2 among the present study's screening tools (11). Furthermore, patients' outcomes can be prognosis by applying clinical classifications (12). We used the definitions of the type of disease according to the Guidelines of diagnosis and treatment protocol for COVID-19 (trial version 7) issued by the National Health Commission of the People's Republic of China (13). This retrospective study aims to demonstrate the methods of the medical assessment for clinical deterioration and classification of the type of disease and to discuss the findings between severe and non-severe patients during practicing triage on admission day.

Material and Methods

The present study followed a retrospective analysis of 117 COVID-19 patients conducted at the Emergency unit of City General Hospital "8th of September", Skopje, Macedonia, after obtaining ethical approval from the institutional Ethics Committee according to the situations for emergency infected disease (14).

All patients had confirmed COVID-19 diagnosis by positive revere-transcription polymerase chain reaction assay of nasopharyngeal swabs.

In this study, we included all patients who arrived in the emergency unit between January 2021 and January 2022. Medical data collected for each patient were: demographic factors (age, gender), medical history (with or without comorbidities), clinical symptoms (shortness of breath defined as clinical evidence of altered breathing), radiological findings (normal, pattern, opacity). The patients underwent monitoring of the level of oxygen saturation and assessment for clinical deterioration.

The blood's oxygen saturation level was measured using a pulse oximeter placed over the patients' fingers.

Clinical deterioration was assessed with the NEWS 2 score calculation using an online calculator (https://www.mdcalc.com/calc/10083/national-early-warning-score-news-2). NEWS2 score is calculated by adding the scores of the following physiological parameters: systolic blood pressure, heart rate, temperature, respiratory rate, oxygen saturation, need for supplemental oxygen and level of consciousness.

According to the definition of the type of disease in the Chinese diagnosis and treatment protocol for COVID-19, we divided the patients into two groups: non-severe (a disease with mild symptoms and pneumonia can be seen on the imaging findings) and severe (severe and critical illness, respiratory rate >30 times/min, in resting state oxygen saturation <93%, respiratory failure requiring mechanical ventilation).

Oxygen saturation, NEWS 2 score and clinical outcomes: length of hospital stay (LOS) and length of home stay (LHS) were compared between the two groups. LOS and LHS were expressed as absolute numbers. LOS was counted from the day of admission till the day of discharge. LHS represents the number of days from the beginning of the symptoms to the day of admission to the hospital.

Results

117 results with confirmed COVID-19 pneumonia were retrospectively compared. According to the type of disease 40% (n=47) of the patients had a severe type. The study population consisted of 43 (59.7%) men and 27 (60%) women in the non-severe group and 29 (40%) men and 18 (40%) women in the severe group at the mean age of 60.19 ± 14.39 for non-severe group and 54.47 ± 13.41 for severe group retrospectively. We identified that 50 (71.4%) non-severe and 31 (66%) severe patients had comorbidities. The participants with severe disease were significantly younger than the participants with non-severe disease (54.47 ± 13.41 *vs*. 60.19 ± 14.39) (t=2.165, p=0.032).

A severe type of disease was significantly associated with shortness of breath (p=0.003), severe general condition (p=0.001) and radiological finding (p<0.001).

LOS and LHS were not associated with the type of disease (p=0.658 and p=0.357).

The frequency of patients with severe COVID-19 was significantly higher in the sub-group with opacities (62.3%) than in the sub-groups with pattern (10.3%) and normal radiological findings (n=0) (χ^2=34.647, p<0.001).

The mean NEWS score was significantly higher in patients with severe COVID-19 (6.7 ± 1.65) than in patients with non-severe disease (4.21 ± 2.36) (t=-6.71, p<0.001).

On the contrary, the mean O_2 saturation was higher in patients with non-severe COVID-19 (89.66 ± 5.3 *vs*. 53.68 ± 20.35) (t=11.85, p<0.001) (Table 1.)

Table 1. Demographic and clinical characteristics of the patients.

	Non-severe (N=70)	Severe (N=47)	Statistic, *p* value
Age (years) (mean ± SD)	**60.19 ± 14.39**	**54.47 ± 13.41**	***t*=2.165 *p*=0.032**
Gender - n (%) Male (n=72) Female (n=45)	 43 (59.7) 27 (60)	 29 (40.3) 18 (40)	χ^2=0.001, *p*=0.976
With co-morbidities - n (%)	50 (71.4)	31 (66)	χ^2=0.395, *p*=0.53
Length of hospital stay (days) (mean ± SD)	13.31 ± 8.66	12.6 ± 8.45	*t*=0.444, *p*=0.658
Length of home stay before hospitalization (days) (mean ± SD)	5.43 ± 7.85	4.34 ± 2.18	*t*=0.926, *p*=0.357
Shortness of breath - n (%)	2 (2.9)	9 (19.1)	χ^2=8.762, *p*=0.003
Severe general condition - n (%)	8 (11.4)	17 (36.2)	χ^2=10.245, *p*=0.001
Radiological findings - n (%) 1 Normal (n=9) 2 Pattern (n=39) 3 Opacity (n=69)	 9 (100) 35 (89.7) 26 (37.7)	 0 4 (10.3) 43 (62.3)	χ^2=34.647, *p*<0.001
NEWS score (mean ± SD)	4.21 ± 2.36	6.7 ± 1.65	*t*=-6.71 *p*<0.001
O_2 Saturation (mean ± SD) (%)	89.66 ± 5.3	53.68 ± 20.35	*t*=11.85 *p*<0.001

Discussion

After we had summarized our results, we wrote the findings between the two groups of patients and discussed them in order to present our work during the triage of the patients.

COVID patients are exposed to clinical deterioration and progression of illness disease (15). For each patient, after he/she arrives in the emergency department, a medical examination starts with measuring his/her vital signs.

Several reports have shown that derangement in admission vital signs, such as low oxygen saturation and elevated respiratory rate, have been observed when the patient is at risk for clinical deterioration (16,17). Another way to assess disease progression at arrival time in the emergency unit is to apply surveillance systems such as screening tools (17,18). Among them, in this study, we applied the screening tool NEWS 2. The NEWS 2 score is calculated as the sum of individual scores for these physiological parameters: systolic blood pressure, heart rate, temperature, respiratory rate, oxygen saturation, need for supplemental oxygen and level of consciousness. This study found that the NEWS 2 score was significantly higher in patients with severe COVID (6.7 ± 1.65), than (4.21 ± 2.36) in patients with non-severe disease (*t*=-6.71, *p*<0.001). We also tried to identify the factors for a high NEWS 2 score. The need for supplement

oxygen and oxygen saturation are the maximum scored parameters in NEWS 2's score calculation with points 5. The results of our study showed a strong correlation between mean low oxygen saturation and severe type of disease ($p<0.001$). One of the reasons for hypoxemia and low oxygen saturation as a consequence of that, is the existence of comorbidities. Patients with comorbidities may have reduced hypoxic response even before the beginning of COVID-19 pneumonia (20). Reported incidence of severe patients with comorbidities in our study was 31%, compared to 50% in the non-severe group of patients. Furthermore, comorbidities such as obesity, hypertension, diabetes Mellitus, kidney failure cancer and heart disease are recognized as risk factor for the severity of disease (20). The fact that comorbidities are more prevalent as the patient gets older, can explain the relationship between age and the severity of COVID-19 (22). However, in our study, patients from the severe group were significantly younger than non-severe patients. A high percentage of comorbidities in the severe group can answer why our younger patients had a severe type of disease instead of a non-severe type. In reviewing the literature, no data was found for a clear cut-off for hypoxemia, but 90% saturation was used by a previous study (23,7). Concerning this data in our study, the patients with a non-severe type of disease also developed hypoxemia and had low oxygen saturation as a repercussion of that. The most obvious explanation for low oxygen saturation is that COVID patients regardless the type of disease, might not complain of dyspnea or other symptoms when hypoxemia was set, and this condition is named silent hypoxemia. Analyzing this data, we noticed that shortness of breath as one of the symptoms of COVID-19 pneumonia was not significantly related to the type of disease. In this study, the Chinese diagnosis and treatment protocol for COVID-19 was applied. According to it, non-severe patients might be with or without pneumonia on imaging findings. Positive chest X-ray findings, such as ground glass opacities, are another reason for hypoxemia even if the patient is without subjective dyspnea (24). We also found a significant correlation between imaging findings and the type of disease $p<0.001$. Compared between the two groups, large number of patients with a non-severe type of disease also had opacity on imaging findings and low oxygen saturation during measurements of vital signs as a result of that.

Previous studies evaluating the relationship between severity with length of hospital stay and mortality found a strong association (25). The finding in our study was contrary to studies related to length of hospital stay. This study has been unable to demonstrate the correlation between severity and length of hospital stay. Our analysis stratified all patients who arrived in the emergency unit. Among them were patients coming from their homes and patients transferred from another hospital. We did not have exact data for the length of hospital stay for patients who arrived from another hospital. So, in our study, the calculation of the length of hospital stay includes only the days of hospital stay in our hospital. This data is also one of the limitations of our study.

Another limitation is the time of measurement of admission vital signs. Because we included all patients as mentioned above, the day of admission and the day of the beginning of symptoms were different and could not be matched. We measured NEWS 2 score at the time of admission but evaluating the NEWS 2 score at regular intervals during the hospital stay would be beneficial.

Conclusion

COVID-19 patients may present with disruption in vital signs without symptoms. Therefore, initial assessment with screening tools is needed for better hospital management, especially in hospital limits like beds and personnel. We also can confirm that the use of screening tools helped us in deciding which patients should be hospitalized for further treatment. The lesson we learned with this triage is that his/ her feelings were not always related to his/ her medical condition. Although the patient felt well, there might be a beginning of a storm of clinical deterioration.
Screening methods can help in that state of mismatch between symptoms and the clinical picture.

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DOES THE APOLIPOPROTEIN E GENOTYPE INCREASE THE RISK OF POSTOPERATIVE DELIRIUM IN ADULT PATIENTS?

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Abstract

Background: The relationship between genetic predisposition and the development of postoperative delirium has not yet been established. The e4 allele of the apolipoprotein E gene has been reported as a genetic risk factor for delirium.

Objective: This paper analyzed the relationship between the frequency of genotypes of the APOE rs7412/rs429358 polymorphism, which contains the minor allele e4, and the occurrence of postoperative delirium.

Material and Methods: The study included patients aged 65 years and older without pre-existing cognitive impairment admitted to the University Clinic for Traumatology and Orthopedics for operative treatment of a fracture of the upper end of the thighbone. The Confusion Assessment Method (CAM) confirmed the delirium diagnosis. APOE rs7412/rs429358 polymorphism genotypes were determined by molecular genetic analysis using the quantitative real-time amplification method (qRT-PCR) on DNA samples extracted from venous blood leukocytes.

Results: The presented results are from analyzed samples and data from 51 patients. Out of these, postoperative delirium was diagnosed in 12 patients, while in 39 patients weren't registered, and they are the control group in the trial.

Conclusion: This study results indicate the association of the studied polymorphism in the apolipoprotein E gene, which contains the minor allele e4, with the occurrence of postoperative delirium in this group of adult patients. A larger group is necessary to reach more valid conclusions.

***Key Words**: adult patients, apolipoprotein E, genotype, postoperative delirium.*

Introduction

Postoperative delirium (POD) occurs frequently in elderly patients, with an incidence that varies widely from 20% to 55% after high-risk procedures that include vascular, orthopedic and cardiac operations (1-4). A meta-analysis of 26 studies of postoperative delirium presented an incidence of 4.0 to 53.3% in patients with hip fractures and 3.6 to 28.3% in elective orthopedic surgeries (5). Postoperative delirium has adverse outcomes, such as increased morbidity and mortality, cognitive and functional decline leading to loss of autonomy and reduced quality of life, prolonged hospital stay, institutionalization and additional health care costs. Patients

with postoperative delirium may be at risk of developing long-term postoperative cognitive dysfunctions and the onset of dementia (6,7).

The pathogenesis of POD is not yet clearly understood. However, there are many evidences from animal and human studies regarding the underlying processes behind this clinical syndrome. Maldonado's landmark review described that potential mechanisms can be grouped into two categories: neuroinflammation and oxidative stress, which likely interact by promoting neurotransmitter dysregulation, and neuronal network dysfunction (8). The neuroinflammatory theory suggests that several noxious stimuli, such as surgical stress and infection, trigger the activation of the inflammatory cascade with the acute release of inflammatory mediators into the bloodstream. Acute peripheral inflammatory stimulation induces activation of brain parenchymal cells (microglia and astrocytes) and expression of proinflammatory cytokines and inflammatory mediators in the CNS. These neuroinflammatory changes cause neuronal and synaptic dysfunction and subsequent neurobehavioral and cognitive symptoms. The oxidative stress hypothesis proposes that brain hypoperfusion induces local ischemia that triggers a chain of events. First, there is increased production of reactive oxygen products, and then the reactive oxygen products lead to excitotoxicity, apoptosis and local inflammation.

Apolipoproteins cannot cross the blood-brain barrier but are still expressed in the central nervous system (CNS) by astrocytes, microglia and oligodendrocytes, where they transport phospholipids and cholesterol for neuronal membrane regeneration and remyelination. There are three ApoE isoforms – E2, E3 and E4 derived from the apolipoprotein E gene allelic variants. Apolipoprotein E (ApoE) is involved in recovering the central nervous system from injury. Apolipoprotein E regulates normal neuronal function through cholesterol transport and cell repair (9). The APOE gene is located on the long arm of chromosome 19. It has the chromosomal location 19q13.2 and encodes apolipoprotein E. The protein itself can be in one of three major isoforms, encoded by variant alleles that depend on the nucleotide sequence of the polymorphic positions rs429358 and rs7412 in the fourth exon of the APOE gene. According to the amino acid residues encoded by codons 112 and 158, the three isomorphs of apolipoprotein E are distinguished, as shown in Table 1.

Table 1. Nucleotide and amino acid sequences in the studied polymorphisms in the APOE gene

APOE-alleles	polymorphisms		codons	
	Rs429358	Rs7412	112	158
ε2	T	T	Cys	Cys
ε3	T	C	Cys	Arg
ε4	C	C	Arg	Arg

Depending on the presence of the ε2, ε3, and ε4 alleles at the APOE gene locus, each individual may have one of the following six genotypes: ε2/ε2, ε3/ε3, ε4/ε4, ε2/ε3, ε2/ε4 and ε3.

ApoE4 is more vulnerable to degradation than other isoforms, thereby limiting lipid mobilization for repair. Hypothesized pathophysiological mechanisms that explain the relationship between ApoE and delirium, include modulation of brain inflammatory response and modification of glial activation, blocking nicotinic acetylcholine receptors, causing an anticholinergic effect that has been hypothesized in delirium, and suppression of cerebral glucose metabolism in APOE ε4 carriers may represent another pathophysiological mechanism. In already damaged brains, the presence of the APOE ε4 allele accelerates the promotion of Aβ aggregation and fibril formation, leading to the progression of dementia (10-12).

The ε4 allele of the apolipoprotein E gene has been hypothesized as a genetic risk factor for delirium.

Material and Methods

This study included 51 patients who underwent emergency surgery due to a fracture of the upper end of the thighbone (femur), aged 65 and older, and ASA groups I, II, or III. Patients with cognitive impairment, dementia or other neurodegenerative diseases, stroke with the residual deficit, use of drugs that affect cognitive functions, abuse of alcohol and drugs, blindness, deafness, contraindication for spinal anesthesia, and admission to the intensive care unit were not taken into the study. We assessed preexisting cognitive impairment with two validated instruments, the Short Mental Test (AMT 10) (13,14) and the Cognitive Decline Information Questionnaire - Short Form (IQCODE - SF) (15). Screening for POD began immediately after surgery and was monitored throughout the hospital stay with the Confusion Assessment Method (CAM) (16).

From patients who met the inclusion criteria for the study, we collected a 3mL venous blood sample with the anticoagulant EDTA-Na2 (disodium salt of ethylenediamine tetraacetate) in a vacuum test tube. Samples were taken only from patients who, after a detailed explanation of the procedure, the goals and their rights, signed a written consent.

The APOE rs7412/rs429358 polymorphism genotypes were determined by molecular genetic analysis using the quantitative real-time amplification method (qRT-PCR) on DNA samples extracted from venous blood leukocytes from patients. Amplification curves were analyzed with the StepOne software (Applied Biosystems) using the allelic discrimination method, which determined the APOE rs7412/rs429358 polymorphism genotype.

The association of the existence of postoperative delirium with the genotypic and allelic frequency of the APOE rs7412/rs429358 polymorphism in patients was analyzed by Pearson's Chi-square test and Fisher's exact test. According to these data, the odds ratio was also calculated. The CI (confidence interval) calculations are performed at 95%, that is, at $p<0.05$. Values of $p<0.05$ are considered statistically significant, while those with $p<0.01$ are considered highly significant. S t atistical calculations were performed using XLSTAT 2016 and GenAlEx 6.5 software add-ins installed on Microsoft Excel 2016.

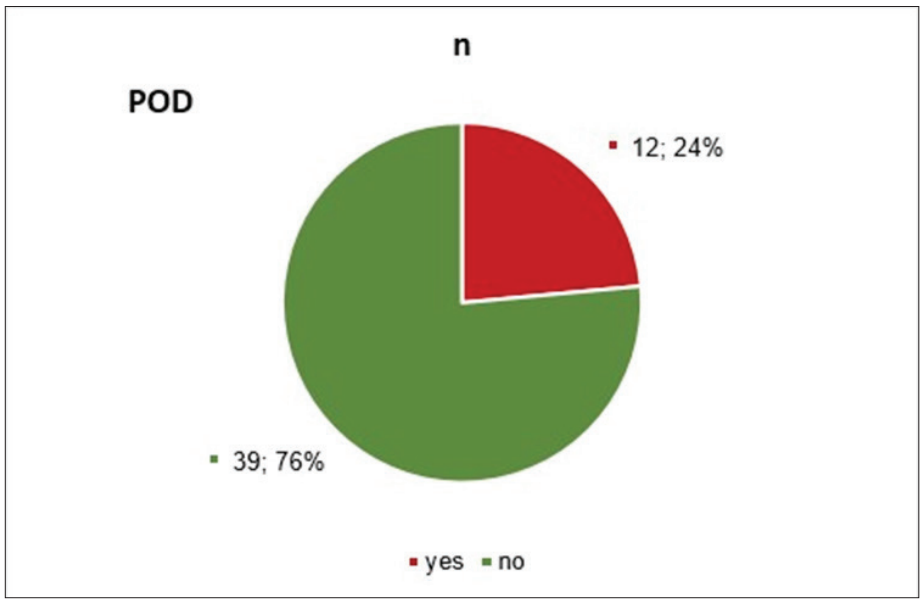
Results

This paper presents the results of the analysis of samples and data from 51 patients who underwent surgery on the upper end of the femur. Postoperative delirium was diagnosed in 12 patients, while it wasn't registered in 39 patients, and they are the control group in the trial (Table 1 and Graph 1).

