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Apotel® 1000mg/6.7ml

I.V. Paracetamol

БЕЗБЕДНА АНАЛГЕЗИЈА

менаџирање на болка кога сте загрижени за безбедноста

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

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

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

Резултат:

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

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

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

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

Табела3: *Споредба на ПОПГ помеѓу двете групи*

ПОГП	
I Група П	II Група НС
0	4

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

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

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

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

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WHEN EARLY RECOVERY REALLY MATTERS

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FARMA TREJD

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CONTENT

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GREENING THE OPERATING ROOM

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Globally, the climate footprint of the Health Care Sector represents approximately 4.4% of the net global emissions which is equivalent of 2 gigatons of carbon dioxide [1]. It is estimated that the operating room contributes to the total amount of the emissions with nearly 40%. Anesthetic gas emissions are one of the three main components of the carbon dioxide footprint as the remaining two are waste production and energy demand [2]. Anesthetic gases including Nitrous oxide and carbon dioxide, as a metabolic byproduct because of their capability to absorb the infrared radiation in the atmosphere and to contribute to a global warming effect as well as because their long lifetime and concentration in the atmosphere, could be considered as greenhouse gasses [3,4]. Those physicochemical properties of the halogenated and even fluorinated anesthetic gases makes them harmful for the ozone layer. The Global Warming Potential (GWP) as an index, was developed to compare and show us how big the effect on the global warming of different types of gasses is. GWP is a measure of how much energy emissions from one ton of a gas is absorbed over a period of time, compared to emissions from one ton of Carbon Dioxide (CO_2) [2,3,4]. GWP of a halogenated fluorocarbon contribution to global warming is equal to 1. Compared to CO_2, which is the reference greenhouse gas with a GWP100 of 1, volatile anesthetics have significantly higher GWP100: sevoflurane 144, N_2O 298, isoflurane 510, and desflurane 2,540. For example, a single anesthesiologist administering N_2O or desflurane can cause the CO_2 equivalent of more than 1,000km of driving in an average workday [5]. The environmental impact of our work demands core changes which will lead to less CO_2 use and production, less gas emission and less waste production. It means that crucial changes in global health care must be made in order to achieve more sustainable environment and future. Hospitalizations could be minimized by improving primary care and expanding outpatient procedures which is expected to contribute to less significant gas emissions as pollution, as well as reducing the use of medications and devices. For example, it is considered that the operating room and the procedural suits are the biggest source of garbage contributing to around 30-70% of total health care related waste. According to one Australian study during the neuroradiological procedures the mean amount of garbage was 8kg per case and the endoscopic rooms were identified as a second hot zone in producing a significant amount of waste [6]. This study's results led to a recommendation that the focus should be put on the use of a multiple use devices, while all single-use devices should be recycled as well [6]. Gill AS et al. have reported that in one hospital in UK yearly were made around 1,000 tonsillectomies which resulted in 1,984kg of waste or approximately 2kg per procedure. This implies that more than 100,000kg of waste will be created in whole UK due to average number of tonsillectomies [7]. The study of Skowno J. et al. has reported that 25% of the total amount of garbage is produced into the operating room while one quarter of that is related to anesthesia practice [8]. Another study has confirmed that using a "Power Down" initiative in a hospital with turning off all the anesthesia and OR machines, equipment and lights when they are not in use led to a saving of 33,000$ and 243 metric tons of CO_2 emissions per year [9].

Many centers in USA have implemented a standard for using reusable scrubs and gowns instead of disposable ones which resulted in saving of 100,000$ per year [10]. When talking about usage of perioperative textiles, it has been confirmed that reusable and disposable ones are similar in cost, comfort and safety, but using a reusable versus disposable textiles has offered substantial reduction of the environmental footprints [11]. It is well known that ORs could contribute to up to 2,000 tons of medical waste per year made up mostly of disposable materials which end up as a medical waste. Medical waste is divided in two categories regarding the fact if it has contact with biological fluids and consequent infectious potential or not. Actually, if medical waste has been in contact with any biological potential, already possesses an infectious potential which automatically means that could not be recycled and reused and is categorized as a Regulated Medical Waste (RMW). The other category which could undergo recycling and reuse is considered as non-infectious and could be a source of new products if recycled and could save significant amount of money because does not undergo special destruction procedures and is categorized as a Non-Regulated Medical Waste (nRMW). Separating the waste in a proper manner in a daily practice has been reported as a problem and a resource of significant amount of nRMW which in fear of possible infection potential is lost in the RMW which is non-recyclable, nor reusable [12]. That fact raises the need for another system of waste separation due to proper categorization.

Depending on the anesthetic technique used in a daily practice, anesthesia teams could or could not contribute to Going Green. It has been confirmed that reusable blades for laryngoscopy produce a significant amount of waste and are sources of carbon emissions when undergo RMW related destruction. Even though they are superior in risk for cross linked infection transmissions, reusable metal blades are better in terms of cost and avoidance of environmental carbon footprint due to their manufacturing and destruction [12]. Reusable LMAs were entitled as the one of the steps that contribute when Going Green in comparison with single use LMAs which demand energy and resources for manufacture as well as for destruction. In the study of McGain et al. it was found that even Central Venous Line Kits when sterilized and reused were described as Go Green friendly because of being less expensive and avoid manufacturing and destruction as well [13]. As it is already established that inhalational anesthetic usage is related to significant environmental hazards, Total Intravenous Anesthesia (TIVA) is a preferred technique when Going Green, but it must be taken in consideration all the waste that will be generated in the process of providing TIVA including the loss of unused medications and the need of destroying of the plastic syringes and systems needed for the continuous delivery of the medication, as well as the energy needed for pump delivery of TIVA [12].

According to Essaki et al., only one single surgical intervention is a source of a waste even bigger than the one that could be made weekly in a family of 4 persons [14]. Therefore, reducing waste from the operating rooms is a must in order to minimize the harmful emissions and environmental hazards. Securing a sustainable and better future is possible with taking actions for minimizing the OR waste with implementing the 5Rs rule. Five Rs rule includes: Reduce, Reuse, Recycle, Rethink and Research.

Reduce: Reducing production of a OR waste could be possible with using reusable devices and materials, for example, using metal reusable laryngoscopy blades, reusable suction canisters, LMAs, facemasks, surgical kit wrappings, hospital made regional anesthesia and central venous placement kits and many more. One of the most important actions that could make a huge difference is careful and proper waste segregation because it has been reported that approximately

85% of the OR waste is solid and nonhazardous which exhibits treatment as a nRMW, but unfortunately around 50-85% of the nRMW is wrongly sorted as a hazardous and potentially infective demanding treatment of an RMW [15]. It really matters how the waste will be treated because hazardous and potentially infective waste demands special procedures of destruction which cost even 8 times more in comparison to the nonhazardous solid OR waste (963$ vs. 121$ per ton) [16]. LED lighting in the OR instead of classical halogen lighting has shown few advantages including better lighting and color, decreased radiant energy and 49% lesser energy load [17]. Polypropylene plastic is main component of the blue sterile wraps which are used for coverage of surgical instruments and some kits, but it is not reusable which means that is one of the major components of the OR generated waste, or more specifically 19% of the total amount of waste is believed to be generated by polypropylene made blue sterile wraps which demand expensive disposal treatment [18]. In terms of cost-effectiveness polypropylene blue sterile wraps could be exchanged with simple green textilewrappings which are reusable and could undergo process of sterilization safely.

Reuse: It has been found that in the hospitals where reusing medical devices is a practice costs are lowered for about 50% [19]. Reuse could be implemented at many points in OR life, including scrubs, surgical gowns and coverings, wrapping materials, canisters, LMAs, laryngoscope blades, airways, facemasks, regional anesthesia sets and even needles.

Recycle: Many surgical and anesthesia sets and devices, as well as their packings are made out of plastic, and in reality, generate significant amount of solid waste which ideally could and should be recycled. Operating room paper should be properly stored and recycled. All together could made to 40% of savings in terms of recycling instead of destroying.

Rethink: Around 5-20% of the anesthetic gases are metabolized by the patient leaving the remaining part to be vented out into the atmosphere creating a contribution to the global warming since inhaled anesthetics have 2,000 stronger global warming potential than carbon dioxide [20]. This fact should lead to preference of TIVA over inhalational anesthesia, or if inhalational anesthesia is used, the fresh gas flow should be as lower as possible or even lower than 1.0 l/min. In order to Go Green if inhalational anesthesia is a must, Sevoflurane is preferred over Desflurane and Isoflurane. Nitrous oxide should not be used at all.

Research: Protocols and propositions should be made based on scientifically proven data in this field which implies the need for structured trials and careful analysis of the data.

Despite raising voices about medical practice, healthcare related procedures and their impact over environmental sustainability, lack of knowledge, poor guidance by the management, institutions and government, and acceptance were found as a limitation that reduce implementation of the measures that will enhance Going Greener Strategy, it was concluded in the WSES STAR investigation [21]. The lack of the environmental sustainability team in most of the hospitals could be a limitation of implementing measures that could turn operating room into a greener area despite that individual efforts could be met in daily practice [22]. When speaking of the environmental impact of practicing Anesthesia and Operation Room related tasks the French Society of Anesthesiology and Intensive Care Medicine has published strict recommendations about how we could minimize the negative environmental impact of our work which are based on all the facts that were already discussed above. Actually, they recommend choosing sevoflurane over desflurane and isoflurane when inhalational anesthesia is chosen as suitable for the patient, but they recommend that Nitrous oxide should not be used at all and the fresh gas flow

should be kept as lower as possible with maximal flow of 1l/min. Routine usage of an anesthesia depth monitoring when practicing inhalational anesthesia, considering the depth and the exhaled fraction of the volatile anesthetic together to prevent inhalational anesthetic overuse, is strongly recommended. Advantages of TIVA over inhalational anesthesia from the environmental toxicity point of view were minimized when emphasized that propofol derived metabolites could be found in the hospital related disposal liquids. Choosing a reusable over single use devices related to practicing anesthesia was strongly recommended as well as using the reusable devices as much as possible. Special attention was dedicated to the need for proper waste segregation and separation, evaluation of the waste and its type, as well as the way it should be destroyed, the need of bins and their positions, as well as the significance of the management of waste disposal.

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A COMPARATIVE ANALYSIS BETWEEN TIVA - TCI AND SEVOFLURANE INHALATIONAL ANESTHESIA - A PILOT STUDY

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Abstract

Introduction: Total Intravenous Anesthesia using Target Controlled Infusion is a sophisticated anesthesia technique that offers several advantages over traditional methods.

Material and Methods: In this pilot study, we randomly assigned 40 patients to two groups, each of which received different general anesthesia techniques. Group 1 (TIVA-TCI) initiated the induction with 20mg of Lidocaine, administered Propofol at 4mcg/ml using Marsh's model, continuously administered Remifentanil at 4ng/ml using the Minto model Target Controlled Infusion Perfusor to target plasma concentration, administered Rocuronium bromide at 0.6mg/kg, and intubation after 90 seconds. We maintained anesthesia by continuously applying Propofol at dose of 2–6mcg/ml and remifentanil at dose of 2–6ng/ml using a Target-Controlled Infusion Perfusor, based on the Brain Electrical Activity Scale neuromonitoring value of BIS, the desired mean arterial pressure and the heart rate. Group 2 (SIA) underwent anesthesia induction using Lidocaine 20mg, Propofol 1-2mg/kg, a continuous Remifentanil infusion ranging from 3-6ng/ml based on the Minto model, and 0.6mg/kg of Rocuronium bromide administered 90 seconds before intubation. Sevoflurane inhalation with a target minimum alveolar concentration of 0.7–1.0 was used for anesthesia maintenance.

Results: The sevoflurane group had increased heart rate, systolic, diastolic and mean arterial pressure, particularly during intubation and extubating. The duration of extubating was shortened in the TIVA group. Additionally, liver function was safer when TIVA was utilized. Patients in the sevoflurane group experienced postoperative nausea and vomiting at a greater rate.

Conclusion: Target Controlled Infusion - Total Intravenous Anesthesia is considered superior in promoting a smoother and more comfortable patients' perioperative experience.

***Key Words*:** *Breast surgery; Heart rate; Mean arterial pressure; Sevoflurane inhalational anesthesia; Total intravenous anesthesia-target controlled infusion; Postoperative nausea and vomiting.*

Introduction

Breast cancer is the most common reason for breast surgery, while other reasons include the removal of a benign tumor, abscess drainage and cosmetic procedures. Once the cancer has been removed, the breast reconstruction might happen right during the original surgery or later.

Anesthesia options include total intravenous anesthesia (TIVA) or a mix of inhaled and intravenous (IV) medicines (1). Total intravenous anesthesia (TIVA) in combination with Remifentanil and Propofol (RP) is the most efficient type of general anesthesia (GA) for patients undergoing medical procedures, both adult and pediatric (2). Increased safety and predictable timing have resulted from the introduction of commercially accessible pumps that use target-controlled infusion (TCI) approaches to better manage plasma concentration levels (2). A microprocessor is embedded in a TCI pump and is programmed with pharmacokinetic models for appropriate medications. The anesthesiologist chooses the medication and pharmacokinetic model that the TCI pump will use, as well as the patient's information including body weight and age, and the target plasma or 'brain' (effect-site) concentration, with the pump deciding the first bolus and continuous administration rates (3). When paired with Propofol in target-controlled infusion (TCI) regimes, Remifentanil is preferred over other opioids for anesthesia due to its special pharmacologic qualities, which include a rapid onset of action, accurate intra-operative control, and a shortened recovery profile (2,4,5). The minimum alveolar concentration (MAC) is the gold benchmark for determining potency (7). The low blood: gas solubility of Sevoflurane enables prompt, seamless induction and recovery from anesthesia, as well as precise control of the stage of anesthesia (8). In order to improve drug administration and anesthesia level, the Brain Electrical Activity Scale (BIS) was developed by measuring the brain electrical activity of individuals who have been sedated (9). By lowering the likelihood of intraoperative awareness, the BIS represents a substantial advancement in the objective measurement of the level of anesthesia and gives anesthesia physicians useful real-time input. Range within 40-60 BIS is suitable for general anesthesia, either inhalational anesthesia or TIVA TCI (10). Additionally, there are growing numbers of severe health effects linked to climate change. When using inhalational anesthesia, the global warm potential of sevoflurane is lowest compared to other volatiles and it is 130. The global warming potential of propofol (TIVA) is around 1% that of sevoflurane volatile anesthesia (11).

The primary objective of this study was to compare the hemodynamic stability, time to induction and time to extubating between the two groups TIVA TCI and sevoflurane inhalational anesthesia (SIA). Additional objectives included comparing the two groups, TIVA TCI and SIA, with respect to the following measures: the Visual Analogue Scale (VAS) for postoperative pain after surgery; liver function as assessed by ALT, albumin, and AST; and postoperative nausea and vomiting (PONV).