Table 1. Prevalence of postoperative delirium in patients,

POD	n	%
Yes	12	23.53
No	39	76.47
Total	**51**	**100.00**

Chart 1. Prevalence of postoperative delirium in patients.



The data on gender and age distribution in the studied two groups of patients (the group with registered postoperative delirium and the control group) are shown in Tables 2 and 3 and in Charts 2 and 3.

Table 2. Gender distribution of the two groups of patients.

Gender	Group with POD		Control group		Fisher's exact test
	n	%	n	%	*p*
male	**3**	25.00	9	23.08	1.000
female	9	75.00	30	76.92	
total	9	**100.00**	39	**100.00**	

Chart 2. Gender distribution of the two groups of patients.

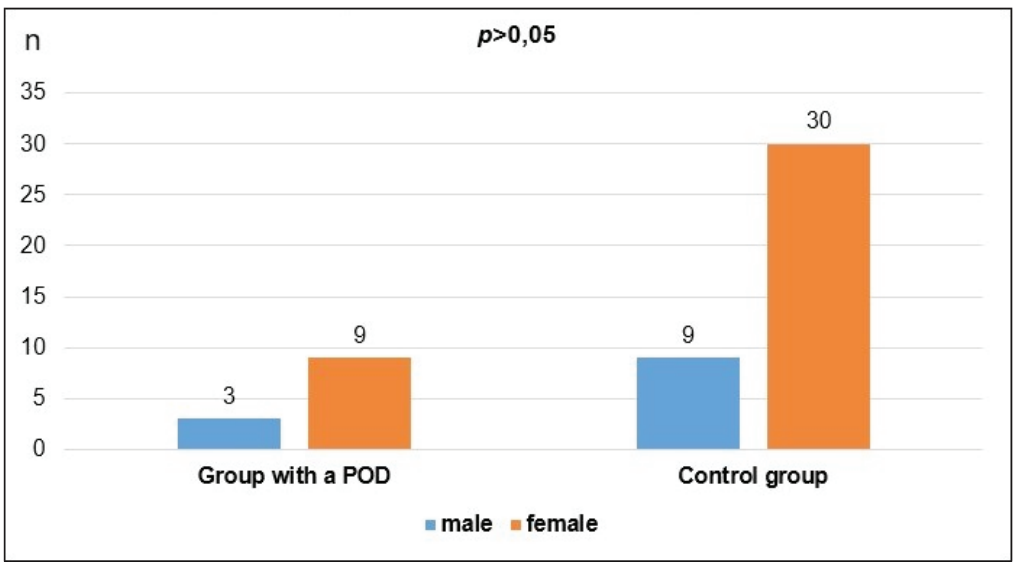
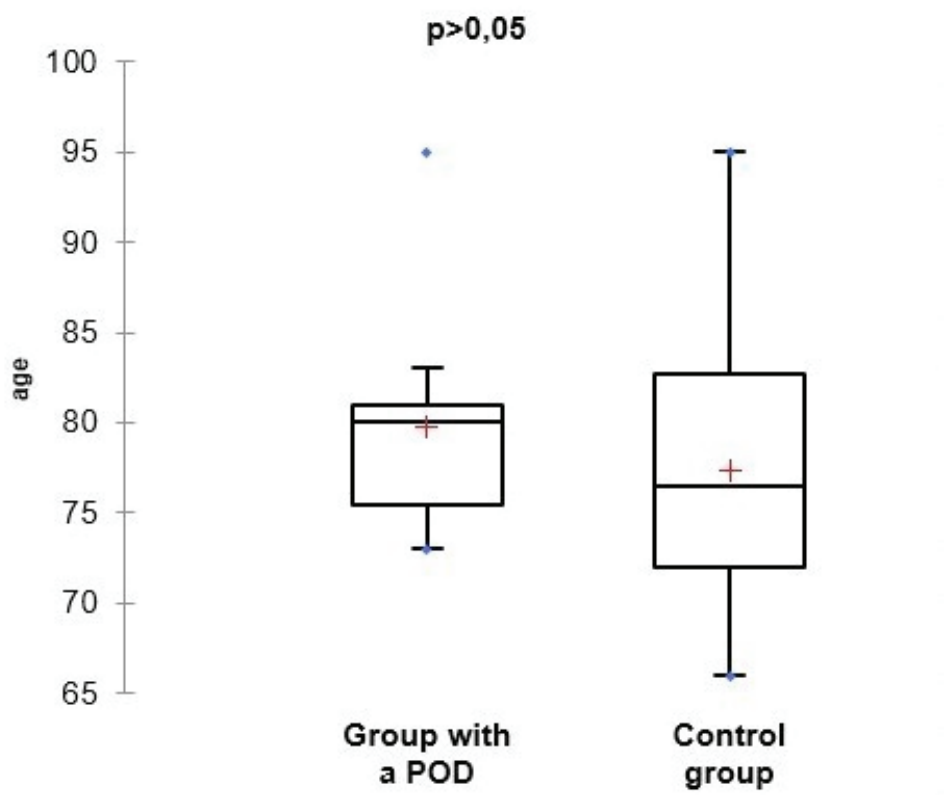


Table 3. Age structure of the two groups of patients.

Parameter (years)	Group with POD	Control group	Student t-test
n	12	39	0.323
average	79.82	77.37	
SD	6.23	7.18	
min. age	73	66	
max. age	95	95	

From the presented data and the results of the statistical analysis of the gender and age structure of the patients, we can conclude that the differences between the two groups do not have statistical significance (p>0.05). This comparison means that the two groups are balanced by gender and age, facilitating their further comparison.

Chart 3. Age structure of the two groups of patients.

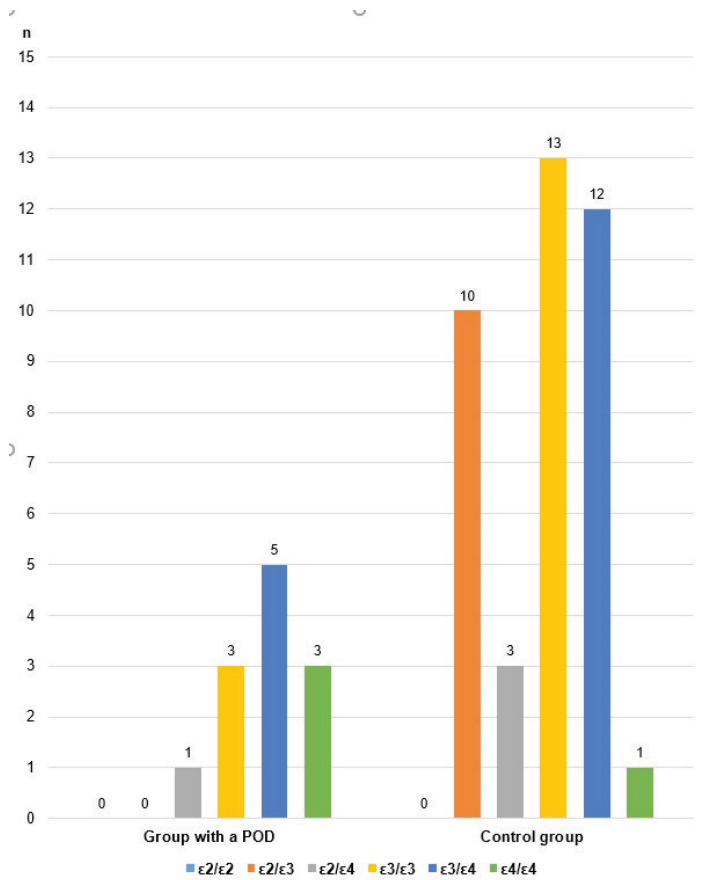


The results of the analyses obtained by determining the genotypes of the rs7412/rs429358 polymorphism in the APOE gene are shown in Table 4 and Charts 4 and 5.

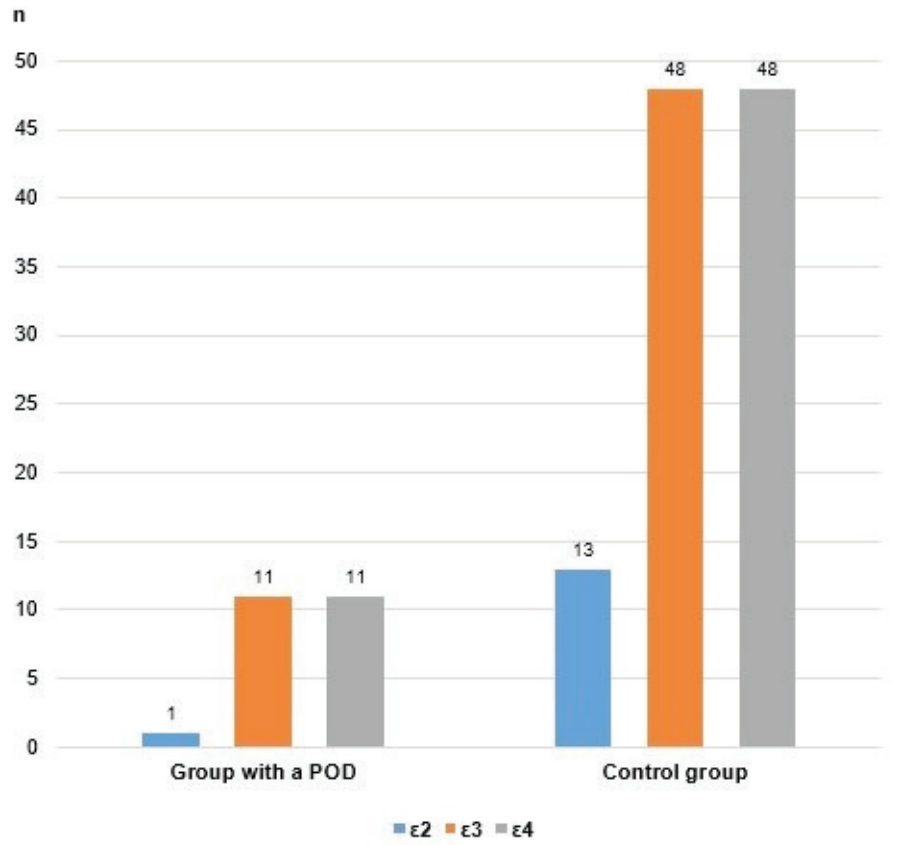
Table 4. APOE rs7412/rs429358 genotypes in both groups of patients

Group	APOE rs7412/rs429358	n	%
Group with POD	ε2/ε2	0	0.00
	ε2/ε3	0	0.00
	ε2/ε4	1	8.33
	ε3/ε3	3	25.00
	ε3/ε4	5	41.67
	ε4/ε4	3	25.00
	Total	**12**	**100.00**
Control group	ε2/ε2	0	0.00
	ε2/ε3	10	25.64
	ε2/ε4	3	7.69
	ε3/ε3	13	33.33
	ε3/ε4	12	30.77
	ε4/ε4	1	2.56
	Total	**39**	**100.00**

Chart 4. APOE rs7412/rs429358 polymorphism genotypes in both groups of patients.



Graph 5. Alleles of the APOE rs7412/rs429358 polymorphism in both groups of patients.



Due to the relatively small number of cases analyzed in this paper, we evaluated the existence of a genetic association of the investigated polymorphism with postoperative delirium by combining the genotypes and alleles according to whether they contain the ε4 allele, with the modified genotypic, as well as with the allelic and additive model. The results are shown in Table 5.

Table 5. Genetic-association analysis.

Genetic model	APOE rs7412/rs429358 genotype/allele comb.	Group with POD		Control group		x^2	p	OR (95% CI)
		n	%	n	%			
Genotypic	**ε2/ε2 + ε2/ε3 + ε3/ε3**	3	25.00	23	8.97	ref.	ref.	ref.
	ε2/ε4 + ε3/ε4 + ε4/ε4	9	75.00	16	1.03	4.238	**0.040**	4.313 (1.007 – 18.461)
	Total	12	100.00	39	00.00			
Allelic	**ε2 + ε3**	12	50.00	61	8.21	7.175	**0.007**	3.588 (1.368 – 9.409)
	ε4	12	50.00	17	1.79			
	Total	24	100.00	78	00.00			
Additive	**0 ε4**	3	25.00	23	8.97	2.374	**0.018**	/
	1 ε4	6	50.00	15	8.46			
	2 ε4	3	25.00	1	.56			
	Total	12	100.00	39	00.00			

According to the obtained calculations, the frequency of combinations of genotypes that do not contain the ε4 allele (ε2/ε2 + ε2/ε3 + ε3/ε3) is significantly higher (58.97%) in the control group, as opposed to a lower representation (25%) in patients with postoperative delirium. This genotype was used as a reference for the calculation according to the modified genotypic model.

On the contrary, the frequency of combinations of genotypes containing the ε4 allele (ε2/ε4 + ε3/ε4 + ε4/ε4) is significantly higher in patients with postoperative delirium (75%) compared to control patients in whom no delirium was registered (41.03 %). This difference is statistically significant ($p<0.05$) with the Chi-square test and confirmed with Fisher's exact test.

The calculated probability index OR is 4.313. Statistically, such value implies that the carriers of one of the genotypes containing the ε4 allele (ε2/ε4 + ε3/ε4 + ε4/ε4) have a 4.3 times higher probability of developing postoperative delirium during traumatological operations, compared to patients who are carriers of a genotype that does not contain the ε4 allele (ε2/ε2 + ε2/ε3 + ε3/ε3). This difference is statistically significant ($p=0.040$). The 95% confidence interval ranges from 1.007 to 18.461.

Analysis with the allelic model also supports a statistically significant association of the presence of the ε4 allele with an increased probability of postoperative delirium. According to this genetic-associative model, carriers of the ε4 allele have a 3.58 times higher chance of developing this complication than patients who do not carry the ε4 allele. In this calculation, the difference is statistically significant ($p=0.007$). The confidence interval at 95% is in the range of 1.368 to 9.409.

Further genetic analysis was performed with the additive model, comparing the frequencies of individuals who are not carriers of the ε4 allele (marked as 0 ε4), than of those who are carriers of one ε4 allele (1 ε4), i.e., of two ε4 alleles (2 ε4).

The calculations performed with the Cochran-Armitage ordinal test show a statistically significant genetic association of the ε4 allele with postoperative delirium ($p<0.05$). Odds ratio (OR) calculation is not possible with this model.

Discussion

In this paper, our interest was focused on the analysis of the association of the occurrence of postoperative delirium with the polymorphism in the apolipoprotein E gene, which contains the minor allele e4, among elderly patients admitted to the medical department of the Clinic for Traumatology and the Clinic for Orthopedics, for operative treatment of the upper end of the femur with spinal anesthesia. The protocol didn't mandate the management of spinal anesthesia to maximize the external validity of the results. To examine preexisting cognitive dysfunction in patients, we used two validated instruments, the Short Mental Test (AMT 10) (13,14) and the Cognitive Decline Information Questionnaire - Short Form (IQCODE - SF) (15). The Short Mental Test (AMT - 10) is a relevant tool for assessing mental status in emergency medicine departments, especially useful for rapid assessment of elderly patients for possible dementia. For the diagnosis of postoperative delirium in patients after surgery and anesthesia, we used the Confusion Assessment Method (CAM), which is the most widely used instrument for the identification of delirium by non-psychiatric personnel, developed using criteria adapted from the Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-V). The CAM has high specificity (89%) and sensitivity (94%) compared to delirium ratings by geriatric psychiatrists (17,18). We should exclude other neurocognitive disorders to confirm the diagnosis of delirium. Also, we should carefully monitor the effect of sedative drugs in evaluating delirium. Given the high prevalence of delirium in older patients and the adverse clinical outcome, current clinical

practice guidelines recommend routinely screening patients for delirium using a validated screening tool. Screening of at-risk patients may improve recognition of delirium, allowing for early intervention that can potentially reduce duration and complications (19).

In this paper, we analyzed samples and data from 51 patients, out of which postoperative delirium was diagnosed in 12 patients. At the same time, it was not registered in 39 patients, and they are the control group in the study. Both groups were balanced for gender and age, facilitating their further comparison. Due to the relatively small number of analyzed cases, we evaluated the existence of a genetic association of the examined polymorphism with postoperative delirium by combining the genotypes and alleles according to whether they contain the ε4 allele with the modified genotypic, as well as with the allelic and additive model.

The results in this paper indicate an association between the frequency of genotypes of the studied polymorphism in the APOE gene containing the minor allele ε4 and the occurrence of delirium after surgery and anesthesia. Carriers of the ε4 allele have a 20-fold higher probability of developing postoperative delirium than those of a genotype that does not contain the ε4 allele.

The relationship between genetic predisposition and the development of postoperative delirium has not yet been established in the literature dealing with this problem. While some have found that the presence of the ε4 allele of the apolipoprotein E (APOE4) gene increases the risk of POD (20,21), others have not reached such a conclusion (22). Meta-analyses (23,24) showed a longer duration, but not a more frequent occurrence of delirium.

The obtained knowledge can potentially be applicable in basic science and prospectively in clinical application by designing better prevention and treatment strategies in this patient population.

Conclusion

The results in this paper indicate a genetic association of the studied polymorphism in the APOE gene with the occurrence of postoperative delirium in adult patients. Carriers of the ε4 allele have a 20-fold higher probability of developing postoperative delirium during emergency operations for fracture of the upper end of the femur compared to patients who are carriers of the genotype that does not contain the ε4 allele. A larger group is necessary to reach more valid conclusions.

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CAN NEURON-SPECIFIC ENOLASE AND S100 MARKERS EVALUATE NEURO-DAMAGE FROM SEVOFLURANE IN CHILDREN?

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Abstract

Sevoflurane, a commonly used inhalation anesthetic agent in pediatric surgery, has revolutionized the field of anesthesia by providing a safe and effective means of rendering unconscious children during surgical procedures. However, amid the benefits it offers, concerns have emerged regarding its potential neurotoxicity, particularly in developing brains. This has prompted the exploration of novel methods to evaluate neuro-damage in pediatric patients exposed to sevoflurane.