Material and Methods

This prospective, randomized, interventional clinical study was carried out at University Clinic for Traumatology, Orthopedic disease, Anesthesiology, Reanimation and Intensive Care Medicine and Emergency Department and University Clinic for Plastic and Reconstructive Surgery, Skopje, involving patients undergoing breast reconstructive surgery after mastectomy due to breast cancer. We obtained approval from the Bioethics Committee of the Medical Faculty in Skopje. Every patient signed informed consent. For this pilot study we included 40 patients that were randomly assigned to two groups, each receiving different general anesthesia techniques. The first group were patients with total intravenous anesthesia-total controlled anesthesia (TIVA-TCI) and the second group were patients with sevoflurane inhalational anesthesia (SIA).

Inclusion criteria: Patients over 25 years to 75 years, with a signed written consent, BMI<35 kg/m^2, American society of Anesthesiologist classification (ASA) I-II.

Exclusion criteria included patients younger than 25 years or older than 75 years, any past medical history of liver disease or preexisting liver dysfunction, renal insufficiency, cardiovascular or neurological disease, Diabetes mellitus, allergic diathesis, Body mass index (BMI) >35, patients using sedative and opioids, patients who had not signed written consent.

Group 1 (TIVA-TCI) initiated the induction with 40mg of Lidocaine, administered Propofol at 4 mcg/ml using Marsh's model, continuously administered Remifentanil at 4ng/ml using the Minto model TCI Perfusor to target plasma concentration, administered Rocuronium bromide at 0.6mg/kg, and attempted intubation after 90 seconds. We maintained anesthesia by continuously applying propofol at a dose of 2–6mcg/ml and remifentanil at a dose of 2–6ng/ml using a TCI Perfusor, based on the BIS neuromonitoring value, the desired mean arterial pressure and the heart rate. Group 2 (SIA) underwent anesthesia induction using Lidocaine 20mg, Propofol 1-2mg/kg, a continuous Remifentanil infusion ranging from 3-6ng/ml based on the Minto model, and 0.6mg/kg of Rocuronium bromide administered 90 seconds before intubation. Sevoflurane inhalation with a MAC of 0.7–1.0 was used for anesthesia maintenance.

Mechanical ventilation, using the MV model-pressure control volume guarantee (PCV/VG) with a mixture of oxygen 50% and air 50%, was then administered. The flow rate was 2L/min, and the tidal volume (TV) was 6-8ml/kg. The respiratory rate was between 10-14 breaths per minute to maintain end tidal CO2 range of 35-45mmHg, and BIS values were between 40-60. Extubating occurred upon patients' responsiveness to verbal commands and tracheal and laryngeal reflexes were restored. After extubating, all patients received 50mcg of Fentanyl. We monitored all patients intraoperatively for non-invasive blood pressure, heart frequency and mean arterial pressure.

We collected blood samples for extended laboratory testing in both study groups at four different time points: T1 (after induction of anesthesia in the operating room), T2 (after extubating in the recovery room-PACU) and T3 (24 hours after the end of the surgery).

We compared the induction time, which is the time from the onset of anesthesia to the disappearance of the eyelash response, the time to extubating, which is the time from the termination of anesthesia to the extubating, blood pressure, heart frequency, liver function, as measured by the values of alanine aminotransferase and aspartate aminotransferase, albumin, postoperative pain as measured by the Visual Analogue Scale (VAS), and postoperative nausea and vomiting.

Results

The statistical analyses were performed using SPSS version 26. The significance threshold for all statistical analyses was set at $p<0.05$. To compare the data, a student's T test was employed.

The sample size was 40 subjects. Both groups were comparable in demographic data. Both groups had a similar average age. All patients in both groups were women. BMI was consistent between the two groups. ASA classifications were also consistent (Table 1).

Table 1. Patients demographics.

	Age	Age	Gender	BMI kg/m2	BMI kg/m2	ASA
	count	mean	count	count	mean	count
Group						
1.0	20.0	45.2	0.0	20.0	23.0	0.0
2.0	20.0	46.6	0.0	20.0	23.49	0.0

BMI-Body mass index (kg/m2); **ASA**-American society of anesthesiologist classification

Heart rate and arterial tension, including mean arterial pressure (MAP) readings showed significant variations between the groups. Significant differences were observed in HR during intubation ($p < 0.05$), intraoperative ($p < 0.05$), extubating ($p < 0.05$) and after extubating ($p < 0.05$). Group 2 (SIA) had higher HR values compared to Group 1 (TIVA-TCI) (Table 2) (Figure 1).

Table 2. Comparison of hemodynamic data between two groups-heart rates in beats per minute.

	Heart rate - beats per minute									
	Intubation					Extubating				
	Count	Mean	Min	50%	Max	Count	Mean	Min	50 %	Max
Group										
TIVA-TCI	20.0	98.8	88.0	100.0	110.0	20.0	95.5	90.0	96.0	110.0
SIA	20.0	115.5	90.0	112.5	160.0	20.0	102.75	90.0	100.0	130.0

TIVA-TCI Total intravenous anesthesia-target controlled infusion group

SIA Sevoflurane inhalational group

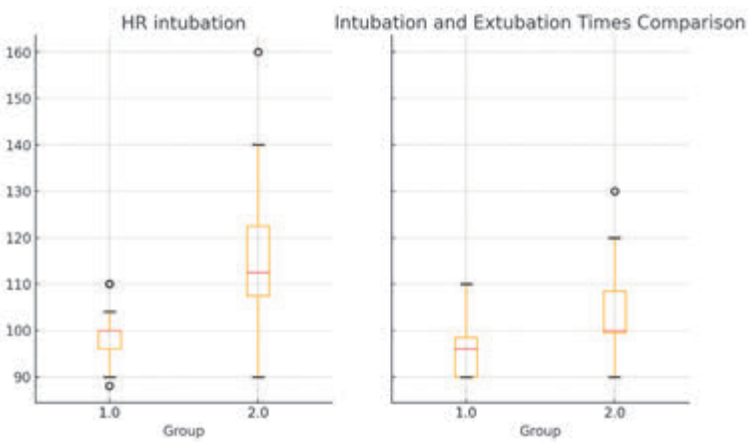

Figure 1. Heart rate comparison at intubation and extubating point expressed in beats per minute.

Significant differences during intubation were noted in systolic blood pressure ($p<0.05$), with Group 2 (SIA) having higher values. Student's T test; $p<0.05$ shows significant difference be-

tween groups; The analysis of the recorded values for diastolic blood pressure showed significant differences during intubation (p=0.002239) and extubating (p=0.042853), with Group 2 (SIA) showing higher values. MAP was also higher in the SIA group with statistically significant differences before intubation and after extubating p<0.05.

Average time to intubation in the TIVA group was 3.2 minutes and in the SIA group 3.9 minutes. Average time to extubating in the TIVA TCI group was 7.9 minutes and in the SIA group was 9.8 minutes respectively.

Regarding the liver function, Group 2 (SIA) had significantly higher ALT levels (p=0.024107) and higher AST levels (p=0.013136) as well as higher albumin levels (Figure 2).

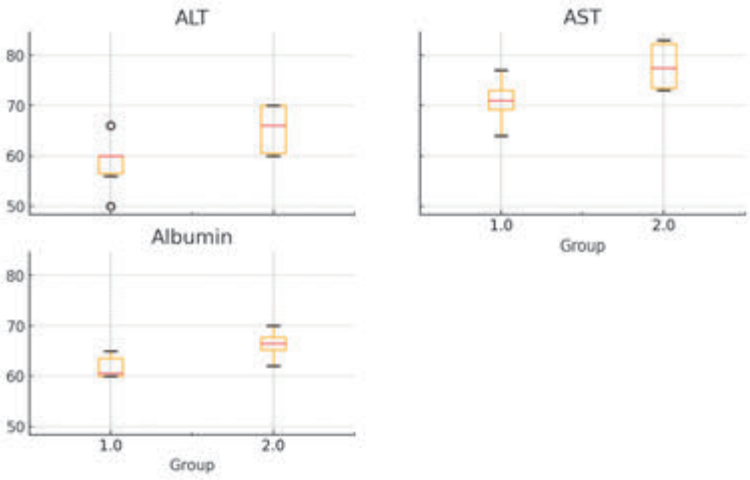

Figure 2. Comparison of liver function between TIVA TCI and SIA group through ALT (U/L), AST (U/L) and albumin (g/L).

Group 2-SIA had significantly higher PONV scores (p=0.029095), indicating a higher incidence or severity of postoperative nausea and vomiting (Figure 3). 3 of our patients in TIVA group had a mild form of postoperative nausea and vomiting, and on the other side 7 of our patients in the sevoflurane group had postoperative nausea and vomiting. One of them had severe form and the other six - mild form. Every patient with PONV was given Metoclopramide 10mg intravenous.

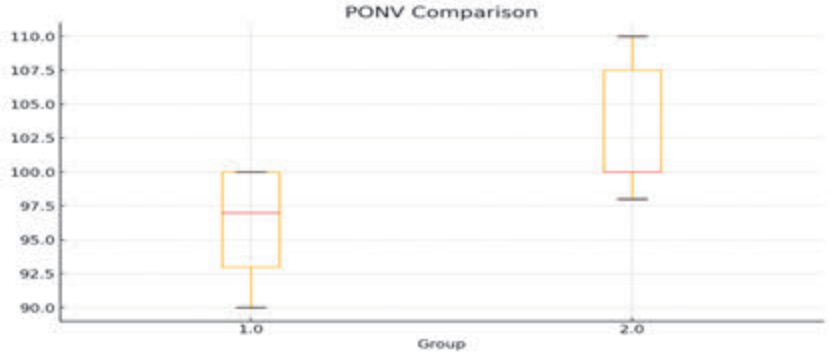

Figure 3. Postoperative nausea and vomiting comparison between two groups-semi-quantitative percentage.

The VAS score for the TIVA-TCI group was significantly lower, with a mean score of 2.5 ± 1.7 compared to 3.9 ± 2.5 in the SIA group, representing a 35.9% reduction in pain levels, demonstrating significantly better pain management with the TIVA-TCI technique.

Only one patient had sore throat reported in the SIA group, while no complications were noted in the TIVA TCI group.

Discussion

In anesthesia, hemodynamic stability is among the most crucial factors. Although the two groups noted a comparable decrease in blood pressure, SIA group's mean arterial pressure and heart rate increased much higher than the Propofol/ Remifentanil group ones. Same results were presented in the study of Juckenhöfel and coauthors (12). A comparable outcome was reported in the study of Shah et al., where sevoflurane group has notably higher heart rates after surgery at 5-, 10- and 15-minutes intervals, while the two groups did not show a significant variance in heart rates during intra-operative intervals, except at 45 and 60 minutes. Patients in Propofol group exhibited significantly low systolic and diastolic blood pressure from after insufflation until the surgery was finished (13). He Lu et al. in their study for spine surgery found out that the TIVA group exhibited lower changes in heart frequency and mean arterial pressure compared to the desflurane group. Furthermore, in the time of extubating, the heart rate and MAP were lower in the TIVA group (14). Our findings suggest that Sevoflurane inhalational group experienced more hemodynamic instability with higher heart rates and higher systolic and diastolic blood pressure especially in the time of intubation and extubating, which is consistent with previous findings. Another concern that anesthesiologists are particularly interested in is extubating time since it might be impacted by various anesthetic medications or procedures. Hence, for the purpose to increase OR efficiency, anesthesiologists must select the right anesthetic medications or procedures to prevent extended extubating. The main conclusions of Lai H et al. retrospective study demonstrate that in comparison to inhalational anesthesia with desflurane, propofol-based TIVA TCI shortened the extubating duration. The TIVA group's 0.9-minute extubating time decrease showed less of a clinical or financial impact on the anesthetic controlled time component of operating time efficiency, even if statistically significant discrepancies were found. Furthermore, they discovered that in patients having open major upper abdomen surgery, the following characteristics are associated with extended extubating: age, gender, BMI and length of anesthesia (1). Our patients were comparable in age, gender, BMI and length of anesthesia. According to our results patients in the TIVA TCI group experienced faster extubating time compared to the SIA group as in the study of Lai H. On the other side, the average recovery and extubating times in the two groups were comparable, according to the findings of Magni's investigation and study of Yang L et coauthors. (15,16). According to surveys, even more so than pain, PONV is the most feared anesthetic side effect. Every episode of PONV causes a 20-minutes delay in postoperative care unit discharge, and 1% of patients undergoing day surgery are hospitalized as a result (17). Pharmacological therapies following anesthesia may be the breaking point for minimizing the frequency of PONV. Volatile anesthetics can increase the incidence of PONV, while TIVA can decrease it claims Yang Li in his study (16). Females, non-smoking status, people younger than 50 years, as well as use of inhalational anesthetics and anesthesia lasting longer than an hour are related to higher risk of PONV (17,18). The main cause of PONV in the very initial postoperative phase has been identified as the quantity of volatile anesthetic exposure. Moreover, postoperative nausea and vomiting have been related to opioids because

of the sensitivity of the chemoreceptor trigger zone in area postrema to them (18). Uncertainty surrounds its exact mode of action however it seems to boost the function of gamma-aminobutyric acid (GABA) receptors, which in turn blocks synaptic transmission in the brain's vomiting center—a group of medulla structures close to the fourth ventricle (19). Johnson K. in his study claims that Because of its benefits, TIVA is an anesthetic method chosen for patients who have experienced postoperative nausea and vomiting in the past or who are at a high risk of experiencing it. On the other side, this approach has some drawbacks and hazards, such as a modest increase in consciousness, an unintended hypotension linked to propofol distribution, and a risk of hyperalgesia with TIVA procedures that use high dose opioids (20). Our study highlights the use of total intravenous anesthesia. Liver function can be checked through Albumin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Kim et al. in their study compared the liver and renal function in patients with thyroidectomy and reported that postoperative liver impairment was clinically inconsequential between the two groups. They showed that although postoperative AST readings in the sevoflurane group were higher than in TIVA group, they were still within the referent range. There were no variations in ALT between the two groups relative to the beginning (21). Sahin et al. supported these results in their publication for volatile anesthetics and TIVA in patients with lumbar discectomy and showed no clinical significance in the liver function between the two groups (22). We reported opposite results in our study since the patients in the sevoflurane group in our pilot trial had increased baseline ALT and AST levels, out of the normal range, indicate a higher level of hepatic impairment. VAS score showed significant difference in pain management between the two groups in our study, with reduction in pain levels in the TIVA TCI group. Comparable results have been published in the study of Tan T et al., Meng W. on the second postoperative day, and in the study of Hofer C. and coauthors where in the group receiving sevoflurane anesthesia, the amount of opioids used to produce a comparable level of postoperative pain was substantially higher (23,24,25).

Conclusion

This study highlights the use of TIVA-TCI for better hemodynamic stability in patients undergoing breast reconstructive surgery. Furthermore, the TCI-TIVA approach has a reduced incidence of PONV and produces better quality recovery in the early postoperative phase. TIVA is considered superior in promoting a smoother and more comfortable perioperative experience for patients.

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EARLY NEONATAL MORBIDITY ASSOCIATED WITH MATERNAL GESTATIONAL DIABETES

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Abstract

Introduction: Any degree of glucose intolerance with onset in pregnancy is referred to as gestational diabetes mellitus (GDM). It is present in 10% of all pregnancies, it has an increasing tendency and represents a risk factor for the mother, pregnancy and fetus. The aim of the paper is to determine the mutuality of the most common disorders in newborns from mothers with GDM, compared to the control group of newborns, from pregnancies without gestational diabetes in our maternity hospital.

Material and methods: Retrospective study, performed at the University Clinic for Gynecology and Obstetrics, in the period from 01.01. to 30.05.2024. The study included mothers with GDM, their newborns, as well as a control group of newborns and mothers without GDM. We evaluated maternal age, body weight, type of diabetes and comorbidities, maternal therapy, family history, way of delivery, Apgar scores, need for resuscitation, birth weight and maturity of the newborn, respiratory adaptation of the newborn, glycemia and needs for correction, hematocrit, Calcium, bilirubin, sucking reflex, jaundice.

Results: The study included 60 parturients, 30 with GDM and 30 parturients without diabetes. In the group of mothers with GDM, the mean age was 33.6 (20%), they had a positive family history of diabetes and hypertension, 26 (87%) were obese, 12 (40%) had high blood pressure, 25 (83%) gave birth by caesarean section. 33% of their newborns were premature, 33% hypertrophic, 13% had hypoglycemia, 10% in need of oxygen support during the adaptation period, 7% with hypocalcemia, 27% with prolonged hyperbilirubinemia. A weaker sucking reflex and weaker muscle tone were noted in half of the newborns of mothers with GDM.

Conclusion: With an increase in glucose intolerance and obesity in the young female population in the fertile period, GDM occurs as a frequent pathology after they become pregnant. Early screening in pregnancy plays a big role in reducing the consequences.

Key Words: *gestational diabetes; neonatal morbidity; newborn.*

Introduction

Diabetes mellitus (DM) is a chronic metabolic disease that is characterized by elevated glycemic values that over time lead to serious damage to the heart, blood vessels, eyes, kidneys and nerves. 422 million individuals in the world have diabetes, and every year 1.5 million die from the consequences of diabetes (WHO) (1).

According to WHO data for 2021, the prevalence of gestational diabetes mellitus (GDM) is highest in Southeast Asia 25.9%, followed by North America and the Caribbean 20.7%. Europe has a prevalence of 15% (1,2). More than half of the women with GDM will develop type 2 diabetes during 3-6 years after birth. It is present in 3-10% of pregnancies, and the consequences of GDM are affecting 18 million newborns per year. GDM is a typical example of how the mother's disease has repercussions on the outcome of the pregnancy and the health of the fetus. Several factors are responsible for their teratogenic effect, among which the main role is played by variations in glycemia, insulin, blood pressure, obesity, mineral deficiency (zinc, calcium, iron), keto bodies, free radicals, but there are also factors that still are being investigated. More severe consequences after the pregnancy itself for the mother and the newborn are found in pre-gestational diabetes than in gestational diabetes, hence the importance of timely diagnosis and distinction of the type of diabetes, through screening methods in early pregnancy (3).

From a pediatric point of view, the most vulnerable period for the newborn from a mother with GDM (NGDM) is the period of organogenesis and the period of metabolic adaptation of the newborn. Physiological hypoglycemia is represented in 2-4% term, 5-10% preterm, but in 50% of newborns from mothers with GDM. Difficult temperature and respiratory adaptation are no less significant. Birth injuries, weaker muscle tone and sucking reflex, electrolyte deviations, jaundice, are part of the difficulties encountered by a large part of these newborns during the first days and even weeks after birth (3). These reasons give great importance to the early detection of diabetes (screening) and its regulation during pregnancy (4).

The aim of this study is to determine the characteristics of mothers with GDM and the representation of the most common disorders in their newborns, compared to a control group of newborns / mothers, in our maternity hospital.

Material and Methods

This is a retrospective study performed at the University Clinic for Gynecology and Obstetrics. The study included newborns in the period from 01.01. to 30.05.2024. Late preterm (34^0 – 36^6) and term newborns (37^0 – 41^6) from mothers with GDM and newborns from regular pregnancies (control group) were included. Early premature newborns, cardiorespiratory unstable newborns, ones with need for a higher degree of circulatory and respiratory support, newborns transferred to Intensive Care Unit were excluded from the study.

In mothers we analyzed age, body mass index (BMI), number of pregnancies, type of diabetes, hypertension disorders, type of therapy, family, personal and obstetric history (previous abortion, fetus mortus) and way of delivery.

In newborns we analyzed Apgar scores, need for neonatal resuscitation or oxygen support, gestational age of the newborn (in term >37 gestational week or preterm < 37 g.w.), weight, level of glycemia. For weight measurement we used WHO growth charts from 2009 and we classified newborns as eutrophic (AGA), hypotrophic (SGA) or hypertrophic (LGA). We measured weight without diapers on an electronic scale, while length was measured with a standard plastic meter. We also analyzed the need for non-invasive oxygen support due to signs of respiratory distress and O_2 saturation <94%. If needed a tent with 0.015m^2 volume, flow 1-5 l/min. with FiO_2 <40%. was implemented.

Glycemia (mmol/L) was controlled by capillary blood with a glucometer (variation of 0.5-1 mmol/L below serum concentration). Possible inaccuracy of the glucometer at very low serum glycemic values in newborns was taken into account. Hypoglycemia was also confirmed by determining serum glycemic values. Skin-to-skin contact and breastfeeding were realized in the first 30-60 minutes from birth monitoring clinical signs of hypoglycemia (hypotonia, apnea or cyanosis, irritability). In the first 6 hours, the newborns had at least one meal, and in the first 24 hours at least 5 meals. Glycemia was controlled in a risk group of newborns (newborns from mothers with DM, late premature, hypotrophic, hypertrophic newborns) in the first 60 minutes after birth, 3-4 times daily during the first 24 hours, always serum glycemic values 30 minutes after meal. Newborns who were not in a risk group and without clinical signs of hypoglycemia, glycemia was controlled 2 and 4 hours after birth. Target glycemia in full-term newborns for the first 24 hours was over 2mmol/L, and in pre-term newborns was over 2.5mmol/L. Glycemia with values 2.2-2.4mmol/l was marked mild hypoglycemia, values 1.6-2.1mmol/l medium hypoglycemia and values <1.6mmol/l as severe hypoglycemia. If the results in all three controls in the first 24 hours were within reference limits, the further examination was stopped.

Recurrent hypoglycemia, with a serum glycemia value of 2-2.5mmol/l within 48 hours of birth, was corrected with nutrition (breastfeeding or milk formula), and with glycemia controls 3 times a day, 30 minutes after meal. In moderate hypoglycemia (glycemia of 1.5-2mmol/l) 10% Glucose 60-90ml/kg/day was given parenterally in addition to the diet. Severe hypoglycemia (glycemia below 1.5mmol/l) was corrected by tube feeding, with a bolus of 10% glucose 2.5ml/kg and 10% glucose 60-90ml/kg/day parenterally. In resistant hypoglycemia, 12% was given Glucose i.v. with previously taken blood for the investigation of insulin, cortisol and growth hormone.

Polycythemia (Hct >65%) was detected by determining the hematocrit (Hct) in a venous blood sample centrifuged at 3000rpm/ 4 min. When interpreting results, it was taken into account that hematocrit values increase in the first 2 hours after birth and spontaneously normalize after 6-24 hours. Hypocalcemia is a serum total calcium concentration of 2mmol/l in term infants or 1.75 mmol/l in preterm infants, or an ionized calcium concentration <0.75–1.10mmol/l. It was investigated in the first 48 hours of birth, in serum. Symptoms of hypocalcemia (hypotonia, poor feeding, tachycardia, tachypnea, convulsions) were closely monitored, and correction was carried out with oral administration of 10% calcium gluconate. Intravenous concentration of total, indirect and direct bilirubin (mmol/l) as a gold standard, Kramer's rule, transcutaneous bilirubinometry, Bhutani nomogram, were tools in the daily control of jaundice in newborns of mothers with gestational diabetes and determining the need for therapy and type of therapy (non-invasive phototherapy / exanguinotransfusion).

Neurological symptoms in newborns were also noted.

Results

The study included 60 parturients, 30 with GDM and 30 in a control group - parturients without diabetes. The characteristics of the mothers are given in Table 1.

Table 1. Characteristics of examined mothers.

			Mothers with GDM	Control group of mothers
Average age (years)			33	28
Previous pregnancies	Abortion		4 (13%)	2 (7%)
	Fetus mortus		2 (7%)	/
Family history	Diabetes and/ or hypertension		6 (20%)	/
Smoking			4 (13%)	6 (20%)
Body mass index (BMI, kg/m^2)	normal <25kg/m^2		4 (13%)	22 (73%)
	overweight 25-29.9kg/m^2		5 (17%)	8 (27%)
	obesity gr.1 30-34.9kg/m^2		15 (50%)	/
	obesity gr.2 35-39.9kg/m^2		6 (20%)	/
Hypertension			12 (40%)	/
Therapy	diet		22 (73%)	/
	+ antihyperglycemic		6 (20 %)	/
	+ insulin		2 (7%)	/
Way of delivery	Vaginal	In total	5 (17%)	20 (67%)
		Induced vaginal	5 (17%)	3 (10%)
	Cesarean section	In total	25 (83%)	10 (33%)
		Emergency cesarean section	10 (33%)	4 (13%)

All neonates have good Apgar scores, in average Apgar score in first minute was 8, in 5th minute was 9, in 10th was 10. There was no need for neonatal resuscitation in any neonate.

Regarding the gestational age of newborns, 10 neonates (33%) from mothers with GDM (NGDM) were late preterm, and 20 (67%) were term, while 6 neonates (20%) were late preterm and 24 were (80%) term newborns from mothers without GDM.

Regarding the weight, the largest number, 18 (60%) of neonates from mothers with GDM were eutrophic, in AGA class, 10 (33%) were LGA, hypertrophic, and 2 (7%) were SGA, hypotrophic. On the other hand, in neonates from mothers without GDM 26 (87%) were AGA, 4 (13%) were SGA, there were no LGA newborns in this group.

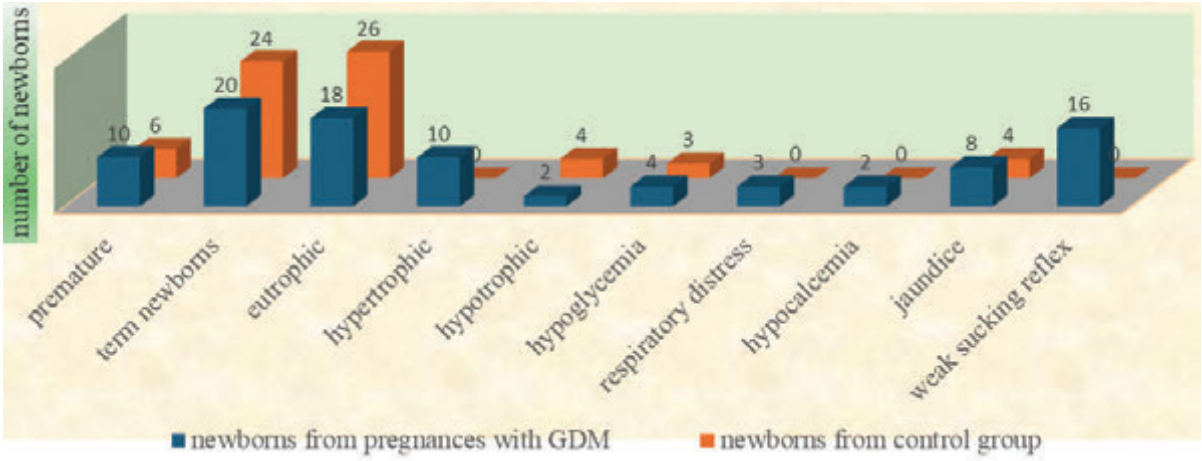
4 (13%) neonates from mothers with GDM had hypoglycemia, one of them was with refractory hypoglycemia, compared to 3 (10%) newborns with physiological hypoglycemia, from the control group.

3 (10%) newborns from the studied group developed respiratory distress, and need for non-invasive oxygen support, while in the control group of newborns, not a single newborn had respiratory distress.

Hematocrit in both studied groups did not deviate from reference values. Hypocalcemia was detected in 2 (7%) newborns from mothers with GDM, its presence was not detected in the control group. Hyperbilirubinemia in 8 (27%) NGDM, lasting 4 days with the need for intensive photo-

therapy, compared to 4 (13%) newborns from the control group. Neurological symptomatology in 16 (53%) NGDM was presented with a weak sucking reflex, which was not observed in a control group of newborns. No anomalies were detected in the two groups of newborns examined.

Table 2. Characteristics of examined newborns.



Discussion

Mothers

Our retrospective study showed a high association between overweight and obesity (87%) with GDM, which coincides with the results of many studies. Pirjani et al. in their prospective cohort study that followed 256 pregnant, obese and overweight patients, showed that 52.5% obese and 27.8% overweight developed GDM (5). In another observational study from Sunande et al., it was established that all pregnant women who in the first trimester of pregnancy had a BMI over 30kg/m^2 had a significantly higher incidence of GDM compared to pregnant women with a normal weight (6). It is already established that the adipocytes function as endocrine glands with a wide effect on all organs, and through the release of leptin, TNF-alfa cytokines, FFA substrates play a major role in energy balance and glucose homeostasis, from which partly the connection between obesity and diabetes can be explained (7).

Hypertension as a complication in our group of subjects was detected in 40% of pregnancies with GDM. These results are higher than those in the comparative study of L. Sohonen, where the frequency of pregnancy-induced hypertension in mothers with GDM was 18.8% (8). HTA was well controlled with oral antihypertensives, which resulted in the absence of complications (in accordance with the recommendations of the Working Group for revision and adaptation of clinical guidelines and recommendations at the Ministry of Health of the Republic of Macedonia in 2018) (9).

In two-thirds of cases, glycemia was well controlled with a dietary diet in pregnant women with GDM, which resulted in good glycemic control and fetal growth. The percentage of mothers with GDM in whom for therapy oral antihyperglycemic drugs or insulin were given for glycemic control was small (27%). A Mediterranean diet is associated with improved glycemic control in women with GDM, and it was confirmed by the study of Fatemeh at al. (10).

According to our results, related to the way of delivery, operative deliveries prevailed in the GDM group, and one third of them were by emergency caesarean section. All patients in the same group had induced vaginal delivery. Compared to the results from the study of Sugiyama et al., the number of operative deliveries in our study was higher (11). The active management of labor and programmed early termination of birth in parturients with GDM as a risk group of pregnancies is in accordance with the recommendations of the American College of Obstetricians and Gynecologists (ACOG) (12). Witkop at al., in their systematic review, concluded that an active versus passive approach in choosing the term and method of delivery can reduce macrosomia and other complications in newborns and mothers with GDM (13).