In this article, we delve into the intriguing possibility of employing Neuron-Specific Enolase (NSE) and S100 markers as diagnostic tools for assessing neuro-damage resulting from sevoflurane exposure in children. These biomarkers, found in blood and cerebrospinal fluid, hold promise in shedding light on the intricate relationship between sevoflurane anesthesia and potential neurological effects. To comprehend this subject fully, it is imperative to explore the background of sevoflurane in pediatric anesthesia, understand the significance of NSE and S100 markers, review pertinent research findings, and consider the practical implications in clinical settings.

Key Words: *neuro-damage, neuron-specific enolase, pediatric anesthesia, S100, sevoflurane*

Introduction

Sevoflurane in Pediatric Anesthesia

Sevoflurane, a halogenated inhalation anesthetic, has gained widespread popularity in the field of pediatric anesthesia due to its desirable properties. It offers rapid induction and emergence from anesthesia, making it well-suited for pediatric patients who require anesthesia for surgical procedures (1). Furthermore, its relatively low pungency and pleasant odor make mask induction more tolerable for children.

Sevoflurane is generally considered safe and effective, providing the desired depth of anesthesia with minimal cardiovascular and respiratory side effects. Its use has been associated with shorter recovery times and reduced post-operative agitation, contributing to its preference in pediatric anesthesia.

However, the growing concern among clinicians and researchers revolves around its potential neurotoxicity, especially when administered to developing brains (2). Several studies in animal models have suggested a link between sevoflurane exposure and neurocognitive deficits. This concern has sparked interest in identifying reliable markers to assess neuro-damage and, ultimately, improve the safety of pediatric anesthesia.

In the subsequent sections of this article, we will explore the role of NSE and S100 markers in evaluating neuro-damage associated with sevoflurane exposure in children, shedding light on the crucial aspects of this ongoing debate (3).

Discussion:

NSE and S100 Markers:

Neuron-Specific Enolase (NSE) and S100 proteins have emerged as potential biomarkers for assessing neuro-damage in various clinical settings, including pediatric anesthesia with sevoflurane. Understanding these markers is essential to appreciate their relevance in evaluating the impact of sevoflurane on the developing nervous system.

1. Neuron-Specific Enolase (NSE):
   - NSE is an enzyme found predominantly in neurons and neuroendocrine cells. It plays a crucial role in glycolysis within neurons, making it a neuron-specific marker (4).
   - Elevated levels of NSE in the blood or cerebrospinal fluid can indicate neuronal damage, as it is released into the bloodstream following neural injury.
   - NSE has been studied extensively in various neurological conditions, such as traumatic brain injury and ischemic stroke, as a marker of neuronal damage (5).

2. S100 Proteins:
   - The S100 protein family comprises a group of calcium-binding proteins primarily found in glial cells (such as astrocytes and Schwann cells) and some neurons (6).
   - S100 proteins are involved in various cellular processes, including regulation of calcium homeostasis and inflammatory responses.
   - Elevated levels of certain S100 proteins, particularly S100B in blood or cerebrospinal fluid, have been associated with glial cell damage and neuroinflammation.

These biomarkers have garnered attention for their potential to provide insights into the extent of neuro-damage induced by sevoflurane anesthesia in pediatric patients. By measuring the levels of NSE and S100 markers before and after anesthesia exposure, researchers aim to establish correlations between marker levels and potential neurological effects (7).

Many research studies and findings have examined the utility of NSE and S100 markers in assessing neuro-damage in children undergoing sevoflurane anesthesia, shedding light on their diagnostic potential and limitations.

Studies and Findings:

Research into the use of NSE and S100 markers to evaluate neuro-damage from sevoflurane anesthesia in children has generated considerable interest in recent years. While the field is still evolving, several key studies have provided valuable insights:

1. Animal Studies:
   - Numerous animal studies have been conducted to investigate the effects of sevoflurane on the developing brain. These studies often measure NSE and S100 markers to assess neuro-damage.
   - Findings from some animal studies have suggested that sevoflurane exposure can lead to increased levels of NSE and S100 markers in the bloodstream, indicating neuronal and glial cell damage.

2. Human Studies:
   - Human studies have also explored the relationship between sevoflurane anesthesia and NSE/S100 marker levels in pediatric patients (8).
   - Some studies have reported associations between elevated marker levels and prolonged exposure to sevoflurane, raising concerns about potential neurotoxicity.
   - However, it's important to note that findings from human studies have been mixed, and not all studies have shown consistent results.

3. Limitations and Confounding Factors:
   - Interpreting NSE and S100 marker levels can be challenging due to various factors, including individual variability, age-related differences and comorbidities.
   - Anesthesia techniques, duration and patient's characteristics can also influence marker levels, making it difficult to establish a direct causal link between sevoflurane exposure and neuro-damage.

While the research on NSE and S100 markers in the context of sevoflurane anesthesia is promising, it is important to approach these findings with caution. More studies are needed to confirm their reliability and to establish clear guidelines for their use in clinical practice.

Limitations and Challenges:

It is noted in the literature that even the benefits of the use of NSE and S100 as markers in assessing neuro-damage associated with sevoflurane exposure in pediatric patients, several limitations and challenges must be acknowledged:

1. Variability in Marker Levels:
   - Individual variability in baseline marker levels can complicate the interpretation of results. What constitutes an elevated level, may differ from one patient to another.

2. Age-Related Differences:
   - The levels of NSE and S100 markers may vary with age, making it challenging to establish age-specific reference ranges for pediatric patients.

3. Comorbidities and Coexisting Conditions:
   - Preexisting medical conditions or coexisting neuroinflammatory processes can influence marker levels, potentially leading to false-positive results.

4. Anesthesia Factors:
   - The choice of anesthetic agents, duration of anesthesia, and surgical procedures can affect marker levels, making it difficult to attribute changes solely to sevoflurane exposure.

5. Lack of Established Thresholds:
   - Currently, there are no universally accepted threshold levels of NSE and S100 markers that definitively indicate neuro-damage. Researchers are working to establish clinically relevant cutoffs.

6. Ethical Considerations:
   - Research involving pediatric patients raises ethical questions, particularly in cases where potential neurotoxicity is a concern. Balancing the need for scientific investigation with patients' safety is crucial.

7. Need for Longitudinal Studies:
   - Long-term follow-up studies are essential to determine whether elevated marker levels correlate with lasting neurological deficits in pediatric patients exposed to sevoflurane.

8. Ongoing Research:
   - The field of anesthesia-induced neurotoxicity is evolving rapidly. New research may uncover additional biomarkers or refine the use of NSE and S100 markers in this context.

Considering these limitations and challenges, it is imperative to exercise caution when interpreting NSE and S100 marker results. These biomarkers should be considered as part of a comprehensive evaluation of the potential neuro-damage associated with sevoflurane anesthesia in children.

Clinical Implications:

The potential use of NSE and S100 markers in assessing neuro-damage from sevoflurane anesthesia in children holds significant clinical implications:

1. Early Detection and Monitoring:
   - NSE and S100 markers offer the possibility of early detection and monitoring of neuro-damage, enabling healthcare providers to identify at-risk patients and implement interventions when necessary.

2. Tailored Anesthesia Strategies:
   - The availability of reliable biomarkers could lead to development of personalized anesthesia strategies, allowing for adjustments in anesthesia dose and duration for vulnerable pediatric patients.

3. Improved Patient Safety:
   - Utilizing these markers may contribute to enhanced patients' safety by minimizing the potential risks associated with sevoflurane anesthesia, particularly in sensitive populations.

4. Research and Development:
   - Continued research in this area may lead to the discovery of additional biomarkers or refinement of existing ones, improving our ability to assess neuro-damage accurately.

5. Ethical Considerations:
   - Ethical considerations regarding the use of sevoflurane in pediatric patients may evolve with advancements in biomarker-based assessments, prompting discussions on anesthesia protocols and informed consent.

It is important to note that while NSE and S100 markers hold promise, they should be considered as part of a broader clinical evaluation. The interpretation of marker levels should be done in conjunction with other clinical assessments to make informed decisions about patients' care.

As the field of pediatric anesthesia and neurotoxicity continues to evolve, ongoing research and collaboration among clinicians and researchers are vital to refine our understanding of sevoflurane's effects on the developing brain and the role of biomarkers in this context.

Conclusion:

The evaluation of neuro-damage resulting from sevoflurane anesthesia in pediatric patients is a complex and evolving field of study. Neuron-Specific Enolase (NSE) and S100 markers have emerged as potential tools in this pursuit, offering a glimpse into the intricate relationship between anesthesia exposure and potential neurological effects.

While promising, the use of NSE and S100 markers comes with limitations and challenges. Variability in marker levels, age-related differences, comorbidities, and the lack of established thresholds underscore the need for caution in their interpretation. Ethical considerations and the ongoing evolution of research in pediatric anesthesia further complicate the landscape.

However, the clinical implications of utilizing these biomarkers cannot be understated. Early detection, tailored anesthesia strategies, and improved patients' safety are promising outcomes that could result from their use. As research in this field continues to advance, healthcare providers, researchers and ethicists must collaborate to refine our understanding of sevoflurane's effects on the developing brain and the role of biomarkers in assessing neuro-damage.

In the journey to unravel the mysteries of sevoflurane anesthesia and its potential impact on pediatric patients, NSE and S100 markers stand as beacons of hope, guiding us towards safer and more informed practices in pediatric anesthesia.

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IMPLEMENTATION OF FOCUSED ASSESSMENT WITH ULTRASONOGRAPHY IN TRAUMA PATIENTS IN UNIVERSITY SURGICAL EMERGENCY DEPARTMENT

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Abstract

Introduction: This article discusses the importance of trauma assessment in healthcare settings and the role of focused assessment with sonography in trauma (FAST) scans as a diagnostic tool. Trauma remains a significant health concern worldwide, leading to high mortality and morbidity rates, particularly in the younger population. Identifying risk factors for death is crucial for improving trauma patient's outcomes.

Objective: The objective of the study is to implement FAST assessments in an inner-city emergency department and examine their impact on the treatment of adult trauma patients.

Material and Methods: The study took place in an urban trauma center and included patients over 18 years old who were presented with trauma, excluding pregnant females, unstable patients and those without consent. FAST scans were performed using ultrasound machines, assessing various abdominal and thoracic views.

Results: The results revealed a high sensitivity of 94.4% and a specificity of 85.71% for FAST scans, making them a valuable tool for detecting abdominal free fluid in trauma patients.

The most of trauma patients in the study were men aged between 25 and 55, with falls, traffic accidents and assaults being the primary causes of blunt trauma. Commonly affected organs included the lungs, liver and spleen. FAST scans were found to be particularly useful for hypotensive patients, helping in triage decisions. While FAST scans demonstrated high sensitivity and specificity, the study suggests that patients with negative results should be observed and may benefit from follow-up scans, as small amounts of free fluid can be challenging to detect.

Conclusion: In conclusion, FAST scanning offers several advantages as a diagnostic tool for trauma assessment including its accessibility, affordability, repeatability, noninvasiveness and quick setup. It complements traditional methods like CT scans, especially in cases of hypotensive patients. Despite their limitations, FAST scans play a significant role in improving the management of trauma patients, helping healthcare professionals to make informed decisions about patients' care. To fully investigate the potential of FAST scans in trauma situations, additional research is required.

Key Words: *diagnostic tools, emergency department, focused assessment with sonography in trauma, trauma patients.*

Introduction

No matter the level of socioeconomic development, trauma is a serious health issue in every country and is still the leading cause of death in the first 40 years of life. It is also related to high morbidity and mortality (1, 2). In our country in 2021, the trauma mortality rate was 6.3 per 100,000 citizens (2).

Risk factors for death must be thoroughly identified and researched in order to reduce mortality in cases of trauma. Numerous of these risk variables, including gender, the amount of time between the injury and operation, shock at the time of admission and cerebral injuries, have been documented in research in recent years. Therefore, providing the best care for trauma patients necessitates a multidisciplinary approach. Quick identification and treatment are thought to be essential to managing the trauma patient successfully, as undetected injuries can result in avoidable fatalities (4).

Nowadays, procedures for identifying blunt trauma have been significantly altered by using Focused Assessment with Sonography in Trauma (FAST) and helical CT scans, which have also improved judgment and allowed physicians to choose patients for conservative treatment (5).

CT scans, which are noninvasive and have emerged as the gold standard for evaluating traumatic abdominal trauma, can yield incredibly precise images (6, 7). However, there are a few disadvantages and drawbacks to CT scans. The primary cause is that unstable patients are unable to use it since they have to be moved from the ER to the scanner. Specialized radiologists and radiographers are needed for the operation in order to execute the examination and interpret the images. Some individuals have reported allergic reactions after using contrast agents (8). Also, it should be remembered that the abdomen CT's effective radiation dose is equal to 400 chest x-rays and 2.7 years' worth of naturally occurring radiation. Yet, the danger is balanced out as follows: The potential radiation danger is outweighed by the advantage of a correct diagnosis in these severe wounds (9, 10).

FAST was the first employed in emergency rooms in the 1990s due to the necessity for a quick diagnostic method that could be applied to the situation. It is done following the primary survey to determine whether there is any free fluid in the peritoneal cavity that could be hemoperitoneum and to enable it (5). CT scanning may be recommended for hemodynamically stable patients in order to provide timely and appropriate therapy. The position and extent of the injury may not be identified in the absence of formal, complete imaging, which might substantially lengthen the time spent in the operating theater for hemodynamically unstable patients undergoing an emergency laparotomy; CTs can identify solid organ damage, unlike FAST scans. Despite FAST's popularity, there is still uncertainty and a lack of proof about any genuine benefit to patient's survival (2, 11, 12).

Despite the fact that there are limited prospective trials conducted in this area, this has the consequence that we are still discovering how helpful it is as a diagnostic tool and in modifying patient's therapy (12, 13).

FAST is frequently the initial imaging test in trauma cases, which is unfortunately not applicable in our country.

Objectives

Therefore, the objective of our study was to implement this FAST assessment in our university emergency department to find out how FAST scan results can be implemented in a typical inner-city ER and whether they affect how adult trauma patients are treated afterwards.

Material and Methods

This prospective clinical observation study was conducted with the approval of the Ethics Committee and the patients' or their guardians' signed informed consent at the University Clinic for Traumatology, Orthopedic Diseases, Anesthesia, Reanimation, Intensive Care and Emergency Centre, Medical Faculty, University "Ss. Cyril and Methodius," Skopje, Macedonia, in the Emergency Department, a premier trauma center in our country. All patients over the age of 18 who were presented with trauma in our department received a FAST scan when they arrived at the emergency room during the period of primary check and stabilization. Excluded were all pregnant female patients, patients who underwent urgent surgical intervention, unstable patients who were transferred to the intensive care unit, and patients without permission to participate.

After evaluation and examination according to the A, B, C, D and E standardized protocols by the attending doctor, each patient who met the inclusion criteria underwent FAST within the first 2–5 minutes of their arrival. Then, all of them were candidates for FAST as soon as possible. Patients originally underwent a FAST scan in the supine position. A FAST examination was performed using a mobile US machine with a curvilinear 3.5–5 MHz probe and a linear 5–20 MHz probe. The examiner stood to the right of the patient to obtain the following five standard views:

The pericardium was examined using the transverse view of the pericardial view, sometimes referred to as the subcostal or subxiphoid view. The most common sonographic window to the heart is the liver in the epigastric area. An alternative method that may be employed if anatomical limitations hinder the implantation of an epigastric probe is the parasternal or apical four-chamber views.

The longitudinal view of the right upper quadrant (RUQ), the Morison pouch view, or the perihepatic view are all terms for the right flank view. It displays the right kidney, right liver lobe, right paracolic gutter and the area between them (the Morison pouch). Once the hepatorenal interface, also known as the Morrison pouch, has been located, the pleural and more cephalad subphrenic spaces are evaluated. The left kidney, spleen, interstice and left paracolic gutter are seen in the longitudinal view of the left upper quadrant (LUQ). What's commonly called the perisplenic or left upper quadrant vision gradually explores four different regions.

Transverse and longitudinal views of the suprapubic region, commonly referred to as the suprapubic view, are explored for free fluid. The bladder and rectouterina, also known as the rectrovesical pouch or the Douglas pouch, are depicted in this region, which is the most reliant peritoneal space in the supine trauma patient utilizing the bladder as a sonographic window in a transverse sweep. The probe would be positioned longitudinally along the midclavicular line at the third or fourth intercostal space in bilateral thoracic images A traumatic pneumothorax can be detected by lung sliding, which is a sensitive but non-specific indication.

All the FAST scans can be divided into four groups:

1. Positive scans with pathology present (on CT),
2. Positive scan but without pathology,
3. Negative scan, but with pathology actually present, and
4. Negative scan without pathology.

The patients' information and details will be kept completely private.

Statistical Analysis

All the statistical analysis were done on the 20. Statistical package for social sciences. Specificity, sensitivity, and positive and negative predictive values of FAST performed by EMRs and RRs were calculated and compared using Chi-square analysis. P-value less than 0.05 was considered statistically significant.

Results

All 30 subjects in our study had experienced blunt trauma as a result of assaults (16.6%), falls (40%), or traffic accidents (43.3%). Nine women (23.2%) and 21 men (76.8%) participated in the study. A minimum age of 18 was required for the sample. The most of the participants were between the ages of 39 and 50, with a mean age of 39±17 years. As is clear from the study, the most of individuals had thoracic injury (n=15) 50% and (n=26) 86.6% had no visceral injury. These participants were followed by (n=3) 10% patients with spleen injury, (n=1) 3.3% patients who had liver injury.

The different angles from which the FAST scans were conducted while all patients were lying in supine position on the examination couch, and three points on the lung were inspected (the upper anterior point, the lower anterior point and the posterior lateral alveolar or pleural point) on each side. The abdomen was examined in three points as well. The longitudinal view of the RUQ, LUQ, showed the most dependent peritoneal space in the supine trauma patient to depict the urinary bladder and rectouterina, or rectrovesical pouch, or the pouch of Douglas and subxiphoid space. The results clearly show that the greatest percentage of FAST scans performed (n=26) revealed no free fluid (86.6%). This was followed by splenorenal views (n=2) 6.6%, hepatorenal views (n=1) 3.3%, and pelvic views (n=1) 3.3%. FAST scans on the lungs revealed pneumothorax in (n=13) 43.33% of the patients. FAST scan with pneumothorax finding is presented in Figure 1. The participants' various organs were impacted overall by blunt injuries. The average time of the examination was 5±3.5 min. The findings showed that the following FAST scan values were attained, with a high 94.4% sensitivity. The results showed that the specificity was 85.71%, the positive predictive likelihood ratio 6.61 or positive predictive value of 3.21% and the negative likelihood ratio 0.06 or negative predictive value of 99.97%. There was not any complication to report in the exanimated cohort.