Newborns

The results of our study showed that 33% of the examined group of newborns were premature, while 67% were in term. The detected higher incidence of preterm births refers to both operative births and spontaneous births, and it is a result of the risky pregnancy itself and the active management of it by obstetricians and programmed early termination of birth. Different studies showed different results, in most of them the values of preterm births are much lower. In Mohammed et al. study there were 92% full-term and 8% premature (14), in Giampiero et al. study 72% were term and 18% premature (15). Hedderson et al. in their cohort study of 46,230 pregnancies indicate the risk of spontaneous preterm births with increasing levels of glycemia in pregnancies, where all other factors that could affect the occurrence of premature birth were excluded (16).

In our study most of the newborns from mothers with GDM were eutrophic (60%). Despite promptly diagnosed and well-controlled glycemia, macrosomia was significantly increased in newborns from mothers with GDM compared to a control group, and the percentage of hypertrophic newborns was higher compared to published results from other studies. Swedish study from 2013 that compares 1,547 newborns from mothers with GDM and a control group of 83,000 newborns, reported an incidence of hypertrophies of 26% and 10.6% in the control group (17). A large cohort study (HAPO) confirms the strong association between the maternal level of glycemia and neonatal adiposity and suggest that it is a result of fetal hyperinsulinism, that is, the mediation of fetal insulin in neonatal adiposity as a growth factor (18). The reasons for this growth have been illuminated since the fifties, with Pedersen's hypothesis, according to which there is a strong connection between the level of glycemia in the mother, fetal insulin production and neonatal macrosomia (19).

On the other hand, among our respondents we noted, in a smaller percentage, restriction in growth of newborns from mothers with gestational diabetes (6.7%). The finding coincides with the results of other studies (20). Intrauterine growth restriction in newborns of mothers with GDM is a result of a complex interaction of physiological, metabolic and molecular factors, and basically it is an interaction between hyperglycemia, microangiopathy, placental abnormalities and altered transport of nutrients (essential fatty acids).

Control of glycemia in term newborns and even more in preterm newborns represents a challenge for neonatologists. Daily fluctuation of glycemia (hyper/hypoglycemia) is also observed in this population and is difficult to monitor with traditional measurement of concentration in capillary blood, which delays the therapeutic intervention. Our results coincide with those published by other authors (21). In practice, there is no firm connection between glucose levels and neurological damage in newborns. Reversible and irreversible damages were detected even

at higher glycemia levels than the target. An individual level of glycemia that can lead to neurological damage is difficult to determine. In our study, we were generally guided by the target values of the Royal Prince Alfred Hospital protocol (22).

10% of newborns in our study group needed non-invasive respiratory support, they were born at term, with a good Apgar score and thermostable. Our results roughly coincide with the results of a retrospective study by Kawakita et al. (23) who examined the risk of neonatal respiratory morbidity in 222,978 newborns of mothers without diabetes, with GDM and pregestational diabetes, and found an association between diabetes and increased risk for neonatal respiratory morbidity beyond that attributable to prematurity. Treatment of diabetes with insulin during pregnancy increases the risk of respiratory morbidity in newborns (due to the influence of surfactant and epithelial cells). The study of Becquet at al. on 18,095 term and late preterm infants from mothers without diabetes, with GDM and with pregestational diabetes on insulin therapy shows that the incidence of admission to the Intensive Care Unit due to respiratory distress was significantly higher in the group of newborns on insulin therapy (24).

Hyperbilirubinemia in newborns from mothers with GDM is one of the consequences in GDM pregnancies. The results of our study (newborns with jaundice and the need for intensive and prolonged phototherapy) are closer to the international rank of 20-25% and are higher than the published results of Mohammed at al. 4-years retrospective analysis (14).

A weak sucking reflex and hypotonus of a mild degree, clinically detected, in our subjects, was presented in half of newborns from mothers with GDM, for the entire time of stay in the maternity hospital. They are early symptoms of neuromuscular immaturity, as a result of disturbed metabolism of fats, carbohydrates, mineral deficiency. For the diagnosis of later consequences like autism spectrum disorders, motor disorders, memory function disorders, language development, intelligence, behavioral and psychological disorders, as well as epigenetic alterations, more extensive and far-reaching studies are needed. The incidence of these disorders tends to decrease by improving glycemic control in mothers (25).

Conclusion

GDM is a common pathology during pregnancy, and it tends to grow with the modern lifestyle.

By identifying women at risk of diabetes before becoming pregnant and advising them to change a lifestyle, nutrition and physical activity, its incidence can be significantly reduced.

Prenatal screening tests (OGTT), for timely detection of glucose intolerance, bring a great benefit to the mother, the outcome of the pregnancy and the newborn. Complications resulting from unrecognized, untreated and untreated metabolic syndrome have far-reaching consequences for the offspring.

Future research is needed with much bigger group of patients to get better recommendations.

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PRE - CONSULTATION STRATIFICATION FOR OPPORTUNISTIC SCREENING OF TYPE 2 DIABETES IN PRIMARY HEALTH CARE: A NOVEL APPROACH IN NORTH MACEDONIA

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Abstract

Introduction: Opportunistic screening for type 2 diabetes (T2D) is currently not a routine practice among family physicians in primary health care (PHC) settings. The efficiency and effectiveness of opportunistic screening approaches for T2D are critical due to the specific nature of PHC work. Stratifying patients with an increased risk of developing T2D in the pre-consultation phase can significantly streamline the process, enabling the identification and focus on high-risk groups.

Objective: This study aims to present the outcomes of patients' stratification in the pre-consultation phase of opportunistic screening for type 2 diabetes.

Materials and Methods: Utilizing an electronic program, each participating physician selected patients aged 45-70 years. During December 2016 - January 2017, a pre-consultation phase questionnaire was completed for each patient, categorizing them into four groups: patients at risk of developing T2D, patients without risk for T2D, patients without sufficient data, and excluded patients based on exclusion criteria.

Results: The study involved 25 doctors from various cities across the Republic of Macedonia, covering a total of 41,836 registered patients. The analysis focused on 14,154 patients within the 45 - 70 years age group. Out of these, 8,754 patients were excluded based on exclusion criteria, 1,354 patients did not have any risk factors for T2D, 1,329 patients were excluded due to incomplete data on risk factors, and 2,659 patients had multiple risk factors for T2D and were included in the screening group.

Conclusion: The pre-consultation phase stratification effectively identified a subset of patients at higher risk for type 2 diabetes, facilitating targeted opportunistic screening. This approach could enhance the efficiency of T2D screening in PHC settings and potentially improve early detection and management of the disease in North Macedonia.

Key Words: *Diabetes Mellitus Type 2, Early Diagnosis, Electronic Medical Records, Family Practice, North Macedonia, Opportunistic Screening, Patient Stratification, Pre-consultation, Primary Health Care, Risk Assessment.*

Introduction

The global incidence of type 2 diabetes (T2D) is constantly increasing at the global level (1). In our country, the rate of people with type 2 diabetes is 7.2% in 2019 (2). The condition of long-term elevated glycemia in patients causes a long-term severe and progressive disease, causing severe complications with the possibility of developing disability and is the fifth cause of death in developed countries and ninth leading cause of mortality globally (3-5). Before T2D develops, there is a so-called prediabetes condition, which implies a disturbance of fasting glycemia with values between 5.6-6.9 mmol/L and 7.8-11.1 mmol/L measured after a 75-g oral glucose load, according to the American Diabetes Association (6, 7). According to World Health Organization, also International Diabetes Association recommends fasting plasma glucose levels of 6.1-6.9mmol/l (8, 9). Up to 10% of these patients will develop diabetes within 1 year. If T2D is diagnosed and treated promptly, there is a percentage of patients in whom the risk of complications will be reduced and they may even convert to normoglycemia as soon as the onset of the disease is delayed (10). In order to be able to treat T2D, it must be first recognized or diagnosed (11).

In our country, population screening is currently being carried out as a preventive goal among general practitioners for early detection of diabetes (12). It is performed for the entire population aged 35-56 without exception. A scored questionnaire of the Finnish Prevention Study (FINDRISC) is used, which consists of the following questions: age, body mass index, waist circumference, physical activity, consumption of fruits and vegetables, use of antihypertensive therapy, history of measured elevated glycemia, family burden with diabetes. Depending on the scores, the patients are categorized into 5 categories: low, slightly elevated, moderately elevated, high and very high risk, where slightly elevated and moderately elevated risk are sent for an oral glucose tolerance test, and high and very high are referred to a higher level of health care (13).

This type of screening involves high costs, workload for family doctors, and is not in accordance with the latest recommendations (14, 15). The experience so far shows that fasting glucose determination as a campaign for the entire population does not achieve the desired coverage and the effect is "low cost-benefit", which would mean that in the total examined population, the proportion of detected is small in proportion to the number of covered patients (16, 17).

Clinically opportunistic screening for T2D is widely accepted as an approach and is defined as a process in which the physician uses the consultation for any patient that needs to investigate the possibility of T2D or prediabetes (18). For the general population, the general or family doctor is the first stop when any health problem appears. The efficiency and effectiveness of the approach to opportunistic screening for T2D in the work of Primary Health Care (PHC) doctors is crucial due to the specifics of their work, such as large number of patients, lack of time, financial efficiency, etc. By stratifying patients with an increased risk of developing T2D who would further be called to do a laboratory test of fasting glycemia, the number of those who will be tested is limited (19, 20). Although at this moment part of the information is entered electronically, there are no appropriate tools and mechanisms in our country, for directly selecting patients with certain risk factors and conditions that are required for this stratification, and some of the risk factors are not subject to electronic entry at all (21). Information from patients' charts can be used to stratify patients, especially in low-and-middle income countries (22).

The objective of this study is to evaluate the feasibility and effectiveness of stratifying patients based on risk factors for type 2 diabetes (T2D) in the pre-consultation phase within primary

healthcare settings in North Macedonia. By utilizing data from electronic health records and patients' card files, the study aims to identify high-risk individuals aged 45-70 years and assess the impact of targeted screening on early detection rates of T2D. Additionally, the study seeks to highlight gaps in current data collection practices and propose improvements to enhance the accuracy and efficiency of risk stratification, ultimately contributing to better management and prevention of T2D in the primary care context.

Material and Method

This study utilized a cross-sectional design to evaluate the stratification of patients based on risk factors for type 2 diabetes (T2D) in primary healthcare settings across North Macedonia. The study was conducted in collaboration with 25 general practitioners from urban and rural areas, covering 17 municipalities (Bitola, Gazi Baba, Gevgelija, Gjorce Petrov, Gostivar, Kavadarci, Karposh, Kochani, Kumanovo, Makedonska Kamenica, Prilep, Radovish, Saraj, Strumica, Tetovo, Centar and Shtip). Majority of specialists in family medicine applied for a call published in cooperation with the Center for Family Medicine. All of them work as family doctors in agreement with the Health Insurance Fund (FZOM).

Participants and Data Collection: The participating doctors were enrolled through an electronic call for participation. Data were collected from an electronic health program used for guiding patients' management according to the requirements of the Health Insurance Fund (FZOM), as well as from patients' card files. The information included demographic details, family history of diabetes, history of gestational diabetes, previous glycemia measurements, presence of hypertension, hyperlipidemia and body mass index (BMI). With the help of a questionnaire for the pre-consultation phase that was prepared according to the submission for the preparation of this study and aligned with the latest recommendations, each doctor filled out a questionnaire for all patients aged 45-70 years who were selected using the electronic program. The data is filled in from the patients' files and the empirical knowledge of the patients by the doctor. Coding of the patients is done in the first part of the questionnaire by entering the patient's card number and initials as a source for verification and validation of the questionnaire itself with confirmation by facsimile by the family physician. In the first part of the questionnaire, the following questions are included: card number and initials for verification of the patients with the doctor's facsimile number, then gender and age and the following exclusion criteria: age under 45 years, have been diagnosed with T2D, pregnancy at the moment, if in the last 3 years all glycemic measurements were <6mmol/L and persons with impaired consciousness and judgment.

Risk Factor Stratification: In the second part of the questionnaire, in accordance with the recommendations of the ADA and the IDF, the following risk factors for the occurrence of T2D were taken into account (14; 23):

1. Type 2 diabetes within a close family (parents, brothers and sisters),
2. Hypertension,
3. High body mass index BMI (>25),
4. Hyperlipidemia,
5. Gestational diabetes (in pregnant women) or a child born weighing more than 4000g,
6. Glycemia measured in the last 3 years with a value between 6.1-7.0mmol/l.

Depending on the answers in the questionnaire, the patients were divided into 4 groups of patients:

- Group of patients who will not be screened due to exclusion criteria,
- Group of patients who, apart from age, have at least one other risk factor for the development of T2D and who will be screened (a person may have one or more risk factors);
- Group of patients who, apart from age, have no additional risk factors for the development of T2D and in whom screening will not be done,
- Group of patients who will not be screened due to lack of data.

Regarding the way of working in this study, a meeting was held at the beginning of December 2016 where the study was presented and possible challenges in its work were discussed. A manual has also been prepared and the same was given in addition to each doctor.

All completed questionnaires were returned to the Center for Family Medicine at the end of January 2017 and in the period February - March 2017 they were entered into a database created according to the questionnaire. Only patients who, apart from age, have another risk factors for the development of T2D and in whom screening would be done, the questionnaires remained with the doctors for the second phase/ consultation.

The data were entered in an excel table and coded with numbers according to the coding of the questionnaire.

Statistical Methods: Descriptive statistics were used to summarize the demographic characteristics and risk factor prevalence in both groups. Chi-square tests and t-tests were employed to compare the differences between screened and non-screened groups. Statistical significance was set at $p<0.05$. All analyses were performed using SPSS software, version 25.0.

This methodological approach aimed to provide comprehensive insights into the current state of risk stratification for T2D in primary healthcare and propose recommendations for enhancing early detection and management practices.

Results

Twenty-five doctors from urban and rural areas, representing 17 municipalities (Bitola, Gazi Baba, Gevgelija, Gjorce Petrov, Gostivar, Kavadarci, Karposh, Kochani, Kumanovo, Makedonska Kamenica, Prilep, Radovish, Saraj, Strumica, Tetovo, Centar and Shtip), participated in this study. These physicians were enrolled through an electronic call for participation. Data were collected using an electronic program designed to guide patients according to the requirements of the Health Insurance Fund (FZOM) and from patients' records. The information utilized included data present in the electronic program, as well as the doctors' personal knowledge and assessments of their patients.

The average number of patients managed by these doctors is 1,673. Within the risk group aged 45-70 years, there were a total of 14,154 patients, averaging 565 (33%) patients per doctor. The screening group comprises 2,659 patients, representing 18.79% of the entire population aged 45-70 years. This group includes patients with at least one positive risk factor out of six identi-

fied risk factors, and they would be offered screening during their next visit to the doctor. Given the uncertainty of the timing of the next visit and the potential for additional risk factors to be documented for some patients, these questionnaires will remain with the doctors and are not included in the analysis presented in this report.

The analysis includes 11,495 patients (81.21% of the category aged 45-70 years) who were excluded from the screening group. This cohort exhibits a nearly equal gender distribution, with 5,482 (47.89%) men and 5,726 (50.02%) women. Chart 1 illustrates the age distribution of the excluded patients, which shows a consistent distribution across age decades: 2,453 (21.94%) in the 45-50 years group, 2,364 (21.14%) in the 51-55 years group, 2,274 (20.34%) in the 56-60 years group, 2,026 (18.12%) in the 61-65 years group, and 1,695 (15.16%) in the 66-70 years group.

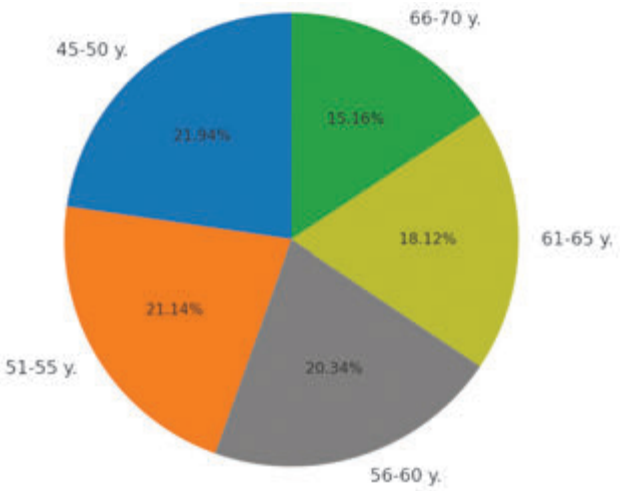

Chart 1. Categorization of patients not eligible for screening in the group 45-70 years old.

Stratification of the patients excluded from screening, due to exclusion criteria, identified that 8,754 patients (61.9%) belong to the 45-70 years age group. Chart 2 shows these patients divided to subsequent categories.

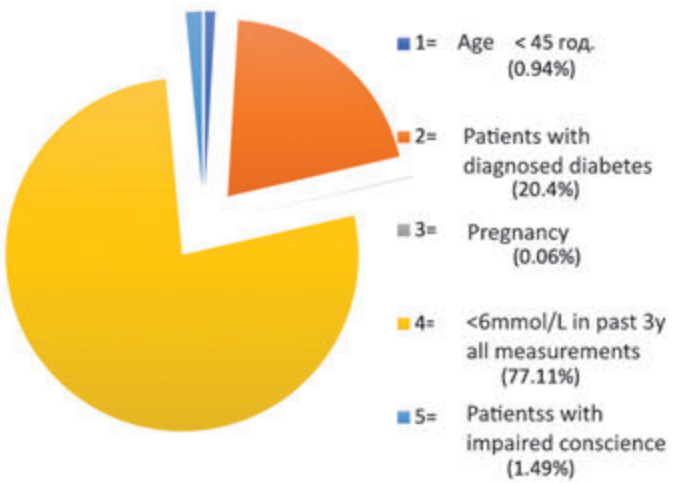

Chart 2. Excluded patients due to different excluding criteria.

Of these, 2,693 (19%) patients either lack a risk factor or have incomplete risk factor data. Within this subset, 1,364 (50.65%) have complete data indicating no presence of risk factors, 931 (34.57%) lack information on one or more risk factors, but have no identified risk factors, and 398 (14.78%) have no data regarding the presence or absence of any risk factors.

Chart 3 displays the distribution of responses regarding the presence of risk factors among the group that will not undergo screening, highlighting the ratios of 'NO' and 'NO DATA' responses. Among the six risk factors assessed, 1,329 (49.35%) patients did not respond to one or more questions out of the total 2,693 patients. Consequently, these patients are excluded from the screening group due to either the absence of risk factors or incomplete data on one or more risk factors.

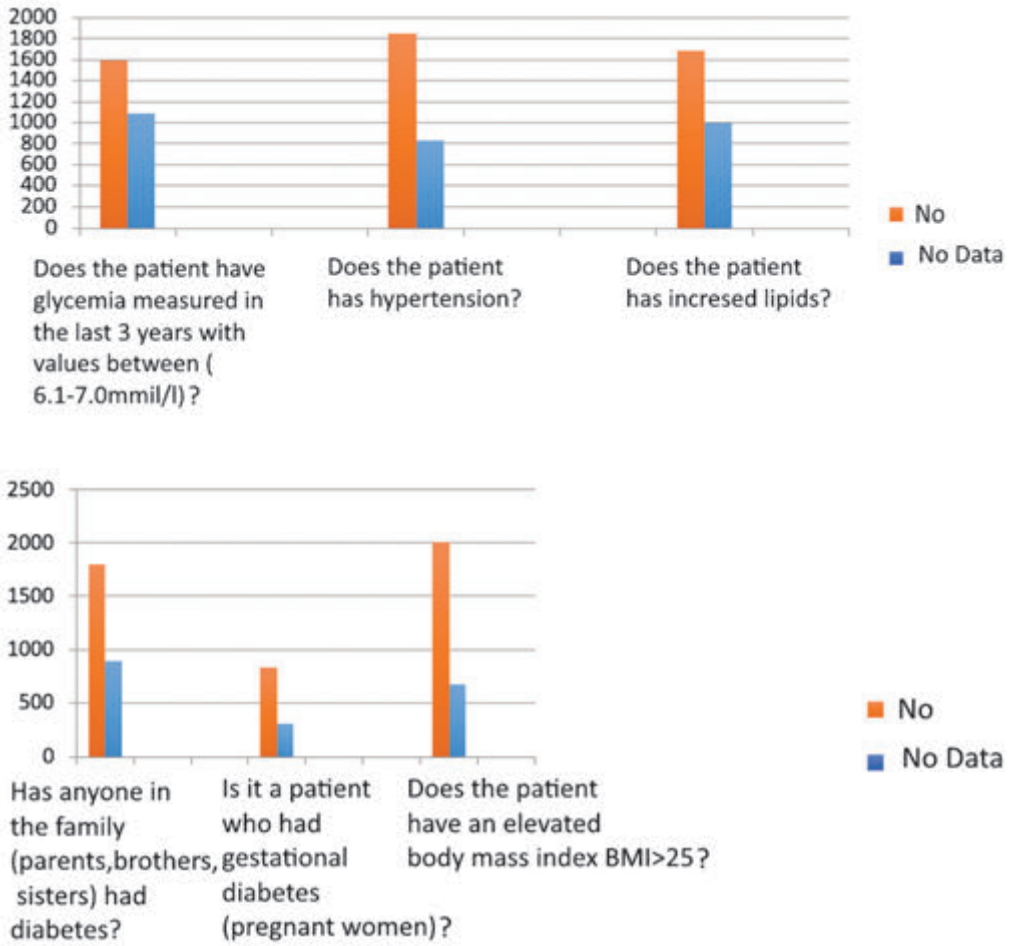

Chart 3. Distribution of responses regarding the presence of risk factors among the group that will not undergo screening, highlighting the ratios of 'NO" and 'NO DATA'.

The findings from this study underscore the significance of risk stratification in the pre-consultation phase for opportunistic screening of type 2 diabetes. The identification of 2,659 patients with at least one risk factor emphasizes the need for targeted screening approaches in primary healthcare settings. This group, which represents 18.79% of the population aged 45-70 years, illustrates the potential for early intervention and management of type 2 diabetes, thereby reducing long-term healthcare costs and improving patients' outcomes.

Conversely, the substantial number of patients (11,495 or 81.21%) excluded from the screening group provides insight into the current health status and risk factor prevalence in the broader patient population. The nearly equal gender distribution and consistent age distribution across age groups indicate a uniform representation of the population in this study (Table 1).

Table 1. Summarized data of the study findings.

Category	Number of Patients	Percentage of Total (%)
Total Patients Managed by Doctors	-	-
Average Number of Patients per Doctor	1,673	-
Patients Aged 45-70 Years	14,154	100
Screening Group	2,659	18.79
Excluded from Screening	11,495	81.21
Excluded Patients' Gender Distribution		
- Men	5,482	47.89
- Women	5,726	50.02
Excluded Patients' Age Distribution		
- Ages 45-50	2,453	21.94
- Ages 51-55	2,364	21.14
- Ages 56-60	2,274	20.34
- Ages 61-65	2,026	18.12
- Ages 66-70	1,695	15.16
Risk Factors Data among Excluded Patients		
- No Risk Factors	1,364	50.65
- Incomplete Data on Risk Factors	931	34.57
- No Data on Risk Factors	398	14.78

The detailed stratification of excluded patients reveals critical gaps in data collection and risk factor documentation. The fact that 2,693 patients (19%) either lack risk factors or have incomplete risk factor data highlights the necessity for comprehensive patients' records and systematic data entry practices. Moreover, the identification of subgroups within this cohort—those with no risk factors, incomplete data on one or more risk factors, and those with entirely missing data on all risk factors—points to areas where healthcare practices can be improved to ensure accurate risk assessment and appropriate screening.

Discussion

This approach of stratifying patients for the presence of a risk factor for the development of T2D is easily feasible in the daily practice of a general family medicine physician. Paradox is the situation in which early diagnosis and prevention of diseases is supported in principle, but not implemented in practice (24). The situation is more concerning in low-and-middle income countries, which lack data regarding this common disease and its screening (25, 26). Part of the

reason for this is that neither the electronic database nor the card file systematically records all the data that represents a risk factor. Due to this situation, there is a possibility that some patients are left out of the screening and belong to a risk group, but there is simply not enough data about them. This is shown by the data from the group of patients who would not be screened because they either have no risk factors or no data. Oot of these, 33.12% of patients did not have data on the presence of diabetes in the family history (in the literature, about 15%)(27, 28), in 27.24% of women therewas no data on whether it is a patient who had had gestational diabetes or a child born with a weight greater than 4000g, 40% did not have data on measured glycemia in the past 3 years, about 30.7% of the patients did not have data on the presence of hypertension, 33% on hyperlipidemia, and 27% did not have data on body mass index. This condition was also present in the CroDiab study (29), which applied a similar approach. Apart from the absence of structured data entry as the reason for the lack of data on all risk factors, the situation when patients did not visit their doctor for a long time for various reasons (moving, travel, work duties, inadequate care for their health, distance of the doctor, etc.), as well as the workload of the doctors (30).

In the second stage (screening) the patients with risk factors enter 2,659 (18.7%) patients who would give answers regarding the incidence of T2D and distribution by region, age and sex, as well as the connection with the mentioned risk factors. The analysis of risk factors in this group will be done after the completion of the study.

Due to previously diagnosed T2D, 12.6% of patients aged 45-70 years were excluded from the study, which indicates a higher prevalence of diabetes in this age group compared to the national one (23). Furthermore, almost half of the total number of patients aged 45-70 years, 47.69% (in the literature 20.5%), are excluded due to the fact that all glycemia measurements in the past years are below 6mmol/l (normoglycemia). This is due to the preventive goals that doctors work in agreement with FZOM for early detection of type 2 diabetes by means of population screening, which is an example of the positive effects of early diagnosis in general (28, 31).

The advantage of this approach is the stratification by risk factors itself, where 81.3% (77.5% in CroDiabGP) of patients do not enter the screening group even in the pre-consultation phase, which is expected to give greater sensitivity to further screening and greater cost efficiency in the same access (29). If it is possible to enter structured data into the electronic database of doctors, it will be possible to select patients according to risk factors and it would be much simpler to get the most suitable candidates for screening in the pre-consultation phase for further glycemic testing.

These findings suggest that enhancing electronic health record systems and implementing standardized data entry protocols could significantly improve the accuracy and efficiency of risk stratification in primary healthcare. Future research should focus on developing and testing interventions aimed at addressing these data gaps and evaluating their impact on screening and patients' outcomes in type 2 diabetes management (32).

Conclusion

This study highlights the feasibility and importance of stratifying patients based on risk factors for type 2 diabetes (T2D) in primary healthcare settings. The findings demonstrate that a significant proportion of patients (81.21%) were excluded from screening due to the absence of risk

factors or incomplete data, underscoring the need for comprehensive and systematic data entry. The exclusion of nearly half the patients due to normoglycemia reflects the effectiveness of ongoing preventive measures. Enhancing electronic health record systems and standardizing data entry protocols are essential to improve risk stratification accuracy and screening efficiency. Future efforts should focus on closing data gaps and evaluating interventions to optimize patient outcomes in T2D management. This approach can lead to early diagnosis, timely intervention, and better healthcare resource utilization, ultimately reducing the burden of T2D.

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ADVANTAGES OF TARGET CONTROL INFUSION - TOTAL INTRAVENOUS ANESTHESIA VS SEVOFLURANE INHALATION ANESTHESIA IN CONTROLLING SURGERY - RELATED STRESS RESPONSE

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Abstract

Introduction: The stress response to surgery, a sequence of pathological and physiological alterations brought on by the stimulation of surgery, can be divided into two main categories: the inflammatory-immune response and the neuroendocrine-metabolic response. It depends on the anesthesia technique and surgical approach.

Material and Methods: The patients were divided into two groups: Sevoflurane inhalational anesthesia (SIA) and Target control infusion-Total intravenous anesthesia (TCI-TIVA). The TCI-TIVA group has used the Marsh model for the propofol and the Minto model for the remifentanil, using target plasma concentration. The SIA group has induction in general anesthesia with Propofol plus Fentanyl, and the maintenance of anesthesia has been achieved with Sevoflurane on MAC 0.7-1.0. We compared the effect of different anesthetic techniques on the surgical stress response through measuring the blood levels of proinflammatory cytokines Interleukin-6, Cortisol and blood glucose, as well as the hemodynamic response.

Results: Interleukin-6 (IL-6) levels rise sharply from T0 (4.78εg/mL) to T2 (10.06εg/mL) and then again at T3 (36.34εg/mL), showing a strong inflammatory response after surgery in the SIA group. IL-6 levels in the TCI-TIVA Group exhibit a comparable pattern, however with a significantly smaller increase at T3 (14.56). When comparing the cortisol levels at T0, both groups show a comparable range of variability. There is a highly significant difference in cortisol levels between TIVA and SIA after extubating and 24 hours postoperatively, as indicated by the T2 p-value of less than 0.001. Glucose levels in the SIA group are comparatively constant from T0 (5.29) to T1 (5.25), then they significantly rise at T2 (6.56) and stay high at T3 (5.71). Glucose levels in the TCI-TIVA Group exhibit less variability, increasing slightly from T0 (5.17) to T2 (5.21) and then staying constant at T3 (5.28). Hemodynamic stability was better with TCI-TIVA than with SIA.