Table1. Effected organs on FAST

Organs effected	N	%
Bladder	/	/
Kidneys	/	/
Liver	1	3.3%
Lungs	15	50%
Pancreas	/	/
Spleen	3	10%

Note. n=frequency, %=percentages

Table 2. Comparative of FAST with radiology findings.

Positive pathology		Negative pathology	Total
Positive FAST	17	2	19
Negative FAST	1	12	13
Total	**18**	**14**	**32**

Table 3. Frequencies and percentages of the demographic characteristics of sample.

FAST variable	N	%
Subxiphoid view	/	/
Right upper quadrant (Morison pouch view)	1	3.3%
Left upper quadrant	2	6.6%
Suprapubic view	1	3.3%
Bilateral thoracic views	15	50%

Note. n=frequency, %=percentages

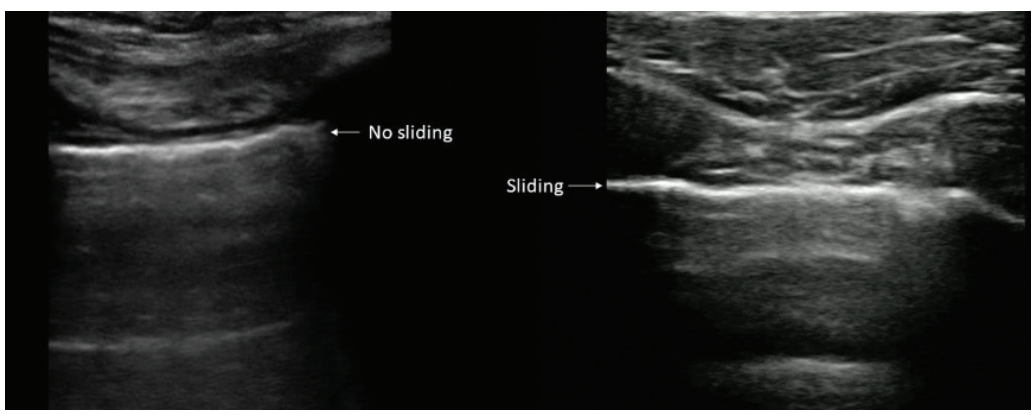

Figure 1. Thoracic views of FAST.

Discussion

In the current study, 30 victims of trauma were evaluated using FAST. The most of participants in the current study were men 21, which is consistent with earlier studies as more men participate in outdoor activities, have car accidents, and sustain other blunt injuries because few women sustain accidental wounds (14). Additionally, the most of participants in the current study were between the ages of 39 and 55. It differs from the findings of other studies where the most of participants were younger since younger people spend more time outdoors than older persons do (15). According to the study, there may have been a greater risk of harm among the patients who rode motorbikes, depending on the type of vehicle and the driver's abilities. As these age

groups tend to be dependent on other people and are not as accustomed to outdoor experiences, there were few patients who were young or old, about sixty.

Additionally, it has been noted that FAST examination is now in expansion as the only imaging method used to diagnose traumatic injuries replacing contrast CT scans. A rapid fix that can be utilized by a not expensive, small device of ultrasound during the initial survey is the FAST method to detect abdominal free fluid. Precise evaluation of people with traumatic injuries is a tough challenge for emergency doctors. While CT of the abdomen is thought to be the gold standard, it does have some disadvantages, such as high cost and time, the need to remove the patient from the ER and radiation exposure, so ultrasound can safely take its place as long as FAST exhibits high values for sensitivity and specificity (16).

The American College of Surgeons recommended FAST as an alternative to diagnostic peritoneal lavage or CT due to the historical data from studies conducted in the early years of FAST scan usage in a trauma setting, primarily during the 1990s. FAST scan was also held in such high regard that it was integrated into the Acute Trauma Life Support (ATLS) program and in Germany it was made a requirement for the surgical residency (17).

A positive result in a FAST scan should be recognized and addressed right away, according to the scan's high Positive Predictive Value and high specificity. However, it is also wise to carefully evaluate what action should be taken that the sensitivity is 46.2% and a quarter of the results are false negative (17).

Our study shows consistency with previous studies by showing that very high values of sensitivity and specificity were obtained, 94.4% sensitivity and 85.71% specificity. CT is considered a gold standard for blunt torso trauma, but it includes shifting the patient, long time of assessment, needs of radiologist specialist availability and also exposes the patient to different types of radiations. As a result, FAST is increasingly being used in emergency departments and in trauma referral centers because of the workload in emergency, as well as radiology departments as it can easily be done on bedside. Therefore, FAST plays a major part in the classification of victims who may require more procedures for hemodynamic stabilization (15).

It was consistent with the current study because certain patients with severe injuries could not be moved for CT scanning owing to a lack of time; therefore, it was preferred to move the badly injured patients directly for treatment operations without undergoing CT scan.

To provide patients with traumatic abdominal injury with the best possible care, early diagnosis of intra-abdominal injury is essential. Although CT is still the best test for evaluating these patients, it may not be possible to do one for a variety of reasons, the most frequent of which are hemodynamic instability or pregnancy. The potential benefits and drawbacks of FAST scan versus CT scanning are evident. It is simple to perform, portable, and may be done at the patients' bedside without exposing them to radiation. A negative scan does not always rule out an occult pathology, which may later require further intervention. It is also user dependent, as this data reveals (17).

According to research, attacks, falls and traffic accidents account for the most of cases of Blunt trauma. The most frequently injured organs in blunt abdominal trauma are the liver, spleen, visceral injuries and kidneys, which is consistent with the results of our study. The most of patients in our study had no visceral injuries (n=26), victims with spleen injuries (n=3), and victims with liver injuries (n=1), showing consistency with prior findings (18).

It is clear from the results of the current study and comparisons to earlier research conducted globally, about the diagnostic accuracy of FAST. It plays a significant role in the diagnosis of trauma patients and is being used more frequently in emergency rooms. However, it is advised

to perform the CT scan of the patient after the FAST scan, if the patient is stable for confirmation of more serious injuries and more accurate results.

Chiu et al. in their study voiced legitimate questions about the sensitivity of FAST scan considering all positive studies that have been published in relation to it. According to their study, 50 out of 196 patients who had free fluid on their CT scans, had no fluid visible on their FAST scans (19). Although the data from this study was inconsequential in terms of these conclusions, Kahan et al. discovered that more than 25% of patients with visceral injuries did not have free fluid on FAST scans conducted at admission. Therefore, the use of FAST for free fluid detection does have its limitations, which physicians must consider as part of a thorough clinical examination. The number of patients who had additional intervention, regardless of their FAST result, indicated that the trauma teams are aware of these limits and the necessity for examination and reassessment (20).

In fact, it has been argued that FAST was the most beneficial in the context of hypotensive patients and that it may be used to 'triage' patients toward laparotomy or additional clinical assessment or investigation rather than simply diagnosing them (21-23).

It has been suggested that if a patient is clinically stable on routine reassessment, a negative FAST scan should be followed up by observation with at least a follow-up FAST scan because small amounts of free fluid are difficult to detect by FAST, even by experienced practitioners, or may not be detected at all. This issue hasn't been the subject of any experiments (17). Serial FAST examinations weren't used in this study. According to evidence, this practice makes FAST more sensitive (24-26).

Conclusion

FAST scanning has been incorporated into current practice because it is easily accessible, affordable, repeatable, noninvasive, and only requires a short amount of setup time. It may also be carried out using transportable equipment, giving patients more flexibility in how they are positioned, than it is feasible with other imaging modalities.

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URGICAL TREATMENT OF PLEURAL EMPYEMA

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Abstract

Thoracic empyema is the accumulation of pus within the pleural cavity. The most frequent cause is direct contiguous spread of infection, the most frequent from lung infection. Current management of empyema is based on local empirical practice as there is no consensus on an optimal regimen. It is estimated that 40% (7-57%) of pneumonia, results with parapneumonic effusion, out of which 10% develop empyema of pleural space.

Treatment covers antibiotics, pleural drainage, pleural drainage and use of fibrinolytics, VATS early debridement, VATS decortication, open decortication, open pleural window and thoracoplasty. The choice of adequate treatment is according to stage of empyema: I (exudative stage) - thoracic drainage, II (fibrinopurulent stage) - thoracic drainage with fibrinolytics and VATS debridement or VATS early decortication and for III (empyema in organization stage) - VATS or open decortication or later thoracoplasty. Early VATS debridement effectively manages simple parapneumonic effusions. VATS decortication has efficacy for managing early-stage empyema.

In the past (2011-15) period 234 patients with empyema were treated, out of which 124 (52.99%) of empyema were treated with pleural drainage, 105 (44.87%) were treated with open decortication and 5 (2.14%) with thoracoplasty.

In the last 6 months of 2023, 21 patients were treated, 19 (90.5%) male and 2 (9.5%) female. Unfortunately, in the last 6 months only 5 (23.8%) of the patients were treated only with pleural drainage, 4 (19%) patients were treated with VATS debridement or early decortication and 12 (57.14%) patients were treated with pleural drainage that finished with open decortication. This situation suggests that, unfortunately, empyema was detected in advanced stage that needed aggressive surgical treatment.

Early detection of parapneumonic effusion and treatment in this stage will prevent development of empyema and need of aggressive treatment.

Key Words: *opens decortication, pleural empyema, thoracic drainage, VATS decortication.*

Introduction

Thoracic empyema is the accumulation of pus in the pleural cavity. The cause of empyema is direct contiguous spread of infection, the most frequent from lung infection. Thoracic empyema remains a significant medical problem. Patients in whom empyema develops suffer significant morbidity, frequently require prolonged hospitalizations, and are at an increased risk of death (1,2).

Current management of empyema is based on local empirical practice as there is no consensus on an optimal regimen (2).

The development of new diagnostic procedures, especially the application of ultrasonography in daily clinical practice, enables early diagnosis of pleural empyema and appropriate aggressive therapy (3).

The aim of this paper is to analyze therapeutic approach to pleural empyema, according to stage of the disease. Also, the aim is to analyze therapeutic approach in two different periods of treatment of empyema in the clinic for thoracic and vascular surgery.

Material and Methods

At the Clinic for Thoracic and Vascular Surgery, in the period of 6 months (01.03 to 01.09.2023) 21 patients were treated with pleural empyema. Out of them 19 were male and 2 females. Mean age was 54+4.1 years.

In 3 patients, empyema was a consequence after COVID 19 pneumonia. 4 patients were detected diabetes mellitus insulin dependent and in 2 patients condition after coronary stenting was detected.

The past period that was analyzed, was five-years period from 2011-2015, in which 234 patients with empyema were treated. The mean age was 51.94 years.

We used standard statistical methods, and for comparing methods in two different periods we used the chi–square statistic, using standard statistical programs SPSS.

Results

Treatment was based according to the stage of the disease: 5 (23.8%) patients were treated with only pleural drainage, 4 (19%) patients were treated with VATS decortication and 12 (57.14%) patients were treated with open thoracotomy decortication (in 9 patients after unsuccessful thoracic pleural drainage and in 3 with unsuccessful primary open thoracotomy decortication) (Table 1).

Among the 12 patients with decortications, the presence of a bronchopleural fistula was detected in 4, which closed spontaneously after 3-6 days. In 1 patient, there was no complete re-expansion on the control X-ray after 2 days, in whom with physical therapy, the lungs expanded completely in the following days. At the control 2 weeks after discharge from hospital in 10 patients there was complete re-expansion and orderly transparency of the decorticated side. In this group we have only one death.

In this group average hospitalization was 7.76 days. In that with thoracic drainage average hospitalization was 4.8 days, in that with VATS decortication 5.4 days and in that with open thoracotomy decortication 11.43 days (Table 2).

These results were quite different, statistically significant, compared to results of treatment of pleural empyema in the past (2011-2015), when out of 234 patients with empyema 52.99% (124) were treated with pleural drainage only, 44.87% (105) with open thoracotomy decortication and 2.14% (5) with thoracoplasty (Table 1).

Table 1. Results of surgical treatment in patients with empyema.

	2011-2015	2011-2015	03-09-2023	03-09-2023	
Surgery	**Patients**	**%**	**Patients**	**%**	**p**
Pleural drainage	124	52.99	5	23.80	<0.05 S
VATS decortication	0	0	4	19.00	<0.05 S
Decortication	105	44.87	12	57.14	0.15 NS
Thoracoplasty	5	2.14	0	0	0.01 S
Total	**234**	**100**	**21**	**100**	

The chi-square statistic is 48.0262. The p-value is <0.00001. The result is significant at p<0.05.

Table 2. Mean hospitalization of surgically treated patients with empyema.

	2011-2015	2011-2015	03-09-2023	03-09-2023	
Surgery	**Patients (%)**	**mean hospitalization days**	**Patients (%)**	**mean hospitalization days**	**P**
Pleural drainage	124 (52.99)	11.4	5 (23.80)	4.80	<0.05 S
VATS decortication	0		4 (19.00)	5.40	<0.05 S
Decortication	105 (44.87)	23.3	12 (57.14%)	11.43	<0.05 S
Thoracoplasty	5 (2.14)	42.2	0	0	<0.05 S
Total	234	17.4	21	7.76	<0.05 S

The chi-square statistic is 48.0262. The p-value is <0.00001. The result is significant at p<0.05.

Discussion

Infection of pleural space occurs according to the spread of infection from nearest tissues and organs. 40% of pneumonia results with parapneumonic effusion, out of which in 10% results with empyema of pleural space. Because of non-intervention or inadequate intervention in the stage of parapneumonic effusion, the process develops into the development of empyema (1,2).

Moreover, the development of pleural empyema proceeds through a three-stage development

1. Exudative phase - during which the space is filled with rare pus with few cells. After removing the pus, the lung easily expands and fills the space.

2 Fibrinopurulent phase - the space is filled with thick pus, with numerous cells and fibrin deposition on the surface of the lung. Fibrin adhesives make it impossible for the lung to expand after removing the purulent content.

3 Organizing phase - there is an organization of fibrin stickers, growth of fibroblasts and blood vessels for the parietal and visceral pleura. An attempt to release this covering from the pleura, especially at a later stage, leads to injury of the lung covering with the formation of bronchopleural fistulas (2).

Although the 3rd stage (the organizing stage) of pleural empyema in some way represents a self-healing process, limiting the infection, it still represents a seat of infectious material, and entrapment of the lung drastically reduces respiratory capacities. That is the reason for applying surgical treatment at this stage of the disease (4,5).

Despite the administration of an appropriate antibiotic -according to isolates, type of infection (intrahospital or community-acquired pneumonia), epidemiological data- it is still insufficient in the treatment of pneumonia complicated by parapneumonic effusion, and even less the existence of pleural empyema (1).

But, it must be emphasized that the detection of parapneumonic effusion in the first stages according to the Light classification, the use of antibiotics combined with minimally invasive techniques such as thoracentesis, pleural drainage with or without the use of fibrinolytic therapy, can completely repair the process, preventing the development of pleural empyema.

The application of VATS debridement, i.e. VATS decortication, methods which, as less invasive, are more often applied recently, could give an effect in the treatment of class 5 and 6 according to the Light classification, i.e. stage 2 (fibrinopurulent stage) and early stages of stage 3 (organizing stage) according to the AATS (American Association of Thoracic Surgeons) classification. The application of VATS debridement, i.e. VATS decortication, in an appropriate stage of the disease, gives better results, compared to open thoracotomy decortication, in terms of a shorter hospital stay, less postoperative pain and less blood loss (6,7).

Treatment of more advanced stage 3 disease (organizing stage) with VATS decortication does not provide an advantage over open thoracotomy decortication. Hereby, VATS decortication takes longer and the effect is not the same as with open intervention, and very often requires conversion to open intervention (6-8).

Unfortunately, in our series, 12 patients out of 21 patients came to the clinic with stage 3 of the disease (organizing stage), with thick fibrous patches on the parietal and visceral pleura, thickening more than 5mm, with the existence of a trapped lung, in which the only possible approach was the application of open thoracotomy decortication (9-11).

The difference in the percentage of patients treated with pleural empyema at the thoracic surgery clinic in the past (from 2011 to 2015) and in the last 6 months (from March to September 2023) is statistically significant (thoracic drainage 52.99% vs 23.18%, VATS decortication 0% vs 19%, open thoracotomy decortication 44.87% vs 57.14%), which , is probably due to an advanced stage of the disease (the advanced stage of the organizing stage, accompanied by thick fibrous plaques on the parietal and visceral pleura, with trapped lung). This should be an incentive to consider parapneumonic effusion more often, when the pneumonia does not respond to antibiotic therapy, and to detect it and treat it invasively (with thoracocentesis or thoracic drainage) in the earliest stage (12).

Today, the application of ultrasonography of the pleura, which is an easily available and non-invasive method, allows early diagnosis of pleural effusion and the possibility of early intervention. The application of chest CT accurately locates the changes, existence of thickening of parietal and visceral pleura, location of effusion, lung entrapment (3,13)

The appearance of pus in the pleural space - pleural empyema, should be aggressively treated immediately with VATS debridement or VATS decortication, preventing the development of an organizing stage (2-3 weeks are enough for it to transform from a fibrinopurulent stage to an organizing stage) (7,8).

Conclusion

Early detection of pleural effusion, secondary to pneumonia, should prompt punctuation to determine the stage and appropriate treatment as soon as possible. Early stages (parapneumonic effusion) can be treated with less invasive procedures (thoracentesis, thoracic drainage), while more advanced stages, especially the presence of empyema, must be treated with more aggressive procedures (VATS debridement, decortication, thoracoplasty).

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CONVERGENCE INSUFFICIENCY

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Abstract

Introduction: Convergence insufficiency is a common disorder of binocular vision characterized by difficulty in establishing near motor fusion. This condition affects approximately 7.5 percent of the population.

Objectives: To present the modern attitudes in diagnostic-therapeutic modalities and follow-up of patients with this bulbomotor entity.

Materials and Methods: When preparing this literature review, two large databases of relevant studies were accessed: PubMed and GoogleScholar. By entering the keywords: convergence insufficiency, etiology, clinical picture, treatment. Large number of papers were received, out of which 25 were selected for the preparation of this paper.

Conclusion: Convergence insufficiency is a frequent disorder in ocular motility that primarily affects the young population. Characteristic symptoms such as: eye strain, horizontal diplopia, asthenopia, headaches, etc. are essential for recognizing this diagnosis, which can be the cause of reduced intellectual performance and impaired quality of life.

Key Words: *clinical picture, convergence insufficiency, etiology, treatment.*

Introduction

Convergence insufficiency (CI) is a common ocular motility disorder characterized by an insufficient amount of convergence required to achieve and maintain clear, binocular vision at near fixation. It was first described in 1855 by Graefe, and later investigated in detail by Duane (1). The classic clinical picture of this condition is characterized by: 1. Exophoria that is more pronounced at near than at distance, 2. Displacement of the near point of convergence to a greater distance, 3. Decreased positive fusional convergence. According to research by Mohney et al. and Govindan et al. this condition is estimated to be present between 10 and 20% of children with exodeviation. The same sources indicate that every year CI has a representation of 64 new cases per 100,000 in youth up to 19 years of age, while the prevalence in adults ranges between 3.4-7.7% (2,3).

It is the most often an idiopathic condition in the young adult population that is probably due to a congenital deficiency or an acquired imbalance of vergence bulbar movements. The center for these movements has long been thought to be located in the reticular formation of the midbrain. At this level, there are neurons that give the convergence signal immediately before and during the convergent movement itself. Recently, it has been known that specific centers located at the level of the pons have an active role in the fast and slow parts of the vergence movement

(4,5). Convergence likely consists of a biphasic response to a change in stimulus position. The first phase is fast and with short latency, triggered by a rapidly moving stimulus or occurring during sudden changes in fixation. This phase is followed by slow vergence movements with somewhat longer latency. The second stage is under the control of visual feedback and is due to the joint action of fusion and accommodative convergence. The first stage is the one that can be influenced by exercises (6).

Apart from idiopathic, CI is also associated with number of other diseases and conditions such as: myasthenia gravis, intoxications, infections, inflammations, neurodegenerative diseases (Parkinson's disease, progressive supranuclear palsy and Huntington's chorea), Parinaud syndrome, head trauma and intracranial ischemia (7-9).

Although it can be asymptomatic, people suffering from this disorder of oculomotor mobility show symptoms such as: eye strain, blurred vision or horizontal diplopia, asthenopia, reduced concentration, difficulties in performing close-up activities, headaches (mostly after long hours of reading, in the frontal or periocular region), all this leads to reduced academic performance and impairment of the quality of life. The most often, the symptomatology is more pronounced during stress, illness, or lack of sleep (10).

Materials and Methods

To prepare this literature review, a search of PubMed and GoogleScholar databases for relevant studies published in journals between 1944 and 2023 was performed. The following Key Words were used in the search: convergence insufficiency, etiology, clinical picture, diagnostic criteria and treatment. From the received publications, 25 were selected which were included in the development of this paper, and which we considered to reflect the modern attitudes towards the management of this common ophthalmological condition the most adequately.

Results and Discussion

The definitive diagnosis of CI is a set of anamnestic data and clinical evaluation that form the diagnostic criteria for establishing this diagnosis:

1. Exophoria greater near than far by at least 4 prism diopters,
2. Displaced near point of convergence (NPC- near point of convergence) of 6cm or more,
3. Insufficient positive fusional vergence (PFV- Positive Fusional Vergence),
4. Symptoms, according to the Convergence Insufficiency Symptom Survey (CISS-Convergence Insufficiency Symptom Survey).

Assessment of Phoria

Phorias represent a natural ocular alignment that is the best evaluated by performing an alternating Cover test and neutralizing eye movements, through which their size is determined. Phorias can be temporally deviated ocular alignment-exophoria or nasally deviated alignment-esophoria. The most of patients with CI have exophoria at near, while orthophoria or mild exophoria at distance. In addition to the Cover test, the investigation of phoria can also be done with the Von Graefe technique or the modified Thorington technique. (11,12)

Estimation of the Near Point of Convergence

The nearest point of convergence measures the magnitude of convergence by tracking the target to the nose. The size is estimated either subjectively when the patient gives data about the occurrence of diplopia, or objectively when the examiner notices a deviation of the subject's eyes outwards. This value is reported in cm and is marked as the convergence break point. A normal NPC value is around 8-10cm, a distance less than 5cm is excessive, and greater than 10 is insufficient. NPC is the most commonly present abnormality and the most commonly used single diagnostic criterion for investigating CI. To determine the NPC can be used: an adjustable target or RAF-ruler, a pen with a lamp or a pen with a lamp and red-green glasses, as well as Jumb convergence (12,13).

Positive Fusional Vergence

PFV is the amount of convergence required to maintain binocular near fusion and the amount required to overcome bulbar temporal disparity. To determine it, the patient is given to look at Snellen's signs, and prisms are gradually added in front of him. The moment when fusion of the images into one is no longer possible, diplopia will occur, and this moment is known as the breaking point. The amount of prism added to cause diplopia is a measure of the amount of fusional convergence. By gradually reducing the size of the prism, fusion can be re-established, and this point is known as the fusion recovery point which is also an indicator of fusion potential. Patients with CI have low fusion amplitude. The determination can be performed by changing the size of prisms in a phoropter 2PD per second or by using a prism bar (12,14).

Convergence Insufficiency Symptom Survey

The CISS is a survey that aims to quantify the severity of a patient's symptoms, based on 15 CI - related anamnestic questions. When performing the CISS, the questions are read aloud, and the respondent chooses one of 5 possible answers that are scored from 0 to 4, based on the frequency of symptoms (never, rarely, sometimes, often or always). At the end, all the points are added up to give the final result. A score of 16 or more is specific for patients with CI, the maximum possible score in this test is 60 (15,16).

Another additional criterion when examining a patient for CI can be the ratio between accommodation-convergence/ accommodation (AC/A ratio). This ratio is usually determined by the heterophoria method using a mathematical formula. It depends on the sum between the interpupillary distance and the difference between the near and far prismatic deviation at fixation at 6m and 33cm. A normal AC/C ratio is between 3:1 and 5:1, while in CI patients, this ratio is < 2:1 (17). Other ways to determine this ratio is by using the addition lens, haploscopic method, Von Graefe or modified Thorington method.

In addition to these criteria, the best-corrected visual acuity for near and distance, as well as with refractometric tests subjective and with cycloplegia, are also determined in the course of the overall evaluation for CI patients. In certain situations, tests for stereoscopic near vision are also used, such as: TNO, Randot dot, Worth four-dot test, etc.

Differential Diagnosis

Before approaching any CI treatment, the patient should be properly examined, anamnestically and clinically followed in order to rule out possible differential diagnostic challenges. Idiopathic CI should be differentially diagnosed from other diseases of oculomotor motility, especially from: exotropia (basic or acquired), diplopia, internuclear ophthalmoplegia, oculomotor paralysis, thyroid ophthalmic disease and myasthenia gravis (18).

Management and Treatment

Before starting any treatment, the patient should be adequately corrected for any refractive anomaly. It should be advised that work at close range be in a well-lit room with adequate rest periods. Orthoptic therapy is the first line of treatment for CI. The idea is to model the plasticity of the fusional reflex convergence system through exercises. Today there are various types of exercises and techniques used in daily clinical practice to treat CI. From a didactic point of view, they are divided into passive and active techniques, depending on the way they control CI. The most commonly used passive treatment of CI is using reading glasses with a prism, while active techniques include pencil exercises at home, various visual techniques at home or in the office, exercises with prisms, stereograms, etc. (19,20).

Conventional therapeutic modalities for convergence include home-based pencil push-ups, jump convergence exercises, stereograms and convergence cards (variable and non-variable tranaglyphs, variable vectograms), as well as prism exercises. In a more recent period, a program for computerized convergence exercises is also used, which is based on a random dot stereogram.

Contemporary treatment attitudes indicate that office treatment of CI supported by home exercises is the first-line treatment for children with CI. According to clinical trials, this method of treatment has been shown to have a success rate of approximately 75% (21). Office part of the treatment includes 4-5 exercises, lasting one hour a day for a period of one week. Office exercises are a combination of prism, Brock string, stereograms, vectograms, fusion cards, etc. While at home, the patient continues with convergence strengthening procedures such as pencil exercises (pencil push-ups) 5 times a week for fifteen minutes. In this way, the treatment of CI is classically carried out, the patient is monitored on a weekly basis or every few weeks depending on the current condition. Orthoptic treatment can be repeated in several sessions (22).

In refractory cases of conventional, classic therapy, the last possible but controversial option is surgical treatment. It includes recession-resection of the lateral and medial rectus respectively, especially of the non-dominant eye. It is important to note that many surgeons and ophthalmologists do not agree with this method of treatment, due to the fact that it is accompanied by a high risk of consecutive esotropia, diplopia and developing A-V syndromes postoperatively (23).

Prognosis and Monitoring

The prognosis for patients with idiopathic CI is generally good. According to the Convergence Insufficiency Treatment Trial Study Group, 73% of people who practiced appropriate therapy for more than 12 weeks had significant improvements in vergence movements (24). The follow-ups of patients with CI should usually be performed every 4 to 8 weeks. Patients with acquired CI due to trauma or other disease need a longer recovery period (25). Although it does not significantly impair the general health of patients, untreated CI is the cause of reduced quality of life and reduced intellectual performance.

Conclusion

Through this literature review, we tried to provide new insights and attitudes in the diagnostic and therapeutic criteria for CI management. As we have shown, it is a frequent disorder in ocular motility that primarily affects the young population. Characteristic symptoms such as: eye strain, horizontal diplopia, asthenopia, headaches, etc. are essential for recognizing this diagnosis, which can be the cause of reduced intellectual performance and impaired quality of life.

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OPHTHALMOLOGICAL MANIFESTATION OF ALBINISM

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Abstract

Albinism is a large group of hereditary diseases characterized by reduced or completely absent synthesis of melanin in tissues of ectodermal origin. Patients with this pathology have frequent affection of the ocular structures, which are manifested by: reduced visual acuity, transillumination of the iris, hypoplasia of the fovea, nystagmus, strabismus, refractive errors and other. Prevention of UV rays, and early and appropriate management of ophthalmic manifestations is a key link in the treatment of patients with this condition. In this paper we have presented the most significant forms of albinism that are known in science today, as well as the spectrum of ophthalmological changes and their possible treatment.

Key Words: *albinism, melanin, nystagmus, ophthalmological manifestations, strabismus.*

Introduction

Albinism is a common term for a large group of hereditary diseases, characterized by reduced or completely absent melanin in tissues of ectodermal origin. That is, skin, hair and eyes. The word comes from the Latin term "albus" - white. The biggest feature of this entity is that patients have hypo or depigmentation of the whole body, with prominent gray to white hair. This authentic look is specific to the so-called oculocutaneous albinism (an autosomal recessive condition), in contrast to the ocular albinism, which mainly affects intraocular structures. Albinism is found in the whole population, but also in other species of the animal world. The incidence is different in different nations, with the highest representation among the indigenous population in Panama and Colombia at 6.3 per 1000 inhabitants, and worldwide it ranges between 1:5000 and 1:40,000 (1).

Oculocutaneous Form of Albinism

The oculocutaneous form is based on a mutation of the OCA gene. OCA1A is the most severe type of mutation where melanin synthesis is completely absent, while other variants such as OCA1B, OCA2, OCA3 or OCA4 are relatively deficient in synthesis. OCA2 is the most common mutation in the world. Different mutations are specific to different ethnicities and nations around the globe (2). The OCA group of genes participates in the tyrosine/melanin biochemical cascade. Mutations in this group lead to impaired synthesis of enzymes and membrane proteins that are very important in melanin synthesis. As consequence, no synthesis of this pigment occurs at all, or after it has been synthesized, it cannot be distributed and deposited in the appropriate cellular compartments to exert its effect. Because of these biochemical disorders, the characteristic phenotype of persons with this entity occurs. In other words, there will be a partial or complete affectation of skin pigmentation, hair, iris color, which directly depend on the size and number of melanosomes. The patients in whom residual enzyme activity is present,

acquire some pigmentation of the skin and hair (blonde to pale brown), in contrast to those in whom there is an absolute deficiency of enzyme activity, who are presented with completely white skin and hair, as well as light blue eyes with a pronounced red reflex from the fundus (3).

Ocular Albinism

Ocular albinism is a lesser-known entity. The diagnosis is mainly made when nystagmus is present since early childhood, transillumination of the iris with pronounced hypopigmentation of the peripheral part of the retina, generally in males with mild hypopigmentation of the skin and reduced vision. It is mainly an X-linked disease, the symptoms of which begin in the first three to six months of life. There are two forms of the disease: Ocular albinism type 1 (OA type 1) and Ocular albinism type 2 (OA type 2) (4).

The first type, also known as Nettleship-Falls ocular albinism, is an X-linked disease, found almost exclusively in male children. It is the most common form of ocular albinism with a representation of 10% of all albinisms. The incidence is between 1:50,000 to 1:150,000 live births. The disease is due to a mutation of the GPR143 gene from the short arm of the X-chromosome (5). This gene encodes a protein that is extremely important for melanosome transport in pigment cells. The phenotypic characteristics depend on the ethnicity of the affected individual. The diagnosis is made by genetic analysis, as well as by family history. In female carriers of a mutated gene, due to the process of lyonization of the X-chromosome, a Mud-splattered-like change in the fundus can be observed.

The second type, also known as Aland Island ophthalmic disease, or Forsius-Eriksson ocular albinism is a much rarer X-linked disease than the previous one, but with similar clinical manifestations. A characteristic finding is the appearance of protanopia and problems with dark adaptation. Unlike OA1, this condition is not associated to fundus changes in female carriers. The disease is proven genetically by analyzing the gene of interest CACNA1F (6).

Differential Diagnosis

Several systemic diseases and hematological conditions are presented clinically in a similar manner to albinism. In other words, pathophysiological mechanisms that are involved with defective transport and packaging of cellular proteins, clinically manifest in a similar way as albinism. Examples of such diseases are: Hermansky-Pudlak syndrome (autosomal recessive disease); albinoidism (autosomal dominant disease); Waardenburg syndrome (autosomal dominant disease); Chediak-Higashi syndrome (autosomal recessive disease); Griscelli syndrome; Elejalde syndrome and others (2,7-9).

Ophthalmological Manifestations of Albinism

1. Transillumination of the Iris

Due to the reduced or completely absent pigmentation in the iris stroma and the posterior pigment epithelium, there are fenestrae through the iris through which a phenomenon of transillumination is observed, in patients with albinism. There are several ways to detect this phenomenon. The slit lamp biomicroscope technique is the most used. A small beam of light is directed through the pupil, during which transillumination defects across the iris surface are displayed in orange, they can be of different shapes and in different distribution and density of arrangement. According to the degree of

their presence, as well as the degree of pigment present, schemes with degrees of transillumination from I to IV are used, where IV is the highest degree of transillumination and complete absence of pigment in the iris (10,11). Although this phenomenon occurs in albinism, it is not specific to it, as other ophthalmic conditions are also characterized by the presence of iris transillumination.

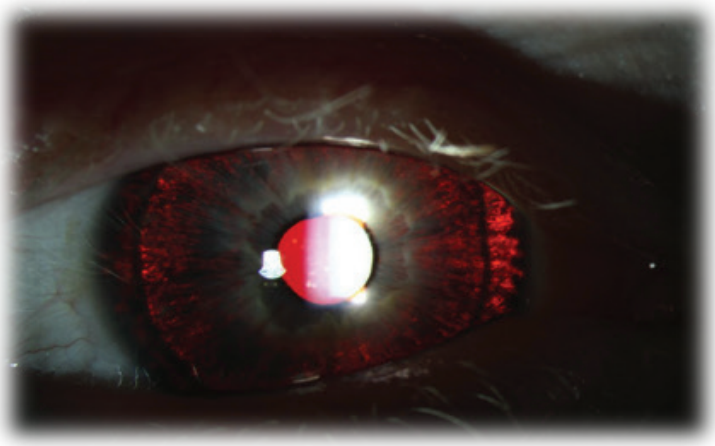

Figure 1. Iris transillumination in a patient with albinism.
Source: https://gene.vision/knowledge-base/albinism-for-patients/

2. Reduced Vision

One of the main characteristics of patients with albinism is reduced vision. It is still not known in science whether there is a stoppage of previously normal visual development, or if the development is hypoplastic from the beginning in people with this pathology. Visual acuity can range from 20/20 to 20/400, but the most commonly ranges from 20/100 to 20/200. Mainly, vision loss is due to foveolar hypoplasia and disturbed morphological characteristics of photoreceptor cells, especially those in the macular region. High refractive errors are quite rare, but some degree of myopia, hypermetropia and astigmatism is often present. Stereoscopic vision is also affected in patients with a marked degree of albinism, but without affectation of color vision (12).

3. Strabismus

Both horizontal and vertical deviations in oculomotor balance may be encountered in patients with albinism. Due to the early development of strabismus, they usually do not show diplopia. Despite the frequent presence of strabismus, amblyopia is rare in these individuals. In contrast, nystagmus is quite a common coexisting manifestation in people with albinism, together with strabismus, and with a large amplitude (12,13).

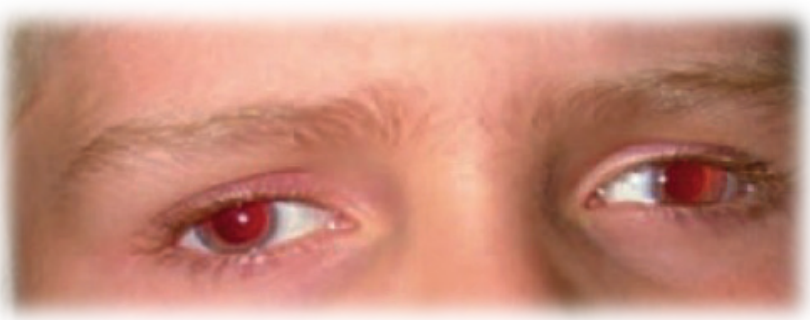

Figure 2. Exotropia with a red fundus reflex present in a child with albinism.
Source: https://www.lecturio.com/concepts/albinism/

4. Nystagmus

The most common type of nystagmus is horizontal according to the direction of stretching, and pendular or indeterminate according to its nature. It is usually clinically manifested, especially in children. In different types of albinism, it can appear differently, and thus affects visual acuity. To get better vision, patients with albinism and nystagmus often hold their head in a forced position in order to minimize its effect. Nystagmus in albino individuals causes changes in the retinal image. In those individuals with a marked degree of horizontal nystagmus, extraocular muscle surgery (according to Kastenbaum-Andreson) is a possible option, with modest postoperative results. Retroequatorial insertion of all four straight horizontal muscles is a possible procedure for significant reduction of nystagmus and improvement of the patient's subjective vision (14,15).