Conclusion: Our findings indicate that TCI-TIVA consistently demonstrates advantages regarding controlling the stress response, inflammation, and metabolic response both during and after surgery as compared to the SIA group. These results provide credence to the prospective advantages of TCI-TIVA over SIA in surgical settings where patient's outcomes depend critically on reducing stress, inflammation, and metabolic disturbances

Key Words: *Blood glucose; Cortisol, Interleukin-6, Sevoflurane inhalational anesthesia, Stress response; Total intravenous anesthesia-target controlled infusion.*

Introduction

Three phases characterize the host's response to surgical trauma: the hypodynamic "ebb phase", which appears in the early hours after tissue trauma, is followed by the hyperdynamic "flow phase", which is hypercatabolic, and the third phase, which is thought to be the recovery period (2), during which the body attempts to restore homeostasis. Initially, corticotrophin-releasing hormone (CRH) is released in response to surgical stress, activating the hypothalamic-pituitary-adrenal (HPA) axis and resulting in metabolic alterations. Adrenocorticotropic hormone (ACTH) is secreted by the anterior pituitary gland in response to CRH. Cortisol release is stimulated by ACTH's action on the adrenal cortex (1, 3). Blood glucose levels are raised when cortisol increases the liver's gluconeogenesis. Depending on the severity of the surgical damage, the cortisol concentration rises a few minutes after surgery and peaks 4-6 hours later (1, 3, 4, 5). The particular immune response includes the generation of antibodies and cytokines. The main cytokines released after surgery are interleukin-1 (IL-1), tumor necrosis factor-a (TNF-a), and interleukin-6 (IL-6). IL-6 is the main cytokine that induces the acute-phase response or systemic changes. The first day after surgery is when cytokine levels are at their peak (1, 4).

The most common reason for breast surgery is to eliminate breast cancer, while benign tumor removal, abscess drainage, and cosmetic procedures are all common justifications. Breast reconstruction can take place either right after the original surgery or later after the malignancy is removed (6). The severity and length of operative trauma, surgical approach, and anesthetic type are some of the elements that influence the stress response to surgery (7). Options for anesthesia include a combination of intravenous (IV) and inhaled medications, or target control infusion-total intravenous anesthesia (TCI-TIVA) (6). The most effective kind of general anesthesia (GA) for patients having medical operations, is target control infusion-total intravenous anesthesia (TCI-TIVA) combined with remifentanil and propofol (RP). Commercially available pumps that employ target-controlled infusion (TCI) techniques to better regulate plasma concentration levels have led to increased safety and predictable timing (8). A TCI pump has an inbuilt microprocessor that is programmed with pharmacokinetic models for the right drugs. The TCI pump determines both the first bolus and continuous administration rates. The anesthesiologist chooses the medication and pharmacokinetic model based on the patient's gender, age and body weight, as well as the target plasma concentration or target effect-site concentration "brain" (9). Target-controlled infusion (TCI) protocols prefer Remifentanil to other opioids for anesthesia because it has special qualities like starting to work quickly, being easy to control during surgery, and taking less time to recover (8, 10, 11). On the contrary, sevoflurane is a potent inhalation anesthetic due to its low blood/ gas solubility that allows for precise control of the anesthesia stage, quick and painless induction, and rapid recovery from anesthesia (12). The gold standard for figuring its potency is the minimum alveolar concentration (MAC) (13).

Using proper neuromonitoring is essential to determine the depth of anesthetic, confirm that the patient is asleep, and rule out pain in addition to non-invasive blood pressure and heart rate monitoring. In order to improve medication administration and anesthetic level, the electrical activity of people's brains during sedation was measured to establish the Bispectral Index Scale (BIS) (14). The BIS provides anesthesia practitioners with valuable real-time input and represents a significant advancement in the objective evaluation of the level of anesthesia by reducing

the chance of intraoperative awareness. This constitutes a substantial development in the objective evaluation of the level of anesthesia. A range of 40–60 BIS is suitable for general anesthesia, whether administered by TCI-TIVA or inhalational anesthesia (15).

This study's main objective was to identify how the stress response to surgery was different for two types of anesthesia: Sevoflurane Inhalational Anesthesia (SIA) and Target-Controlled Infusion Total Intravenous Anesthesia (TCI-TIVA).

The study's secondary objective was to investigate and compare the levels of three specific physiological markers: cortisol, Interleukin-6 (IL-6) and blood glucose.

Materials and Methods

Participants: The patients in this prospective, randomized, interventional clinical study, were undergoing breast reconstructive surgery following a mastectomy for breast cancer. The study was conducted at the University Clinics for Plastic and Reconstructive Surgery, Skopje, and the University Clinic for Traumatology, Orthopedic Disease, Anesthesiology, Reanimation, Intensive Care Medicine and Emergency Department. The Bioethics Committee of the Medical Faculty in Skopje granted us approval. Written informed consent was signed by each patient before enrolling in the study. In this pilot trial, fifty patients were divided into two groups at random and given distinct general anesthetic protocols. The inclusion criteria were patients between the ages of 25 and 75, an ASA I–II classification and a BMI of less than 35 kg/m^2. Patients with a prior medical history of liver disease or preexisting liver dysfunction, renal insufficiency, diabetes mellitus, use of sedatives and opioids, or who refused to sign written informed consent were excluded from the study.

Procedures: All operations began around 8:00 a.m. to avoid the variations in stress hormone levels. In order to maintain uniformity, every patient underwent anesthesia from the same anesthesia team for each procedure. Both groups had neuromonitoring with BIS, and when the BIS reading was below 60, muscle relaxant Rocuronium bromide at 0.6mg/kg was administered. After 90 seconds, using C-MAC video laryngoscopy, patients were intubated and mechanically ventilated on PC/VG mode with 2L flow, air and oxygen mixture, TV 6-8ml/kg, to maintain an end-tidal CO_2 range of 35–45mmHg. The respiratory rate was set between 10 and 14 breaths/min. BIS values were maintained between 40 and 60. During the procedure, each patient's non-invasive blood pressure, heart frequency, and mean arterial pressure were monitored. Extubating occurred once the surgery was complete, the patient responded to verbal directions, and their tracheal and laryngeal reflexes recovered. Each patient received 50mcg of fentanyl after being extubated.

Intervention Conditions: Patients were randomly divided into two groups, each receiving a distinct general anesthetic protocol:

Group TCI-TIVA: Patients in this group received general anesthesia with Target-Controlled Infusion-Total Intravenous Anesthesia (TCI-TIVA). The Marsh model was used for Propofol, and the Minto model for Remifentanil, using target plasma concentration**.**

Group SIA: Patients in this group received general anesthesia maintained with Sevoflurane Inhalational Anesthesia (SIA). Induction was with Propofol plus Fentanyl, and maintenance of

anesthesia was achieved with Sevoflurane at MAC 0.7-1.0.

Measures: At four distinct time intervals, blood samples were taken for laboratory testing in both groups: T0: Before surgery; T1: After anesthesia induction in the operating room; T2: After extubating in the recovery room (PACU); T3: 24 hours after the conclusion of surgery.

Blood glucose levels, proinflammatory cytokines (cortisol and Interleukin-6), and blood flow response were monitored to evaluate the effects of the different anesthesia types on the postoperative stress response.

Statistical analysis: Statistical analysis between two groups were performed with Student t-test. SPSS statistical software (version 27.0 SPSS, Inc., North Castle, NY) was used for the analysis; two-tailed $P < 0.05$ was considered significant. Data are shown as mean ± standard deviation if not otherwise stated.

Results

There were 40 participants in the sample. Demographic information was comparable for both groups. Each group's average age was comparable 46±6.2 TCI-TIVA vs. 45±8.7 SIA group. Every patient in both cohorts was a female. The two groups' body mass index (BMI) were similar 23±2.1 TCI-TIVA vs. 23±1,9 SIA group. Additionally, ASA classifications were reliable.

Interleukin-6 (IL-6) levels increase notably from T0 (4.78) to T2 (10.06) and then sharply at T3 (36.34), indicating a significant inflammatory response post-surgery in the SIA group. In the TCI-TIVA Group: IL-6 levels show a similar pattern but with a much lower increase at T3 (14.56) (Table 1).

Table 1. Comparison of IL-6 between SIA and TCI-TIVA.

Type of Anesthesia	IL6_T0	IL6_T1	IL6_T2	IL6_T3
SIA	4.78	5.31	10.06	36.34
TCI-TIVA	4.8	4.93	9.65	14.56

SIA-Sevoflurane inhalational anesthesia; TCI-TIVA-Target control infusion-Total intravenous anesthesia; IL-6 in pg/ml.

No significant difference in IL-6 levels is observed in TO, T1 and T2 between the two groups ($p > 0.05$), while a significant difference is observed in IL-6 levels 24 hours post-surgery ($p < 0.001$), with the TCI-TIVA group showing lower levels compared to the SIA group (Figure 1).

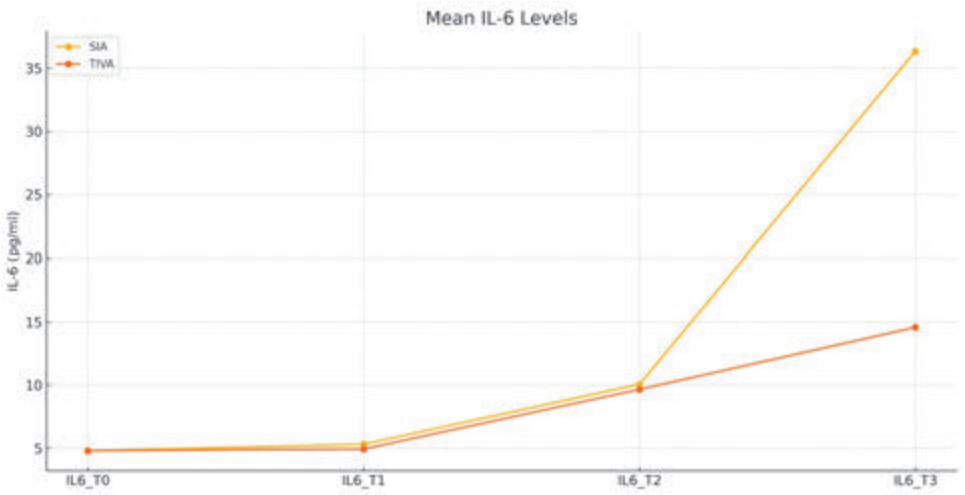

Figure 1. IL-6 (pg/ml) levels in T0, T1, T2 and T3.

When comparing the cortisol levels at T0, both groups show a comparable range of variability. There is a highly significant difference in cortisol levels between TCI-TIVA and SIA following extubating, as indicated by the T2 p-value of less than 0.001. At T3, the pattern seen at T2 is still in place. Even 24 hours after surgery, the SIA group's cortisol levels are noticeably higher than those of the TCI-TIVA group (Table 2) (Figure 2).

Table 2. Mean values of cortisol at different time points.

	CORTISOL (nmol/L) T0	CORTISOL (nmol/L) T1	CORTISOL (nmol/L) T2	CORTISOL (nmol/L) T3	Total
TCI-TIVA	338.85	350.19	383.5	361.95	358.62
SIA	366.98	404.03	784.25	721.85	569.28
Total	352.91	377.11	583.88	541.9	463.95

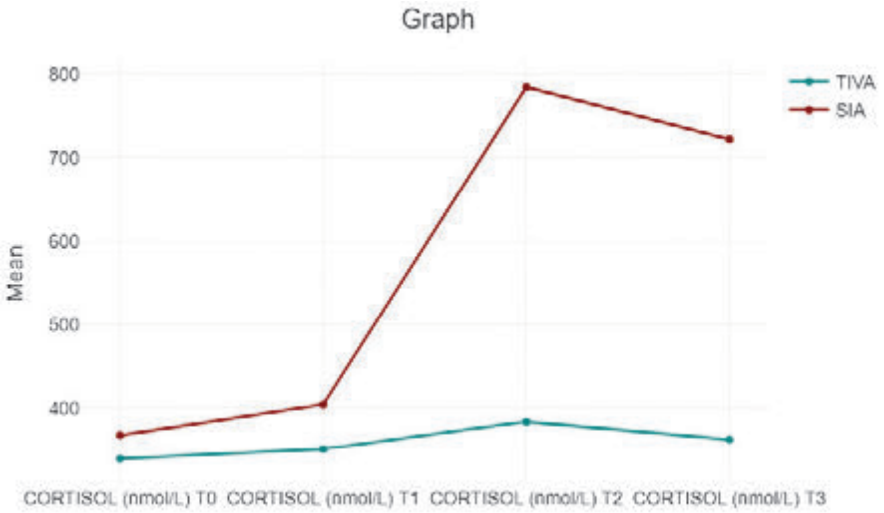

Figure 2. Trend of cortisol between the groups at different time point.

In the SIA group glucose levels remain relatively stable from T0 (5.29) to T1 (5.25), then increase slightly at T2 (6.56), and remain elevated at T3 (5.71). In the TCI-TIVA Group glucose levels show less variability, with a slight increase from T0 (5.17) to T2 (5.21) and remain steady at T3 (5.28) (Table 3).

Table 3. Comparison of glucose blood levels between SIA and TCI-TIVA.

Type of Anesthesia	**Glucose_T0**	**Glucose_T1**	**Glucose_T2**	**Glucose_T3**
SIA	5,29	5,25	6,56	5,7
TCI-TIVA	5,17	5,12	5,21	5,28

No significant difference is observed in glucose blood levels between the groups in T0 and T1. A significant difference is observed in glucose levels between the two groups after extubating ($p < 0.001$) and 24 hours after surgery. The TCI-TIVA group maintains more stable glucose levels compared to the SIA group (Figure 3).

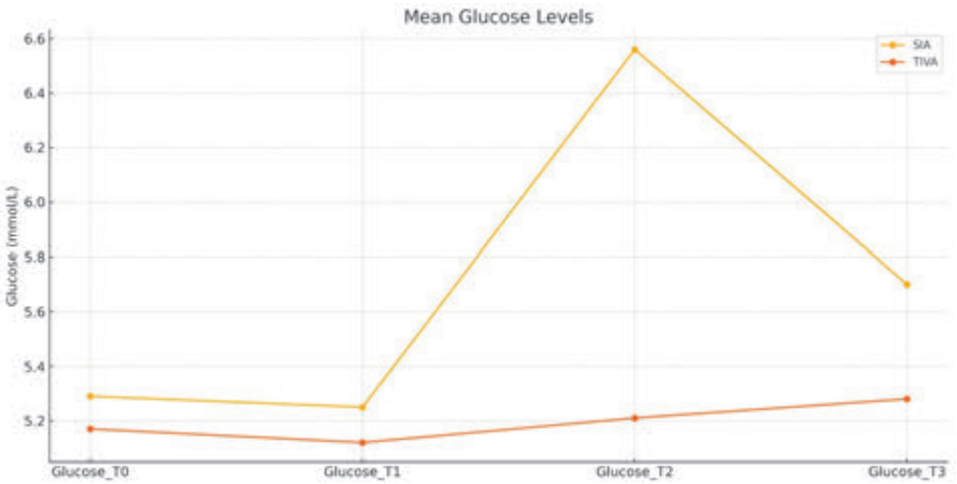

Figure 3. Glucose blood levels (mmol/L) in T0, T1, T2 and T3.

There were notable differences in heart rate and mean arterial pressure (MAP) values between the groups. There were notable variations in heart rate (HR) during intubation ($p < 0.05$), during the procedure ($p < 0.05$), during extubating ($p < 0.05$), and following extubating ($p < 0.05$). HR values were greater in Group 2 (SIA) than in Group 1 (TCI-TIVA).