5. Photosensitivity and Photoaversion

Patients with albinism often have photophobia, an increased sensitivity to light. The reason for this is generally due to reduced melanin pigment in the cellular structures of the iris and retina. Due to this, there is an inadequate focusing of the light rays, or rather they are scattered and cause dispersed irritation of the photoreceptor cells. In order to improve photosensitivity, patients with this condition are advised to wear hats and protective glasses when in bright environments (16).

6. Abnormal Decussation of the Visual Pathways

Each of the mammals has its own characteristic in the percentage of optic nerve fibers that cross at the level of the optic chiasm. For man, that value is about 53%. This ratio is extremely important for achieving adequate stereoscopic vision. In people with albinism, this percentage is disturbed and can be up to 90% crossing. The consequence of this is seen in an inadequate arrangement of the optical fibers at the level of the lateral geniculate and inadequate projection at the level of the visual cortex, which will ultimately have repercussions on stereoscopic vision and in the appearance of strabismus in these individuals (12,17). Monocular visual evoked potentials are important for defining this condition and can be used as a diagnostic tool in non-specific forms of albinism.

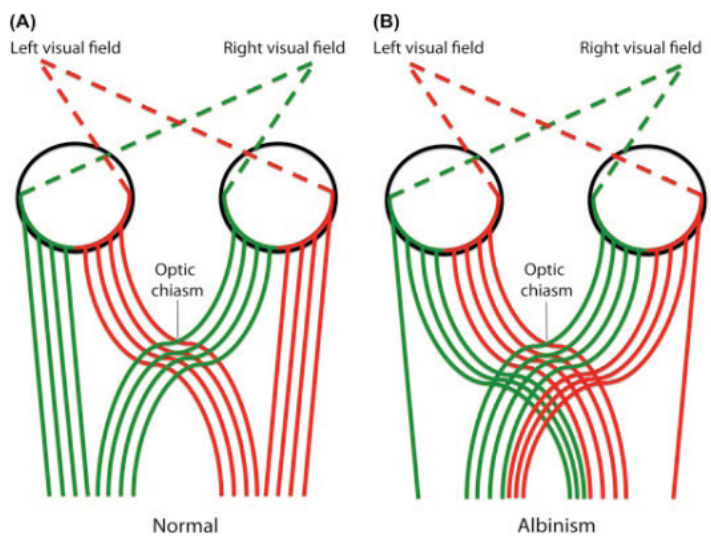

Figure 3. Comparison of chiasm decussation in an individual without and with albinism.
Source: https://www.sciencedirect.com/science/article/abs/pii/B9780128133163000076

7. Foveal Hypoplasia and Changes of the Fundus

The overall aspect of the fundus is characteristic in patients with albinism. That is, due to the absence of melanin pigment in the retinal pigment epithelium (RPE), a so-called transparent

retina occurs, through which the choroidal blood vessels can be seen, and the scleral reflection, which gives a whitish appearance to the fundus.

Another major feature of fundoscopic examination in these patients is the loss of the foveolar depression due to its hypoplasia. During organogenesis, as a result of disturbed tyrosine metabolism and dysfunction of melanin vacuoles in the RPE, inhibition of signaling occurs, which is important for the development of the fovea and the macular region in general. In the absence of such signal stimuli, the development of this part of the retina lags and remains functionally and morphologically hypoplastic. Foveolar hypoplasia is accompanied by the partial or complete absence of the foveolar avascular zone in these patients, as well as microvascular bridges at the level of the fovea that cross the horizontal meridian of the eye (18).

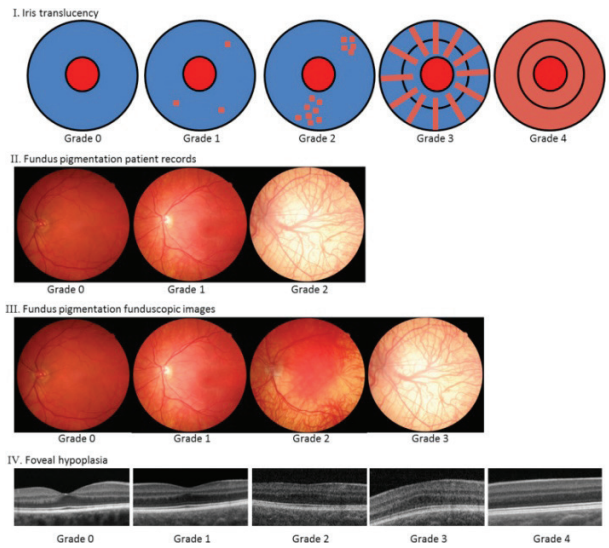

Figure 4. Ocular phenotypic spectrum of albinism.
Source: https://www.sciencedirect.com/science/article/abs/pii/S0161642018305748

Prognosis and Treatment

There is still no causal treatment in patients with albinism. Prevention of exposure to UV rays is extremely important in these individuals because they are at high risk of developing squamous or basal cell skin cancer. Therefore, a much-reduced exposure to the sun, wearing protective clothing, etc. is recommended. Regarding ophthalmological problems, timely recognition of persons with ophthalmological manifestations of the disease is of great importance. Initially, to prevent the development of amblyopia, to correct refractive errors and of course to achieve the best possible visual function. Albino patients who have strabismus or nystagmus may have an improvement if they undergo surgical treatment of the extraocular muscles (2,19).

Several preparations are under investigations that have the potential to find clinical application in the treatment of these patients. One of them is L-DOPA as a replacement therapy because it is an intermediate in this metabolic pathway. Other potential substances are aminoglycosides that would help in bridging non-sense mutations in genetic-biochemical processes at the cellular level. Recently, the drug Nitisinone has been approved by the FDA as an inhibitor of tyrosine degradation in patients with hereditary tyrosinemia. In the future, more studies are expected that would show the possible benefit of this preparation in patients with albinism. The idea is that the reduced degradation of tyrosine will lead to its increased concentration which may induce stimulation of tyrosinase and melanin synthesis. Until now, several animal studies have given good results using this agent (20,21).

Conclusion

Like many other systemic diseases that give ophthalmological manifestations, albinism is one of the entities that presents itself through an ocular affection. The recognition of ocular abnormalities in patients with this pathology is of great importance for timely diagnosis of the condition, all with the aim to provide appropriate treatment and management of the problem, both systemic and local-ophthalmological. Impairment of visual function still remains a major ophthalmological problem in people with ocular or oculocutaneous albinism.

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PERIOPERATIVE ANESTHETIC MANAGEMENT IN A CHILD WITH BECKWITH-WIEDMAN SYNDROME

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Abstract:

Beckwith-Wiedemann Syndrome (BWS), a rare genetic disorder, poses distinctive challenges for anesthesiologists due to its associated physical anomalies and potential complications. This case report details the anesthetic management of a 2-year-old boy with BWS undergoing a procedure for agenesis testis bilateral. Key considerations include macrosomia, hypoglycemia risk, airway abnormalities, cardiovascular anomalies, and abdominal wall defects. The patient successful perioperative care involved meticulous preoperative assessment, careful planning, and collaboration with specialized medical teams. Anesthesia comprised a combination of medications, monitoring, and airway management techniques tailored to the patient's unique needs. The discussion emphasizes the importance of considering macrosomia, hypoglycemia, anatomical abnormalities, and other factors in anesthesia planning for BWS patients. Vigilant postoperative monitoring is highlighted. The conclusion underscores the necessity for experienced anesthesiologists familiar with the challenges associated with BWS, emphasizing the significance of tailored approaches, comprehensive assessments, and collaborative care for the safety and well-being of these patients during surgical interventions.

***Key Words**: Beckwith-Wiedemann Syndrome, macrosomia, airway management, perioperative care*.

Introduction

Beckwith-Wiedemann syndrome (BWS) is a complex overgrowth disorder with an estimated incidence of 1:13,700 live births. It is caused by variety of genetic or epigenetic alterations within two domains of imprinted gene on chromosome 11p15. It is mainly characterized by macroglossia, omphalocele and gigantism.

Perioperative anesthetic management might be complicated by anatomical airway abnormalities, recurrent hypoglycemia, electrolyte imbalance and possible cardiovascular anomalies. Prior preparation, preoperative assessment and strategies to manage airway obstruction is essential for the successful administration of anesthesia. Hereby we present the airway management and anesthesiologic considerations of a 2-years old boy who underwent a procedure for "agenesio testis billateralis".

Case Report

The patient is a 2-years old boy and weighting 11kg. His medical documentation included results from magnet resonance and there was described "agenesio testis billateralis" and enlarged lymph nodes in 10mm in inguinal region. He was operativelytreated for omphalocele 2 years ago. The Mallampati grade was III, the blood oxygen saturation was 98% in room air and there were no abnormalities in laboratory parameters and cardiac function. Prior to the OR admission, premedication was administered. We had monitoring of electrocardiogram (ECG), NIBP, heart rate and blood saturation. Infusion with 0,9% NaCl was started on peripheral vain, and we administrated Fentanyl, Propofol, Suxamethonium chloride, and after successfully intubation Rocuronium. We placed a 4mm cuffed endotracheal tube using video-laryngoscope (Storz) with the Macintosh blade size 2. Anesthesia was maintained with Sevoflurane 2vol% in air and oxygen (50% - 50% concentration). Heart rate was 126-128bpm, blood saturation 100% and end-tidal carbon dioxide was 40 - 42mmHg. The surgical procedure was completed in 2 hours and 15 minutes without any complications. Neuromuscular blockade was reversed with Neostigmine and Atropine. After extubation his respiratory and hemodynamic conditions were stable.

Discussion

Beckwith-Wiedmann syndrome is caused by mutation in the genes and this patient's diagnose was based on a chromosomal analysis postpartum. Anesthesia management in BWS is a challenge because of the abnormal airway anatomy, gigantism, visceromegalia, cardiac defects and endocrine abnormalities (hypothyroidism, hypoglycemia). Nephro-urological anomalies in patients with BWS is 28% - 61% including cortical and medullary cysts and higher incidence of hypercalciuria and nephrolithiasis. The importance of hypercalciuria is related to perioperative renal dysfunction. Cardiac defects occur in up to 13% -20% of patients. It's necessary to have careful pre-operative evaluation. Besides for routine evaluation tests and clinical exams, a preoperative chest radiograph is required, not only to diagnose some evidence of cardiac anomaly, but also to exclude thoracic neuroblastoma. Polycythemia and hypothyroidism, though less common, should be ruled out before surgery due to their adverse effect on perioperative events in terms of bleeding and delayed weaning from mechanical ventilation. Preparation before the induction of anesthesia is especially important in cases that may show potential for difficult ventilation and intubation. In the operating room, different-sized masks, tracheal tubes, nasal and/ or oral airways, a stylet, laryngeal masks, fiberscope and video laryngoscope, as well as a tracheostomy set should be kept available (1,2). Premedication is usually avoided if there is a suspicion of possible airway compromise following sedation, although it was used in our case without any complications. Inhalational induction is comparatively safe because of the fact that during mask ventilation overdose of sedatives may cause tongue to fall back into the retro lingual space leading to severe airway obstruction. Awake intubation is an alternative, but it is avoided due to discomfort and pain, and it may increase in intracranial pressure (2). Comprehensive cardiac evaluation including ECG, echocardiography and CT angiography is only necessary when cardiac anomaly is suspected during clinical examination. Abdominal ultrasound is required to access for organomegaly, nephrocalcinosis, medullary sponge kidney and other structural abnormality (3). In our case, the following strategy was followed for the anesthetic administration: induction with fentanyl and propofol, ventilation via a mask and performing a rapid sequence intubation with use of Suxamethonium chloride for shorter need of ventilation, and a video laryngoscope which is a tool of choice for suspected difficult intubations. Cuffed endotracheal tube is preferred because the size of trachea is not easy to predict in BWS patients (larger size trachea in BWS), further, to avoid risks incurred during changing of tracheal tube (in situation of difficult endotracheal intubation). After achieving intubation, rocuronium

was administered for neuromuscular blockade. There is no contraindication for any of the anesthetic agents. Opiates should be used cautiously to avoid postoperative airway obstruction and apnea. All the neuromuscular blocking agents can be safely used unless there is a general contraindication (renal or hepatic insufficiency). Reversal of neuromuscular blockade is safe with neostigmine. Other considerations are that BWS patients are more prone for metabolic stress response and electrolyte shift during perioperative period. Patients with BWS can be at risk for pre-operative hypoglycemia, but mainly in the neonatal period, and our case was a 2- years child with no such problem (4,5). The postoperative care depends upon the age of the child, type of surgery performed, underlying cardiac problem and presence of hyaline membrane disease. Careful management of glucose and electrolyte homeostasis is mandatory in selected cases.

Conclusion

Planning and preparation for difficult ventilation or intubation include different-sized masks, tracheal tubes, nasal and/ or oral airways, a stylet, laryngeal masks, fiberscope and video laryngoscope, as well as a tracheostomy set. It's necessary to have knowledge how to manage complications if you have during the treatment (hypoglycemia, low cardiac output, slow metabolism of anesthetics and difficult ventilation).

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ADENOMA OF THE ADRENAL GLAND IN WOMEN PREPARING FOR PREGNANCY

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Abstract

Introduction: The clinical presentation of pheochromocytoma varies depending on the location and extent of catecholamine secretion. Whenever possible, surgery is the preferred treatment for these tumors and can cure more than 90% of the patients. However, managing these patients requires a collaborative approach involving multiple medical specialists. Increased awareness of the importance of optimizing patients' symptoms and conditions before surgery has resulted in established procedures.

Aim: We want to present a case where, based on laboratory investigations, the patient did not have any concessions, although a biopsy of the adrenal gland due to clinical symptoms revealed increased secretion of adrenalin and aldosterone. Also based on the patient's clinical presentation during surgery, the patient's symptoms, along with the results of the imaging and intraoperative manifestations, resembled those that are typically associated with pheochromocytoma.

Material and Methods: In this report, we present a management of a case of active adrenal gland adenoma in a young, 18-years-old female with a history of paroxysmal hypertension, palpitations, and excessive flushing of the face who underwent adrenal gland biopsy and was diagnosed with an adrenal gland tumor and underwent left adrenalectomy, resulting in a favorable outcome.

Results: Biochemical tests were within normal ranges, except for a slightly increased CRP of 51.64mg/L, Direct Renin Immunoassay (CLIA) 56ng/l and Noradrenalin 514ng/L. A sampling of the adrenal gland showed hyperfunction on the cortex of the adrenal gland: cortisol 3.3μ/dL, aldosterone 443ng/dL, and adrenalin 333pg/mL.

Conclusion: Early diagnosis, multidisciplinary collaboration, appropriate preoperative medical management and prompt surgical intervention are crucial in reducing morbidity and mortality and preventing complications such as cardiovascular disease in patients with active adrenal glands.

Key Words: *adrenal gland adenoma, hypertension, Pheochromocytoma, venous sampling.*

Introduction

Pheochromocytoma is a rare tumor that affects only one to four out of every million people each year. It can cause high blood pressure. Even though it causes hypertension in less than 1% of the cases, it is very important to think about this tumor when evaluating people with hypertension. Pheochromocytoma arises from chromaffin cells in the embryonic neural crest that produce catecholamines. These cells are primarily located in the adrenal medulla, but they can also occur in other areas, known as paragangliomas (1).

The clinical presentation of pheochromocytoma varies depending on the location and the extent of catecholamine secretion and may include the classic symptoms of hypertension, headaches, palpitations and excessive sweating. Diagnosing pheochromocytoma requires detecting excessive catecholamine release and documenting the anatomical location of the tumor (1).

When possible, surgery is the preferred treatment for these tumors and can cure more than 90% of the patients. However, managing these patients requires a collaborative approach involving multiple medical specialists, such as endocrinologists, surgeons, cardiologist and anesthesiologists. Increased awareness of the importance of optimizing patients' symptoms and conditions before surgery has resulted in established procedures. Significant advancements in surgical and anesthetic techniques have also played a significant role in reducing the historical morbidity and mortality rates of patients undergoing surgical tumor removal (2,3).

We want to present a case where, based on laboratory investigations, the patient did not have any concessions, although a biopsy of the adrenal gland due to clinical symptoms revealed increased secretion of adrenalin and aldosterone. as Also, based on the patient's clinical presentation during surgery, the patient's symptoms, along with the results of imaging and intraoperative manifestations, it was resembled of those typically associated with pheochromocytoma.

Material and Method

In this report, we present the medical management of a case of an active adrenal gland in a young, 18-years-old female, non-smoker with a BMI of 24.2., with a history of paroxysmal hypertension, palpitations and excessive flushing of the face who underwent adrenal gland biopsy and was diagnosed with an adrenal gland tumor. She underwent a left supra-adrenalectomy, resulting in a favorable outcome.

The patient was admitted to the Clinic of Urology. Because of paroxysmal attacks of hypertension, and in order to avoid damage to target organs, and taking into account the age of the patient who plans to become pregnant and give birth, surgical intervention with a supra-adrenalectomy was indicated with consent of the patient.

Our patient reported episodes of hypertensive crisis a few months before hospital admission, and those episodes were with peak blood pressure levels of > 170/120mmHg, tachycardia 110/min, attacks of palpitation, associated headache, facial flushing and diarrhea over past 5 months.

At first cardiologist was consulted. The electrocardiogram was normal and showed sinus rhythm, the echocardiogram showed ejection fraction of 42%, compensated heart, thyroid gland with homogenic structure and beta blocker (5mg/day) and alprazolam (0.25mg/day) was prescribed by cardiologist.

A CT scan of the abdomen with contrast revealed a small focal lesion (a left-sided adrenal mass) measuring approximately 9mm by 6mm on the left adrenal gland (Figure 1). The mass appeared to

have a mostly homogenous contrast enhancement. Pattern and correlation with laboratory hormonal parameters were suggested for differentiation purposes, in conjunction with control CT scans.