Systolic blood pressure, diastolic blood pressure and mean arterial pressure readings during intubation and extubating showed significant differences ($p<0.05$), with greater values observed in Group 2 (SIA).

Discussion

The regulation of inflammatory and stress reactions brought on by anesthesia and surgery is associated with a higher quality of recovery (16). Because propofol suppresses the release of

cortisol and inflammatory mediators while blocking the generation of pro-inflammatory cytokines, it is thought to have anti-inflammatory and antioxidant effects (1,16,17). On the other hand, volatile anesthetics such as sevoflurane and isoflurane have been shown to increase pro-inflammatory cytokines, especially IL-6 and reduce neutrophil activity and lymphocyte proliferation (18). In order to mediate the acute phase response, IL-6 is essential. When an inflammatory stimulus is potent enough to have multiple systemic side effects that disrupt usual homeostatic processes, the result is an acute phase response of inflammation (19). In their study, Sofra M et al. observed a significant increase in IL-6 (6 – 8 hours after surgery) in both the TCI-TIVA and balanced inhalational anesthesia groups. The average value of this pro-inflammatory cytokine was 132pg/ml, indicating that the anesthetic method had no bearing on the increase in IL-6 (20). In contrast IL-6 was significantly higher in the inhalational group with isoflurane and fentanyl than in the TCI-TIVA group at the end of surgery, while these proinflammatory cytokines have not been statistically different values 12 hours after surgery (18). This is supported by the findings of Ihn CH et al. in which IL-6 levels were comparable at the various time points in both TCI-TIVA and SIA group. They noted intraoperative variations in IL-6 in the TCI-TIVA group, with a considerably lower level at intubation and a greater level at extubating when compared to baseline, while IL-6 in the SIA group was significantly elevated only at extubating time when compared with baseline (21). El Azab and colleagues, in their study on cardiac surgery with cardiopulmonary bypass noted significantly lower IL-6 in the group with TCI-TIVA than in the group with inhalational anesthesia prior to initiation of the procedure. However, there were no changes between the groups during or following the procedure (22). Our results are somewhat in agreement with the study of Ihc CH et al., we observed higher IL-6 levels at the time of extubating in both groups and the peak was 24 hours post-surgery with the TCI-TIVA group showing lower levels compared to the SIA group. This suggests that TCI-TIVA may better control the inflammatory response in the longer postoperative period. Concerning the neuroendocrine response, free cortisol in the blood decreases ACTH secretion and blocks CRH release in normal circumstances by acting as a negative feedback loop at the anterior pituitary and hypothalamic paraventricular nucleus. On the other hand, ultradian pulses in cortisol and ACTH significantly rise right after surgery. After then, within 24 hours, ACTH concentrations recover to normal in response to consistently high but less frequent cortisol pulses. Cortisol levels can stay elevated for seven days following surgery (1, 23). Propofol can reduce cortisol with a single induction dosage, but it cannot stop the release of cortisol and aldosterone as a reaction to surgical stress. During surgery, circulating cortisol secretion was totally eliminated by a continuous infusion of propofol at deep anesthetic dosages (24). The results in our study showed that cortisol levels were significantly lower in the TCI-TIVA group, suggesting that TCI-TIVA might be more effective in controlling the physiological stress response compared to SIA. Our results are comparable to the findings of Ozkan et al., Ihn CH et al., Mujagic et al and Onk D et al. Ozkan S et al., making a comparison of the effects of TCI-TIVA and sevoflurane anesthesia on the endocrine response in upper abdominal surgery and noticed lower cortisol concentration in the TCI-TIVA group postoperatively (25). Throughout the procedure, cortisol levels in the TCI-TIVA group stayed similar to baseline, whereas in the SIA group, levels were noticeably higher at intubation and extubating compared to baseline said Ihn CH et al. (21). Mujagic study's findings demonstrated that patients treated under TCI-TIVA with propofol-fentanyl had significantly lower average blood levels of cortisol and prolactin intraoperative and shortly after surgery than patients treated under general balanced anesthesia with isoflurane-fentanyl. It is desirable, according to the data, that patients receiving TCI-TIVA had a weakened endocrine physiological response to stress during and immediately after surgery as in contrast to the inhalational group (7). TCI-TIVA was more effective in inhibiting

cortisol release, which escalated due to the stress reaction, than inhalational anesthesia with desflurane in patients who underwent Coronary artery bypass surgery said Onk D in his study (26). Unlike our results, Soto et al. when comparing the glycemia, and cortisol levels at various time periods in their trial to baseline levels, neither the TCI-TIVA nor the inhalational group demonstrated any significant increases. They said that the hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis was effectively suppressed by both anesthetic methods (27). Also, no significant differences were noted between the TCI-TIVA and SIA group in the levels of catecholamines and cortisol in anterior resection of rectum in the study of Treda E et al. (28). Growth hormone, cortisol, glucagon, and catecholamines are "counter-regulatory" hormones whose levels rise in response to surgery or trauma. Their action leads to changes in the metabolism of carbohydrates and peripheral insulin resistance and results in hyperglycemia (29,30). Blood glucose levels were higher in the inhalational group with sevoflurane in the time of intubation, incision and extubating compared to TCI-TIVA group noted Ihn CH et al. (21). This was supported in the study of Mujagic et al., where they showed higher glucose levels in the group with isoflurane in the start of surgery, at the end and 2 hours after surgery, probably showing better attenuation of TCI-TIVA on the hormonal stress response (31). Increased glucose level was observed intraoperative in the inhalational groups with sevoflurane and isoflurane by Ozkan S et al. (25). Our findings are comparable to these, glucose blood level was significantly lower after extubating and postoperatively in the TCI-TIVA group. According to this, TCI-TIVA appears to be associated with a lower inflammatory response and more stable glucose metabolism, which could be beneficial for patient recovery. As opposed to these results, Soto et al. proved that during the procedure and for two hours afterward, the plasma glucose levels in both groups stayed constant (27). Considering the hemodynamic responses in our study, TCI-TIVA group experienced better hemodynamic stability. The SIA group had higher MAP and HR especially at intubation and extubating time. The studies by Ozkan S et al. and Juckenhöfel and coauthors showed the same outcomes. Significant increases in systolic and diastolic blood pressure were noted in the inhalational groups, particularly at intubation and extubating (25, 32). Similar results were observed in the Shah et al. study, where the heart rates of the sevoflurane group were significantly higher after surgery, but there was no significant difference in the heart rates of the two groups at intra-operative intervals, with the exception of 45 and 60 minutes (33). Similar results reported Ihc CH et al., with better control and consistency of blood pressure and heart rate in the TCI-TIVA group (21). In their spine surgery trial, He Lu et al. discovered that the TCI-TIVA group changed less in heart frequency and mean arterial pressure than the desflurane group. Moreover, the TCI-TIVA group's heart rate and mean arterial pressure dropped during the extubating process (34). However, another study was not in agreement with our results. No significant differences between the groups in systolic and diastolic blood pressure were shown nor in the study of Soto et al., nor in the study of Lasinska-Kowara et al., though demonstrate hemodynamic stability in both groups equally (27, 35).

Other studies have demonstrated that during the post-surgical phase, women who are overweight (OW) or obese (OB) who have just been diagnosed with breast cancer (BC) have considerably higher levels of pro-inflammatory markers such interleukin-6 (IL-6) and interleukin-1β (IL-1β). Future research should focus more on OW/OB BC patients since they are a vulnerable category, as these elevated levels are linked to worse health outcomes. Nonetheless, according to our inclusion criteria, none of the patients' BMIs exceeded 35kg/m2, and all patients' BMIs fell within the normal range during our examination. As such, our study emphasizes the significance of comprehending how normal BMI patients respond to various anesthetic procedures in relation to their stress markers, such as IL-6, even if it did not particularly focus on the inflam-

matory response in OW/OB persons (36).

Further investigations are necessary to fully understand the overall stress response and hormone fluctuations in patients undergoing different anesthesia protocols. These studies should aim to explore the interplay between various stress markers and hormonal changes at different stages of surgery and recovery, providing a more comprehensive understanding of the physiological mechanisms involved and their potential impact on postoperative outcomes.

Conclusion

Our findings demonstrate that TCI-TIVA consistently outperforms the SIA group in terms of managing inflammation (IL-6) and the stress response (cortisol levels) before and after surgery. Furthermore, TCI-TIVA improves glucose levels and metabolic stability, especially during the crucial postoperative phase. These findings lend credence to the hypothesis that TCI-TIVA may perform superior to SIA in surgical settings where patient outcomes depend on lowering stress, inflammation, and metabolic issues.

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EFFECTIVENESS OF STOP / START INSTRUMENT IN PRIMARY CARE ON POLYPHARMACY IN ELDERLY PATIENTS WITH MULTIMORBIDITY

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Abstract

Introduction: People with multimorbidity, who use several drugs at the same time, especially the elderly, are predisposed to a greater number of side effects.

Objective: The effectiveness of the STOPP/START instrument in primary care units in patients older than 65 years with multimorbidity and polypharmacy.

Material and method: A multicenter prospective randomized clinical trial conducted by 18 primary family physicians, during 12 months in 2022/ 2023. Patients older than 65 years with multimorbidity and polypharmacy were included. On 174 patients, an intervention with the STOPP/START instrument version 2 was initiated. The patients were screened for prescription at base line and after a period of 6 months after intervention.

Results: After using the STOPP/START instrument, 416 (29.19%) drugs were stopped in 162 patients (93.10%), with the highest proportion of stopping cardiac drugs (168 drugs in 104 patients), followed by psychiatric drugs – 96 (23.08%) in 86 (49.42%) patients. With the START intervention, 245 drugs were prescribed in 127 patients, with the highest proportion being cardiac drugs – 134 (54.69%) in 89 (51.15%) patients, followed by psychiatric drugs – 41 (16.73%) in 36 (20.69%) patients. With the STOPP/START instrument, 248 drugs and 12 OTC less than ZERO time were prescribed to the patients.

Conclusion: The implementation of appropriate interventions for polypharmacy affects can be reflected in reduction of negative effects from drug interactions, and thus reduction of unplanned outcomes.

***Key Words**: elderly, multimorbidity, primary care, polypharmacy, STOPP/START intervention.*

Introduction

Prescribing medicines is perhaps the most important intervention for people with multimorbidity (1). If multiple drugs are administered inappropriately, the term "Polypharmacy" is used (2). As a result, numerous adverse effects occur, which may lead to adverse events such as hospitali-

zation or death (3). Deprescription is a systematic joint process of decisions and actions between the doctor and the patient, where the drugs are written off because they have no effect, that is, the harm is so great that it exceeds the benefit. STOPP, which is based on physiological systems, contains a list of 65 explicit rules for avoiding certain drugs. START is also systems-based and lists 22 common cases of potentially appropriate drugs and combinations in patients with specific medical problems (4, 5). In its second version published in 2015, the list includes revised criteria divided into groups depending on body systems in 14 green and red boxes with recommendations approved by 19 experts from 13 European countries (4).

These criteria cannot replace clinical judgment in individual cases but may serve to guide prescribing and description by physicians (5).

Material and Methods

The research is a multicenter prospective randomized study, which was conducted during 12 months in 2022/ 2023. The research included 174 respondents older than 65 years with multimorbidity (3 or more chronic diseases) and polypharmacy (5 or more drugs in the last 3 months) who were given an intervention with the STOPP/START instrument version 2.

The data obtained during the study were statistically analyzed using the SPSS software package, version 22.0 for Windows (SPSS, Chicago, IL, USA). The analysis of the qualitative series was done by determining the coefficient of relations, proportions and rates, and they were shown as absolute and relative numbers. The quantitative series were analyzed using measures of central tendency (mean, median, minimum values, maximum values), as well as measures of dispersion (standard deviation). Difference test was used to compare proportions. Spearman's rank correlation coefficient was used to determine the relation between numerical variables and irregular frequency distribution. Univariate linear regression analysis was used to determine and quantify independent significant predictors of polypharmacy. A level of $p<0.05$ was considered to be statistically significant.

Results

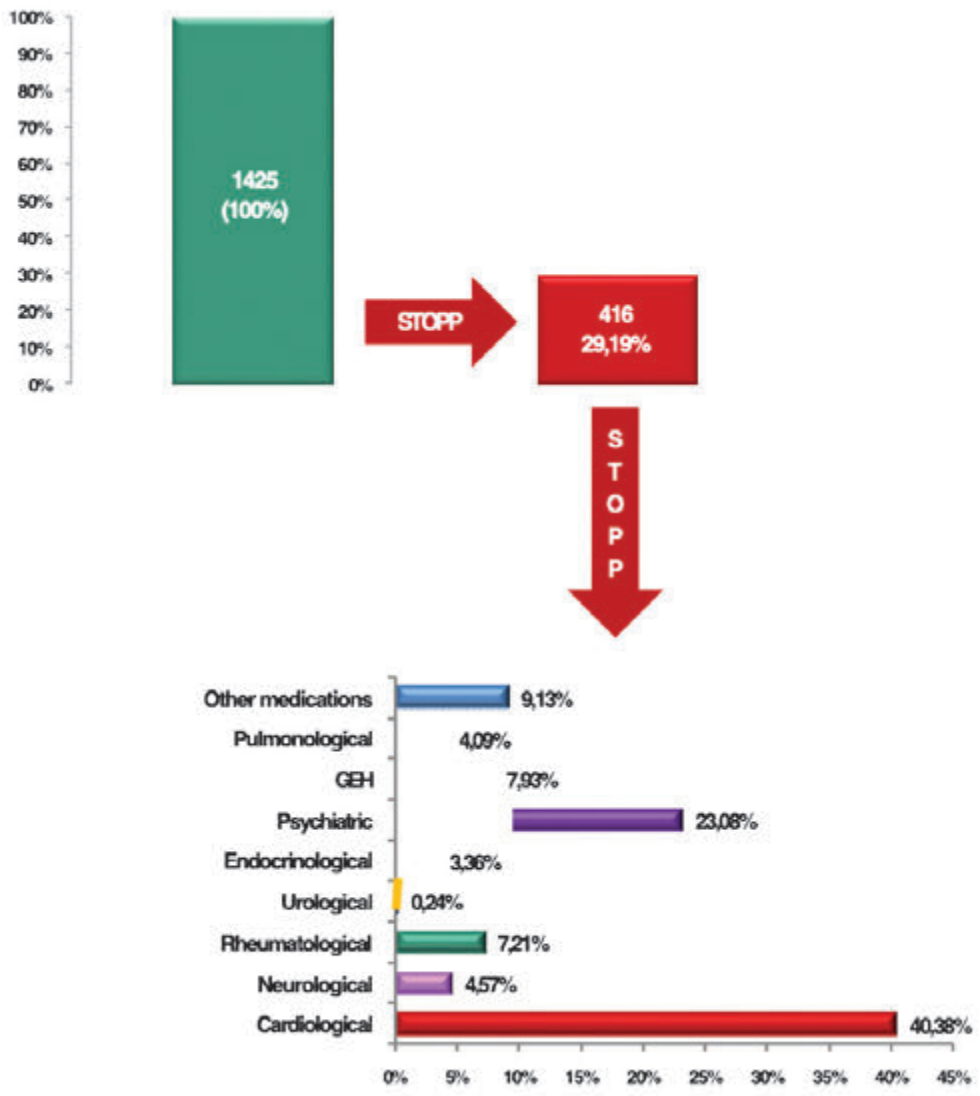
After the evaluation of therapy in patients with the STOPP/START instrument, 416 (29.19%) of 1,425 currently prescribed drugs were stopped. The change of drugs was made in 162 (93.10%) patients, during which a min/max of 0/7 drugs were stopped. The analysis of the total number of discontinued drugs/ supplements (N=416) indicated that (Table 1 and Graph 1):

Table 1. STOPP/START of drugs/supplements at ZERO time.