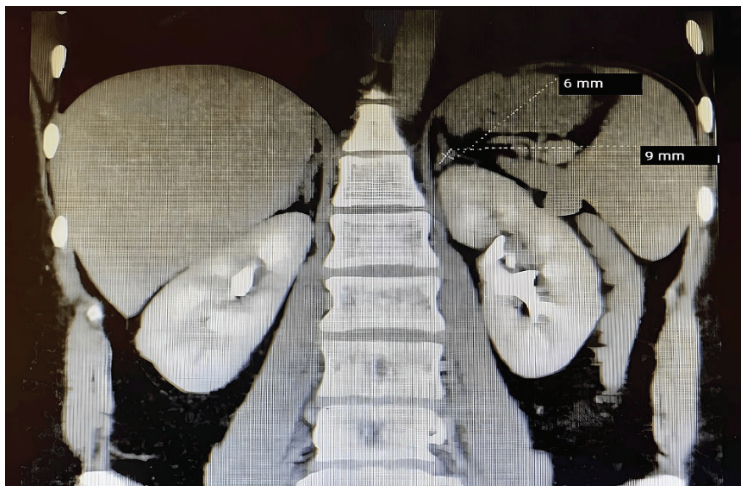

Figure 1. Abdominal CT scan showing a homogeneous lesion, measuring approximately 9mm by 6mm on the left adrenal gland.

Results

Biochemical tests were within normal ranges, except for a slightly increased CRP of 51.64mg/L, Direct Renin Immunoassay (CLIA) 56ng/l and Noradrenalin 514ng/L. Other hormonal status tests and clothing test were all normal.

A sampling of the adrenal gland was required by our urologist for the separate evaluation of the hormones of the adrenal gland, and because this method is not performed in our institution or in any other institution, this examination was performed abroad. Results showed hyperfunction on the cortex of the adrenal gland: cortisol 3.3μ/dL, aldosterone 443ng/dL and adrenalin 333pg/mL. After sampling of the gland, multidisciplinary collaboration of urologist, cardiologist, endocrinologist and anesthesiologist was made for adrenal gland laparoscopic removal due to clinical signs, and an provisional diagnosis of active adrenal gland tumor and secondary hypertension due to adrenal pheochromocytoma was confirmed by clinical signs. The patient was scheduled to undergo an excision of an adrenal mass and was referred to the anesthesiologist for evaluation.

Table 1. Biopsy results from the adrenal gland sampling.

Sampling Results			
	Cortisol normal range (2.5-11.9μ/dL)	Aldosterone normal range (3.7-43.2ng/dL)	Adrenalin (1-140pg/mL)
Left adrenal vein	3.3μ/dL	443ng/dL	333pg/mL
Left peripheral vein	1.2μ/dL,	19.8ng/dL	10.2pg/mL
Right adrenal vein	1.6μ/dL,	5ng/dL	4pg/mL
Right peripheral vein	1.3μ/dL,	16.2ng/dL	12.1pg/mL

During the pre-op visit, the patient seemed calm, and there were no signs of pallor, cyanosis, jaundice or a rash. Preoperative standard investigations were performed. ECG, BP, systemic examination, airway assessment, biochemical laboratory and chest X-ray were all within normal ranges, and the

patient was assigned ASA grade 2. Informed consent for high-risk surgery was obtained, and the patient continued taking her antihypertensive medications until the morning of the surgery.

Premedication with Diazepam 5mg was administered the night before and the morning of the surgery, and the patient fasted overnight. An intravenous saline solution of 1000mL was infused over 8 hours overnight. A preoperative preparation was performed with hydrocortisone 100mg administered the night before and the morning of the surgery according to our institutional protocol.

After the patient's arrival in the operating room, an 18-gauge intravenous needle was inserted, and a 0.9% NaCl solution was initiated. Non-invasive devices were fixed to monitor vital signs, including automated non-invasive blood pressure, pulse oximeters and electrocardiograms. A 20-gauge needle over the right radial artery for invasive blood pressure monitoring after induction of anesthesia was placed. The patient's baseline pulse rate was 80 beats per minute, blood pressure was 140/80mmHg and oxygen saturation was 97%.

The patient underwent general anesthesia, was pre-oxygenated with 100% oxygen, premedicated with dormicum 2mg, and induced with fentanyl 0.15μg and propofol 200mg. Muscle paralysis was achieved using rocuronium 50mg, and the patient was intubated with a 7.5-mm endotracheal tube. A nasogastric tube was inserted, and the patient was mechanically ventilated with a tidal volume of 7ml/kg at a respiratory rate per minute that was adjusted according to ETCO2, which we maintained between 35 and 42mmHg. Anesthesia was maintained using desflurane with a MAC of 6.0V% and remifentanil at 0.5mcg/kg/min. During anesthesia, the antibiotic Ceftriaxone, 2 grams and antiemetics were administered. The patient was generally stable until tumor manipulation, at which point she became hemodynamically unstable. Her blood pressure increased to 200/120mmHg, and her heart rate rose to 120 beats per minute. This was managed by increasing the depth of anesthesia and administering the short acting β blocker esmolol 30mg. After ligation of the vein and gland excision, the patient experienced hypotension of 60-40mmHg. This was corrected by replacing the volume with 1 liter of saline solution and boluses of phenylephrine at 200mcg and 0.75mcg/kg/min by intravenous continuous infusion.

The total duration of the operation was 55 minutes without significant blood loss. The patient was extubated at the end of the surgery on the operation table after receiving fentanyl 0.05mg and reversing the residual muscle paralysis with IV 1 milligrams of atropine and IV 2.5 milligrams of neostigmine.

After her surgery, she was transferred to surgical ward with adequate monitoring and postoperative therapy. Postoperative recovery was uneventful, and the patient was discharged on the third postoperative day without any complications. Surgery resulted in a significant improvement in BP control, and she showed no signs or symptoms of hypertension during a follow-up visit within 1 week of the surgery.

Discussion

Based on available literature and to our knowledge there is no single sign or symptom that can reliably diagnose or rule out pheochromocytoma. Instead, doctors can learn more from the combination of certain symptoms, findings from a physical exam and lab tests. Additional research is needed to determine the precise diagnostic value of these clinical findings. For now, the diagnosis of pheochromocytoma relies on a high degree of clinical suspicion, laboratory tests and appropriate imaging studies (4).

The clinical presentation of paroxysmal headaches, sweating, heart palpitations and hypertension, combined with abnormal results from 24-hours urine of fractionated metanephrine, and

vanillylmandelic acid, also known as para- vanillylmandelic acid or P-VMA, are tests that suggest a diagnosis of pheochromocytoma, which is reinforced by the existence of an adrenal mass. Nevertheless, it is crucial to recognize that this constellation of symptoms is not universal and is observed in less than 25% of the patients diagnosed with pheochromocytomas (5).

Our presented case matches the results presented by Gerrero and colleagues in their article. They show that phaeochromocytomas can be presented differently based on factors such as tumor size and catecholamine production. It remains unclear whether the size of a pheochromocytoma is related to hormone levels, clinical presentation or complications during the perioperative period. According to their study, there is a direct relationship between the size of a tumor and the levels of hormones it produces. Tumors with smaller sizes typically have lower levels of catecholamine secretion, while larger tumors have a greater potential to secrete hormones and exhibit greater variability in their secretory capacity. Furthermore, larger tumors were found to have the highest ratios of hormone production (6).

In our case, the patient was clinically diagnosed with pheochromocytoma due to presenting typical symptoms; the adrenal mass was a very small focal lesion; and every biochemical analysis was within normal limits except the Direct Renin Immunoassay (CLIA), which was increased and associated with hyperaldosteronism (Conn's syndrome); and noradrenaline were associated with pheochromocytoma (7). These findings were confirmed with a biopsy of the adrenal gland. Although an adrenal gland biopsy is an invasive procedure, the existing literature suggests that to help avoid potentially fatal consequences, an adrenal biopsy should only be carried out if the anticipated results are likely to change how the patient is managed specifically and after catecholamine-producing tumors have been biochemically excluded (8).

Minimally invasive surgery is the preferred option for treating this condition, with preoperative preparation including alpha-1-blockers (such as doxazosin or prazosin) and increased sodium intake for at least two weeks prior to surgery. Chronic pharmacological treatment options may include alpha1-blockers, beta-blockers (only after starting alpha1-blockers and in the presence of symptomatic tachycardia), calcium channel blockers, ACE inhibitors and central action agonists. In cases of paroxysmal hypertensive crises, emergency treatment with sodium nitroprusside or injectable phentolamine and volume replacement may be necessary. Effective treatment of neoplasms typically requires complete and timely removal to alleviate symptoms, cure hypertension, and prevent the spread of cancer cells. For individuals with malignant pheochromocytoma and metastases that cannot be surgically removed, systemic therapy with MIBG-131 is often recommended. In cases where MIBG-131 does not stop the progression of the disease or if metastases do not have MIBG uptake, cytotoxic chemotherapy may be necessary (9,10).

In our case, we administered a short-acting beta blocker before performing venous ligation on our patient, who presented with hypertension and tachycardia, and was slightly hemodynamically unstable. After the venous ligation, we administered a vasoconstrictor, phenylephrine, to stabilize the patient's hemodynamics and maintain her blood pressure within normal limits. This approach allowed us to successfully manage the patient's condition and ensure a safe and effective outcome. Management of perioperative hemodynamically unstable patients is presented in the literature with short-acting b blockers before ligation of the vein and vasoconstrictive therapy after removal of the gland (11).

We think that the surgeon's speed in ligating the vein affects the patient's intraoperative stability. The tumor size may be the reason for the normal levels of vanillylmandelic acid and metanephrine in 24-hours urine, as well as normal hormone levels, or it was due to early diagnosis and appropriate preoperative and perioperative management by the anesthesiologist, leading to a quick and successful resolution of the case without complications.

However, the most important of all is appropriate preoperative, perioperative and postoperative management with a multidisciplinary team approach, which we think is the key to success.

Conclusions

This case report highlights the importance of considering pheochromocytoma as a possible diagnosis in patients with paroxysmal hypertension, even if laboratory investigations initially appear normal. Early diagnosis, multidisciplinary collaboration within multiple specialties and adequate preoperative medical management significantly diminish morbidity and mortality during the perioperative phase among these patients. Prompt treatment with surgical excision of active adrenal gland can result in complete resolution of symptoms and prevention of complications like cardiovascular disease.

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ACUTE PULMONARY THROMBOEMBOLISM AFTER HIP ARTHROPLASTY

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Abstract

For presentation of this case, we provided written consent from the patient.

69-years-old female patient came in hospital for operative treatment of total endoprosthesis of the right hip. She had multiple comorbidities regulated by chronic therapy. According to the pulmonary embolism severity index there was an increased risk for pulmonary thromboembolism (PTE). She received thromboprophylaxis Nadroparin calcium (Fraxiparine 0.6 ml sc) on the day of the hospitalization and it was regularly ordinated on daily basis. Perioperative and intra-operative, the patient was stable. Intraoperative, the patient was in OET anesthesia, in the course of 4 hours, we administered 3200ml of clear fluids and 350ml transfusions of deplasmatized erythrocytes. After extubating and leaving the operating room there was sudden drop in saturation 60-80%. She was transferred to intensive care, re-intubated, sedated, imaging methods were performed such as x-ray and CT angiography, where a diagnosis of pulmonary thromboembolism was established. Anticoagulant therapy was started immediately. There was an improvement in her condition, then she was extubated, conscious and oriented in space and time. After 2 days in intensive care unit she returned to the ward.

Key Words: *fluids, general endotracheal anesthesia, pulmonary thromboembolism.*

Introduction

Intraoperative acute pulmonary embolism is a serious complication in orthopedic patients and requires a risk assessment by anesthetists (1). Six hours fasting from food and 2 hours from liquids is generally recommended, and the patient should be encouraged to minimize the fasting period, thus avoiding dehydration (2). The most series of studies do not distinguish between emboli occurring during and after surgery, but Koessler et al. reviewed 4 series of patients undergoing total hip arthroplasty and found that the incidence of symptomatic intraoperative PE was between 0.6% and 10% (3). Cardiomegaly is the most common finding on chest radiograph in patients with PE. The anesthesiologists must be careful and monitor parameters that occur in this type of patients who are on mechanical ventilation, anesthetized. Hypotension and tachycardia are symptoms associated with PE (5).

Case Presentation

For presentation of this case, we provided written consent from the patient.

A 69-years-old female patient was presented to the Department of Orthopedics and Traumatology in our General Hospital as an elective admission for operative treatment of a total endoprosthesis of the right hip.

While doing the anamneses, we came to valuable information that the patient has been operated three times. Arthrosis changes appeared for the first time in 2005 when an endoprosthesis was implanted on the left hip. Due to the progression of degenerative changes, the right hip was operated, and arthroplasty was done in 2015. In 2020, due to an infection at the site of the implanted prosthesis, it was removed.

After clinical, paraclinical and radiological analyses, an indication for operative treatment was established. The patient had several comorbidities - hypertension, diabetes type 2 and dyslipidemia, extremely obese type 3 (BMI 46.5), chronic renal failure stage 4 (without dialysis treatment). Accordingly, she received a beta blocker, angiotensin II receptor blockers (ARB), statin and insulin subcutaneously. Hemostasis and d-dimers were tested regularly from the first day of her hospitalization and they were in reference value. She didn't consume alcohol, was not addicted to cigarettes and other drugs. An acetabular defect of the right acetabulum was determined according to Paprosky classification - grade I. The type and risks from the operation and anesthesia were explained to the patient and the family. There was high risk of thromboembolism and Nadroparin calcium (Fraxiparine 0,6ml) was ordinate. The operative treatment started on 21.01.2022 in OET anesthesia. The patient was placed in a supine position in the operating theatre. We did latero-anterior approach in layers and en route hemostasis, then the right hip was approached. The acetabulum was processed, an acetabular component number 49mm (All-Poly Acetabular Cup- Zimmer) was applied. Then the femoral canal was processed, and femoral stem No. 7.5 Original M.E. was implanted. Muller-Zimmer, a +3.5mm/28mm head (VerSys-Zimmer) was placed on the stem. The operative wound was washed, repositioned, closed in layers, dressed, and bandaged. We implanted total cemented endoprosthesis.

During the induction we gave Midazolam 2mg, fentanyl 0.05mg, propofol 160mg, 2% lidocaine 40mg, rocuronium 50mg. During the intervention we had two syringe pumps for our total intravenous anesthesia - TIVA, propofol 400mg/50ml/5-10ml/h, remifentanil 2mg/40ml/5-10ml/h. Fentanyl was added according to vital signs as well as a non-depolarizing myorelaxant. The patient received 1700ml NaCl 0.9% Physiological Saline, 1000ml Ringer's, 500ml plasma expander HES 6%, 350ml transfusions of deplasmatized erythrocytes. The operation lasted 4 hours. During the operative period the patient was stable. On Figure 1 we can see the values of blood pressure and heart rate intraoperatively. Antibiotic, analgetic, gastroprotective, antiemetic therapy was given. The saturation during surgery ranged from 98%-100%, and the capnograph had values within normal limits.

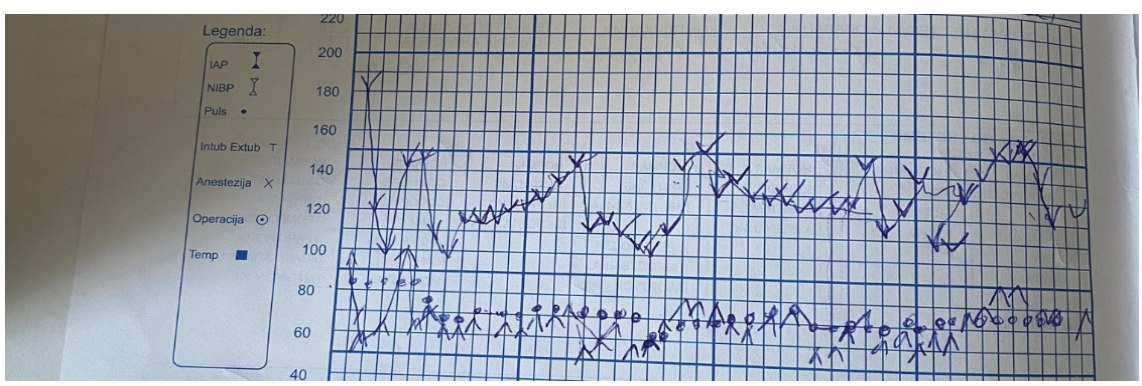

Figure 1. Systolic pressure is noted with the port facing up, diastolic pressure is noted with the port facing down, pulse is noted with a dot. One square indicates a 5-minute interval.

Table 1. Drug dose and hour during surgery when given.

Drugs given during intervention/ timeline	0-1 hour	1-2 hour	2-3 hour	3-4 hour
Fluids	1200ml (NaCl 0.9%)	1000ml (Ringer), 500ml 6% HES	500ml (NaCl 0.9%)	
Midazolam	2mg			
Lidocaine 2%	40mg			
Fentanyl	0.1mg	0.25mg	0.1mg	
Rocuronium	70mg	40mg	10mg	
Propofol				
Remifentanil				
Tranexamic acid	1,0gr/i.v.			
Paracetamol	1,0gr/i.v.			
Ketoprofen	160mg/i.v.			
Tramadol			100mg/i.m	
Clindamycin		600mg/i.v.		
Cefriaxone			2gr//i.v.	
Famotidine		20mg/i.v.		
Metoclopamide		10mg/i.v.		
Ephedrine		6mg/i.v.		
Furosemide				10mg/i.v.
Methylprednisolone		80mg/i.v.		
Blood transfusion			350ml RBE (red blood erythrocytes)	
Neostigmine				2.5mg
Atropine				1.0mg

When the operation was done, the patient was awakened, extubated, and placed into the ward. After a short period of time, the patient developed breathing-dyspnea with cyanotic skin and mucous membranes. The patient was awake, on auscultation there were decreased breath sounds. Saturation - Sp02-59-83% was with oxygen mask. Immediately we gave methylprednisolone 120mg, dexamethasone 4mg, aminophylline 250mg, furosemide 20mg, and another dose of nadroparin calcium (Fraxiparine) 0.6mg s.c. After the given therapy, the condition did not improve. Due to the drop in saturation and no improvement in her overall condition and symptoms, the patient was transported to the intensive care. We intubated her, after which she was placed on mechanical ventilation and her saturation improved significantly to 99%. Propofol sedation was started. At that time, we suspected that patient might be developing pulmonary embolism. A chest X-ray was taken, where reduced transparency was noted on the left side of the lung in the middle and basal parts, as well as an increased cardiac shadow. Cardiomegaly is a very common X-ray sign in patients with pulmonary embolism (PE) (5). After the X-ray image, a CT angiography was performed, defect in the filling of the pulmonary artery of the lower lobe in the left lung was noted, truncus pulmonalis and other pulmonary arteries were in the reference value.

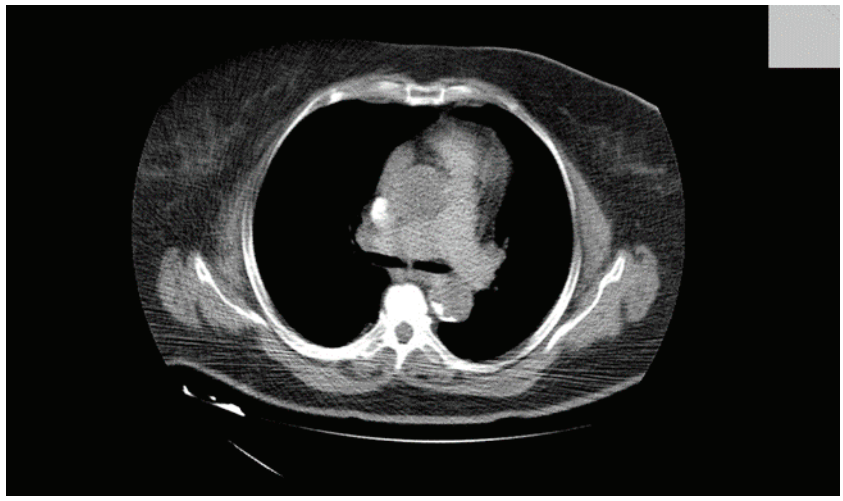

Figure 1. Thromboembolism shown on CT with contrast.

We discussed whether we should include thrombolytic therapy with streptokinase drugs. Because of the fear of bleeding, we decided to continue with factor Xa inhibitors - Nadroparin calcium. Hemostasis was done and d-dimers were 9000ngr/ml. In consultation with doctor specialist – transfusiologist, Amp.Nadroparin calcium (Fraxiparine) 2x0.6ml, or 5700 I.E. were prescribed s.c. The next day, 12 hours after intubation sedation was turned off. The patient was awake, on auscultation vesicular breathing, slightly weakened on left basal part of left lung. We placed her on continuous positive airway pressure-CPAP Fi02=0.5; PEEP=0.5 Sp02-99%. Her condition was improving hour by hour and we transported her to the ward. Blood tests were done every day, on the first day post-operatively, there was reduction of blood elements and reactive leukocytosis as a result of anemia. We substituted blood through transfusion of erythrocytes, and the condition was improving. The drain was removed on the first postoperative day. The operative wound was without signs of inflammation and infection. Other inflammatory parameters such as sedimentation were normal, C-reactive protein was slightly elevated. Therefore, a swab from the wound was taken. It was negative for pathogenic aerobic and anaerobic bacteria and fungi were not detected. Physical medicine was performed during the entire hospital stay, from the second day post-operatively was in vertical position, good condition and instruction for home were given. At home, she would need to regulate her blood sugar - glycemia, to receive her chronic therapy, as well as to continue with Amp.Nadroparine calcium (Fraxiparine) 0.8ml -7600 I.E. s.c. for 14 days and Tbl.Rivaroxaban 15mg 2x1. To continue with regular blood checks for hemostasis and d-dimers and according to the results to continue therapy.

Diagnosis

Angiography is considered the gold standard for the diagnosis of PE. It is an expensive method, not available in all hospitals and not without risk. According to Stein et al., there is a 4% incidence of serious complications (including death and renal failure) in intensive care units in patients who underwent CT angiography (4).

Discussion

Our patient had several risk factors: hypertension, diabetes, obesity type 3, serious surgery - hip arthroplasty. A prospective study by Goldhaber et al. showed that obesity (BMI>29kg/m2) and cigarette smoking (N>35 cigarettes/day) are independent risks factors for PE in women, with

a relative risk of 2.9 and 3.3, respectively (7). PE may be viewed as part of the cardiovascular disease continuum and common risk factors - such as surgery, cigarette smoking, obesity, hypercholesterolemia, hypertension and diabetes mellitus. Common ECG findings associated with PE are ST segment and T wave abnormalities. Non-specific ST changes, ST elevation and depression, or T wave inversion, are found in approximately 50% of patients. Complete right bundle branch block and T wave inversions in the precordial leads are the findings that correlate best with severity of PE. The diagnosis is established with the help of CT angiography, and aggressive treatment should start immediately with low molecular weight heparin. Systemic therapy for thromboembolism includes thrombolytic therapy with streptokinase drugs. Postoperative, thrombolytic therapy can lead to increased bleeding, so anticoagulant therapy (Enoxaparin or fraxiparine 1.0mg/kg every 12 hours or 1.5mg/kg once a day) can be therapy of a choice. Reperfusion is usually established with this therapy at the site of TE, the incidence of hemodynamic instability decreases. Collapse of the patient and increased risk of hemorrhagic brain infarction and serious non- brain hemorrhage (8) can occur. Hemodynamic instability is a major and significant risk factor before, intra and in postoperative period in PE (9).

Conclusion

Patients from risk groups should be evaluated before operation and properly treated. Time management is one of the key factors in the patient's overall well-being and survival. Experienced physician who is good in teamwork is important. In differential diagnosis it should be considered.

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ANESTHETIC MANAGEMENT FOR ABDOMINAL HYSTERECTOMY IN HEART TRANSPLANT RECIPIENT

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Abstract

Every year, the number of heart transplants in the world, but also in our country, is increasing. Because of high survival rates and increased life expectancy, heart transplant patients are likely to require elective or emergent non-cardiac surgical procedures. Heart transplant recipients present unique anesthetic challenges due to modified autonomic physiology and modified drug response. We present the perioperative management of 41-years-old woman,with a heart transplant before 30 months, admitted to the hospital for elective abdominal hysterectomy.

Key Words: *abdominal hysterectomy, anesthetic managemen, heart transplant.*

Introduction

Heart transplantation is a huge successful story. The idea to put a human heart from a dead person into person who is in terminal heart disease was shocking in 1967, when Barnard was the first to perform a heart transplantation.For patients with final stage of heart failure, heart transplantation can be the only way to stay alive. More than 140,000 heart transplants have been performedtill now. Worldwide, the number of transplants is increasing annually, with an average of 4,000-5,000 heart transplants per year, more than half of which are in the United States[1]. Many transplant patients are a pediatric population.

In Macedonia, heart transplantation started in 2020, and so far, a total of 9 heart transplantations have been performed.

Patients that had cardiac transplantation have around 90% chance to survive one-year if they are in North America and around 80% if they are in Europe or some other parts of the world that report to the International Society for Heart and Lung Transplantation (ISHLT)(1). Five-years survival is 70%, while median survival is greater than 12 years, but unfortunately only 20% survive ≥20 years (2).

Because of advances in cardiac surgery, high survival rates and enlarge lifespan, all heart transplant patients, a lot of them still children, have high possibility to need elective or emergent non-cardiac operation after the heart transplant.

All patients after heart transplantation deserve special care. They all have modified autonomic physiology andmodified drug response because of the denervation of the donor heart. All transplant patients have side effects from continuous use of immunosuppressive drugs and serious additional comorbidities that need a lot of preoperative preparation. A preoperative assessment is performed together with the patient's heart transplant team.

Case Report

A 41-years-old female was admitted in our hospital for an elective surgery. The patient had a left adnexal cystic formation with elevated tumor markers. She had had a right adnexectomy 4 years ago because of endometroid adenocarcinoma of the right ovary, stage Ia. Hysterectomy with left adnexectomy was indicated.

Patient hada history of an orthotopicheart transplant, performed30 months ago.Heart transplantation was a result of end stage heart failure due to dilated cardiomyopathy. Transplantation was Redo cardiac surgery. The first surgery was for ASD and VSD closure at the age of two, and the second six years later for mitral valve replacement. Heart transplantation was performed with a biatrial technique which led the patient for need of permanent pacemaker (PM) due to the complete atrioventricular block as a result of surgical discontinuation of the cardiac conductive system. The immunosuppressive therapy of the patient was Tacrolimus and Mycophenolatemofetil.

The preanesthetic evaluation included new cardiology examination with cardiac ultrasound, complete laboratory examination, coagulation status, level of immunosuppressive drugs. Consultations with her cardiac anesthesiologist and her cardiologist were established.

Subjectively, the patient had no complaints. From a cardiological point of view, the patient had no contraindications for gynecological surgery. The patient was objectively cardiac compensated, with regular blood pressure, on ECG rhythm of PM (regularly controlled by electrophysiologist) with regular record. Echocardiographic regular finding was with normal function of the graft with EF 71%.

On the day of the surgery the morning dose of immunosuppressive drugs were given, together with double antibiotic prophylaxis, glucocorticoids and proton pump inhibitor. In the operating theatre standard non-invasive monitoring was applied.

Pre-induction, heart rate (HR) was 90/min, blood pressure (BP) was 122/75 mmHg and SpO_2 was 98%. Preload was performed with infusion of 1/2L normal saline prior to induction of general anesthesia. After 3 minutes of preoxygenation, anesthesia was induced with 2mg midazolam, 0.1mg fentanyl, titrated doses of propofol (1mg/kg) and ketamine 20mg (0.03 mg/kg). Rocuronium 0.6mg/kg was used for muscle relaxation and intubation. A mixture of oxygen, air and sevoflurane (1-1.5%) was used to maintain anesthesia. Analgesia was providedby a multimodal approach (intermittent fentanyl boluses, non-steroid anti-inflammatory drug, paracetamol, Mg). The surgery lasted 95 minutes. HR strictly remained in the range of 88–91 beats/min and no dysrhythmias were noted perioperatively. The patient was extubated after the return of airway reflexes, then followed in the Intensive Care Unit for the next 24 hours. She was hemodynamically stable, on double antibiotic therapy, LMWH 1.5 mg/kg, requiring high doses of analgetic (paracetamol, NSAIDs, morphine). The next day, after 24 hours, the patient was transferred to the ward, immunosuppressive drugs were started, level of Tacrolimus was monitored daily. She left the hospital after 6 days.

Discussion

All heart transplant patients require detailed evaluation and preparation before the planned non-cardiac surgery. Complications that may occur during the surgery depend on the period in which the transplant was performed. Patients in the early period after transplantation, the first year, are much more sensitive. In the initial period of transplantation, all elective operations

should be cancelled and postponed for later. During this period, patients are exposed to an increased risk of complications: acute rejection (acute graft dysfunction is usually manifested as right ventricular dysfunction), complications related to immunosuppression, infection, exacerbation of concomitant diseases (renal dysfunction, hepatic dysfunction, diabetes mellitus as a result of steroid use, hypertension, lung diseases).

In the period of one year after the transplantation, the late period, the risk of acute rejection is reduced, and the immunosuppressive regimen is usually stabilized. But this period brings other concerns and the possibility of complications such as: allograft vasculopathy (usually this is the main risk for non-functioning graft and for rejection in the period one year after transplantation), risk for disturbance of the immunosuppressive mode, as well as the risk of malignant disease.

Our patient was transplanted 30 months ago thus belonging to the late group, a stable immunosuppressive regimen has already been established for her, so she wasin the best possible condition for operative elective intervention.

The transplanted heart has certain specificities, both in hemodynamics and in pharmacology. The main feature of the transplanted heart is cardiac autonomic denervation, which is the result of the explantation of the own heart. The transplanted heart has a higher heart rate because parasympathetic innervation is missing. The maneuvers of Valsalva are not effective, but the Frank-Starling effect persists, so the denervated heart responds to increased venous return, preload by increasing stroke volume and cardiac output. The denervated heart is very much dependent on appropriate intravascular volume and preload, thus heart transplant patients are referred to as "preload dependent (3).

In order to avoid acute vasodilatation and hypotension, we managed our patient under pure general anesthesia without central neuraxial blockade, although different anesthetic techniques (general, regional) have been successfully used in patients with a history of transplantation (4,5).

If general anesthesia is chosen, it is important to perform appropriate volume replenishment and reduce the risk of hypotension during induction of anesthesia. Availability of a direct-acting vasopressor agent is mandatory.

Neuraxial techniques are acceptable, but it should be noted that they may cause severe hypotension with a severe decrease in systemic vascular resistance, marked vasodilatation and decreased venous return to the heart, all of these as a result of denervated heart and lost sympathetic innervation. But, prior application of fluids in combination with a vasopressor will alleviate or prevent hypotension.

In terms of pharmacology, the transplanted heart responds differently to certain drugs. Ephedrine as a vasopressor that has an effect through autonomic system is not effective, while direct acting phenylephrine is effectiveas a result of alpha and beta receptors that in the transplanted heart are intact. We were ready with infusion and bolus doses of phenylephrine at induction and during anesthesia of our patient.

The transplanted heart to vasodilator agents like nitroglycerin and hydralazine, as well as anesthetic agents with vasodilator effects like propofol, can not respond with a compensatory reflex tachycardia and this can lead to deep hypotension. Therefore, these agents should be administered slowly, in small doses. Propofol in our patient was administered slowly and in minimal doses.

For the treatment of bradycardia, anticholinergic drugs are not very effective, but chronotropic agents with direct action are much more effective.

Among commonly used anesthetics and side effects, it is useful to mention that although rare, heart block and asystole have been described after administration of neostigmine in patients with cardiac transplantation (6). The probable explanation is reinnervation of parasympathetic in the transplanted heart(4).

Almost all heart transplant patients receive chronic corticosteroid therapy and are highly likely to have adrenal suppression. For this reason, extra glucocorticoids are usually given in relation with the expected stress. In our patient, we gave her a daily dose, but also an additional dose of Methylprednisolone.

Prophylaxis of surgical infection with antibiotics is mandatory because transplant patients are on chronic immunosuppressive therapy. Our patient received dual antibiotic prophylaxis.

Our patient had standard non-invasive monitoring that we practice for all patients. The possibility of additional invasive monitoring was prepared if necessary. But, it is important to mention that the high incidence of fatal infections with invasive lines outweighs the benefits derived from invasive monitoring.

One of the most important things in the operative course is to avoid perioperative hypovolemia. Every volume loss, blood loss, must be treated promptly. It is crucial to give enough volume, to maintain the preload and to keep the patient stable, and application of direct-acting vasopressors can also be helpful.

Regarding the postoperative period, we have a small amount of data on the outcome of heart transplant patients subjected to noncardiac operative interventions. The most common problem remains infection. A retrospective study of 116 noncardiac surgical procedures after prior cardiac transplantation showed that infection happened in 7% of these procedures and was the most common postoperative complication(7). It is important to be aware that the immunosuppressed patient does not show the typical signs and symptoms of sepsis - fever and leukocytosis. That's why, a high level of suspicion is needed, and to be aware that these patients had a lot of hospital staysand they all know many things related to their illness. They also have continuous relation and trust with some of the transplant team.

Conclusion

Anesthesiologic treatment of heart transplant patients is a challenging for any anesthesiologist and requires knowledge of specificities associated with altered autonomic physiology and modified drug response. It is important to keep the anesthetic technique simple and always to maintain the preload.

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BREAST CANCER TUMOR CHARACTHERISTIS AND METASTATIC BONE SCINTIGRAPHY FINDINGS

Dear "Macedonian Journal of Anaesthesia "Readers,

In the Vo.7 No 2, October 2023 issue of Macedonian Journal of Anaesthesia, an oversight occurred in the article titled
"BREAST CANCER TUMOR CHARACTHERISTIS AND METASTATIC BONE SCINTIGRAPHY FINDINGS"
UDK: 616.71-033.2-073.916:616.19-006.6 by Jankulovska A, and co-authors.
Unfortunately, content of Table number 3 was inadvertently omitted from the published version of the article.
The missing table, along with its relevant data, is provided below.

Table 3: Sites of multiple skeletal metastases in patients with breast cancer

	No. of sites (= patients)	Percentage of no. of sites *(total no. of lesion sites=210)	Percentage of patients ** (total no. of patients= 66)
Skull	23	10,9	34.8
Spine	52	24.8	78.8
Cervical	4	1.9	6
Thoracic	40	19	60.6
Lumbar	34	16.2	51.5
Sacral	15	7.1	22.7
Sternum	20	9.5	30.3
Rib	40	19	60.6
Clavicle	1	0.5	1.5
Scapula	12	5.7	18.2
Humerus	13	6.2	19.7
Pelvis	29	13.8	43.9
Femur	20	9.5	30.3
Total no. of lesion sites	210		
Super scan	1		

Abbreviations: No, number

* Calculated as: (no. of patients with osseous metastasis at the site)/(total no. of lesion sites) × 100.
** Calculated as: (no. of patients with osseous metastasis at the site)/(total no. of patients) × 100.

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Thank you for your continued support of Macedonian Journal of Anaesthesia.

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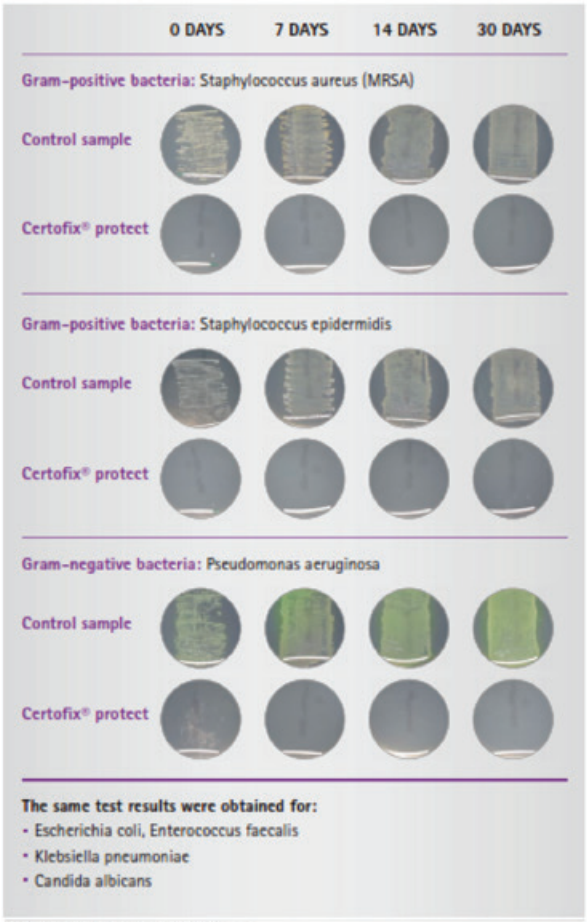

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