Parameters (ZERO time)	STOPP			START		
	Medications N (%)	Patients N (%)	Min/ Max	Medications N (%)	Patients N (%)	Min/ Max
Total						
Medication/supplement	416 (29.19%)	162 (93.10%)	0/7	245 (100%)	127 (72.99%)	0/5
Types of medications						
Cardiological	168 (40.38%)	104 (59.77%)	0/3	134 (54.69%)	89 (51.15%)	0/4
Neurological	19 (4.57%)	19 (10.92%)	0/1	11 (4.49%)	8 (4.60%)	0/2
Rheumatological	30 (7.21%)	28 (16.09%)	0/2	11 (4.49%)	8 (4.60%)	0/2
Urological	1 (0.24%)	1 (0.57%)	0/1	1 (0.41%)	1 (0.54%)	0/1
Endocrinological	14 (3.36%)	12 (7.70%)	0/2	21 (8.57%)	16 (9.19%)	0/2
Psychiatric	96 (23.08%)	86 (49.42%)	0/3	41 (16.73%)	36 (20.69%)	0/2
GEH	33 (7.93%)	32 (18.39%)	0/2	16 (6.53%)	15 (8.62%)	0/2
Pulmonological	17 (4.09%)	15 (8.62%)	0/2	10 (4.08%)	5 (2.87%)	0/2
Other medications	38 (9.13%)	31 (17.,82%)	0/3	0 (0%)	0 (0%)	0/0

GEH = Gastroenterohepatology
Mean = Average; SD = Standard deviation; Min/Max

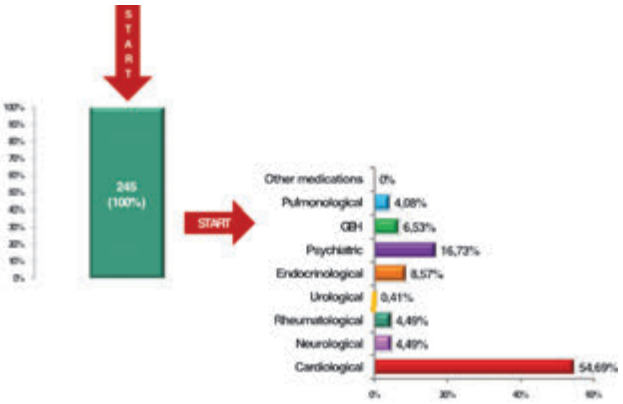
- Cardiac drugs had the largest proportion of stopped drugs/ supplements – 168 (40.38%) in 104 (59.77%) patients with a maximum of 3 drugs stopped per patient;
- The second largest proportion of stopped drugs/ supplements were psychiatric drugs – 96 (23.08%) in 86 (49.42%) patients with a maximum of 3 drugs stopped per patient;
- The proportion of other, GEH and rheumatological discontinued drugs/ supplements was 38 (9.13%) in 31 (17.82%) patients vs 33 (7.93%), in 32 (18.39%) patients vs 30 (7, 21%) in 28 (16.09%) patients respectively. The maximum number of discontinued drugs per patient was 3 for other drugs and 2 for GEH and rheumatological drugs each;
- Urological drugs had the smallest proportion of stopped drugs/ supplements – 1 (0.24%) in 1 (0.57%) patient with a maximum of 1 drug discontinued.



Graph 1. STOPP intervention of drugs/ supplements at ZERO time.

With the START instrument, 245 (100%) new drugs were prescribed in 127 (72.99%) patients with a min/max of 0/5 new drugs per patient. The analysis of the total number of started medicines/ supplements (N=245) indicated that (Graph 2):

- Cardiac drugs had the highest proportion of started drugs/ supplements – 134 (54.69%) in 89 (51.15%) patients with a maximum of 4 drugs started per patient;
- The second largest proportion of drugs/ supplements started were psychiatric drugs – 41 (16.73%) in 36 (20.69%) patients with a maximum of 2 drugs started per patient;
- Proportion of endocrinological and GEH drugs/ supplements started was 21 (8.57%) in 16 (9.19%) patients vs 16 (6.53%) in 15 (8.62%) patients respectively. The maximum number of drugs/supplements started was 2 for both endocrinological and GEH drugs;
- The assessment did not indicate the need to start other new drugs.



Graph 2. START intervention of drugs/ supplements at ZERO time.

State after STOPP/START intervention: After 6 months of the STOPP/START intervention, it was observed that 174 (100%) patients were prescribed a total of 1,177 drugs/ supplements or 248 drugs less than ZERO time. The average number of drugs prescribed after the STOPP/START intervention was 6.76±2.33 with a minimum of 3 and a maximum of 13 drugs. In 50% of the patients after the STOPP/START intervention, the number of prescribed medications was ≤6, and in 25%, <8 medications were prescribed. After the STOPP/START intervention, the average reduction in prescribed medications was 1.42±1.29 (Table 2).

Table 2. Analysis of the number of drugs/ supplements after STOPP/START intervention.

Parameters	after STOPP/START					
	Total N (%)	Consumers N (%)	Mean ± SD	Median (IQR)	Total difference1	Consumers difference2
Medications						
Medications	1177 (100%)	174 (100%)	6,76±2,33	6 (5-8)	248	248
OTC						
OTC	136 (100%)	83 (47,70%)	0,78±1,05	0 (0-1)	12	6
Types of medications						
Cardiological	430 (36.53%)	165 (94.82%)	2,47±1,35	2 (2-3)	69	2
Neurological	59 (5.01%)	36 (20.68%)	0,34±0,72	0 (0-0)	22	6
Rheumatological	73 (6.20%)	51 (29.31%)	0,42±0,75	0 (0-1)	14	17
Urological	57 (4.84%)	38 (21.83%)	0,33±0,66	0 (0-0)	0	-1
Endocrinological	208 (17.67%)	121 (69,54%)	1,19±1,04	1 (0-4)	6	5
Psychiatric	65 (5.52%)	48 (27.59%)	0,37±0,67	0 (0-1)	63	46
GEH	65 (5.52%)	64 (36.78%)	0,37±0,49	0 (0-1)	16	14
Pulmonological	52 (4,42%)	28 (16.09%)	0,29±0,77	0 (0-0)	13	6
Other medications	122 (10,36%)	71 (40.80%)	0,70±1,09	0 (0-1)	25	5

1 Difference = Number of medications: Zero – STOPP/START; 2 Difference = Number of consumers: Zero – STOPP/START
OTC = Supplements; GEH = Gastroenterohepatology Mean = Average; SD = Standard deviation; Median; Min/Max; IQR=Percentiles

After the STOPP/START intervention, the number of prescribed OTCs was 136 and it was reduced by 12 prescriptions, i.e. by 6 consumers. The average number of OTCs after STOPP/START was 0.78±1.05 with a min/max of 0/5 OTCs. In 50% of the patients after STOPP/START the number of prescribed OTCs was ≤1. After the STOPP/START intervention, the average reduction in prescribed OTCs was 0.07±0.42.

The largest proportion of reduced medications was in the CARDIOLOGY group (N=69) followed by PSYCHIATRIC (N=63), OTHER medications (N=25) and NEUROLOGICAL (N=22). The smallest proportion of reduced drugs was in the group of ENDOCRINOLOGY drugs (N=6), and there was no reduction in UROLOGY drugs (N=0) (Table 2).

The proportion of medicines' users was highest among PSYCHIATRIC (N=46), RHEUMATOLOGY (N=17) and GEH (N=14). The smallest decrease in the number of consumers was for CARDIOLOGY drugs (N=2). There was an increase in the number of consumers by N=1 only for UROLOGY drugs.

Discussion

In our study, 416 (29.19%) out of 1,425 currently prescribed drugs were stopped after the assessment of therapy in patients with the STOPP/START instrument. The change of medications was made in 162 (93.10%) patients. Cardiac medications had the highest proportion of discontinued medications/ supplements, followed by psychiatric medications. The maximum number of discontinued drugs per patient was 3 for other drugs and 2 for GEH and rheumatological drugs each; urological drugs had the smallest proportion of stopped drugs/ supplements – with a maximum of 1 drug stopped.

With the START instrument, 245 (100%) new drugs were prescribed in 127 (72.99%) patients. The analysis of the total number of started drugs/ supplements (N=245) indicated that the highest proportion of started drugs/ supplements were cardiac drugs, followed by psychiatric drugs. The maximum number of drugs/ supplements started was 2 for both endocrinological and GEH drugs; the assessment did not indicate the need to start new other drugs.

After this intervention, 174 (100%) patients were prescribed a total of 1,177 drugs/ supplements or 248 drugs less than ZERO time. After the STOPP/START intervention, the number of prescribed OTCs was 136 and it was reduced by 12 prescriptions, i.e. by 6 consumers.

In the most recent study by Gareri et al. 2024 (6), the average number of drugs used in the sample was 9.4 drugs/ patient. The most common comorbidities were cardiovascular diseases (ischemic heart disease, hypertension, atrial fibrillation, heart failure). Potentially inappropriate drugs (PIM) were a total of 74 (36.1%) drugs. In ten patients, proton pump inhibitors (PPI) were stopped without a set indication, out of a total of (46.3%). In ten patients, over-the-counter drugs were prescribed (mostly supplements of the osteoarticular system, multivitamins), which were not necessary. The so-called "duplicate" or double drugs were 26 (12.7%) and were also discontinued. In another study (7), the STOPP/START identified a high prevalence of inappropriate drugs in elderly patients with advanced kidney disease (CKD), following which they were also discontinued. In the study by Ryan et al., the STOPP/START criteria identified a total of 346 PIMs prescribed for 284 (21.4%) patients. The most inadequate were drugs for the gastrointestinal system, in particular (PPI), followed by drugs whose primary effect is on the central nervous

system, the musculoskeletal system and the cardiovascular system. Potentially inappropriate therapy associated with NSAIDs has been observed in patients with hypertension, osteoarthritis, and in patients with a history of peptic ulcer disease, gout, heart failure, CKD and dyspnea. A total of 333 (PPO) for 302 (22.7%) patients were identified with the START criteria. In a recent Japanese randomized controlled trial, the STOPP/START intervention was conducted in 106 participants (49.3%) in the intervention group, and 117 (51.5%) in the usual care group out of a total of 442 participants (average age 81.8 years) (9).

Conclusion

In our research, more than 90% of the respondents had medications stopped, mostly cardiac drugs, followed by psychiatric drugs. With the START intervention, all respondents from the sample were prescribed 250 drugs less than "Zero time", primarily cardiac drugs, followed by psychiatric therapy. The STOPP/START instrument is a criterion for individual judgment for safe treatment, which would lead to rational prescription of drugs in people with multimorbidity.

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EFFICACY OF PREEMPTIVE MULTIMODAL OPIOID - FREE ANALGESIA IN KIDNEY TRANSPLANT RECIPIENTS

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Abstract

Chronic Kidney Disease (CKD), marked by a glomerular filtration rate (GFR) of less than 60 ml/min, is a progressive condition affecting over 10% of the global population. It is expected to be among the top five chronic diseases by 2040. As CKD advances to end-stage kidney disease (ESKD), with a GFR below 15 ml/min/1.73m^2, patients often require renal replacement therapies, such as dialysis or kidney transplantation. ESKD increases the risk of cardiovascular diseases, frequent hospitalizations and higher mortality.

Kidney transplantation is the primary long-term treatment for ESKD, with living donor transplants offering better outcomes due to reduced ischemia and lower complication rates compared to deceased donor transplants. Effective pain management is crucial following transplantation, as traditional opioid analgesics carry risks including respiratory depression and graft failure. Therefore, a multimodal approach integrating non-opioid and regional techniques is preferred.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are generally avoided in kidney transplant patients due to nephrotoxicity risks. Acetaminophen is commonly used, but it requires caution in those with liver conditions. Alternatives such as lidocaine and GABA analogues provide effective pain relief with fewer opioid needs. Regional anesthesia techniques, including neuraxial blocks and fascial blocks like the Transversus Abdominis Plane (TAP) and Quadratus Lumborum (QL) blocks, offer significant benefits in pain management.

Multimodal analgesia strategies, combining these methods, enhance pain control, promote early recovery and reduce opioid reliance, though ongoing research is needed to refine these approaches and optimize patients' outcomes in kidney transplantation.

Key Words: *kidney transplant; multimodal analgesia; opioid-free analgesia.*

Introduction

Chronic kidney disease (CKD) is defined as a glomerular filtration rate of less than 60ml/min. The condition is characterized by kidney damage, and persistent albuminuria that lasts for more than three months. It is a progressive disease that affects over 10% of the population and will become one of the most common non-transmissible chronic diseases worldwide (1). The World Health Organization predicts that chronic kidney disease will be the fifth most common chronic disease by 2040. Chronic kidney disease is one of the leading causes of death in today's world (2).

However, CKD is not only a health issue, but it also poses significant social and socio-economic challenges, particularly in developing countries. Risk factors for the occurrence of CKD are diabetes mellitus, hypertension, obesity and age. End-stage chronic kidney disease (ESKD) is the last stage of renal failure, defined as a glomerular filtration rate of 15ml/kg/ 1.73m2. As CKD gets worse at this stage, patients may need to use some of the available treatments to stay alive for a long time, such as renal replacement therapy, chronic dialysis (hemodialysis or peritoneal dialysis), or a kidney transplant. But this progression also entails a significant increase in the risk of cardiovascular diseases, frequent hospitalization and increased mortality. A Scottish study revealed that at least one comorbidity affected 98.2% of patients with CKD (3). Hypertension, heart failure, diabetes and coronary heart disease, are the most common conditions in CKD patients. Estimates indicate that cardiovascular disease contributes 20 times more to excess mortality than the general population, particularly in the last two decades. That is why it is essential to promptly identify CKD, monitor it, and with increased efforts, improve prevention and treatment measures.

The only long-term treatment option for end-stage CKD is kidney transplantation, and kidney transplant surgery rates are expected to increase in the coming decades. When possible, living donor kidney transplantation has several advantages, especially when performed as a preventive strategy. Recipients have a better quality of life and a lower risk of dialysis-related complications. It also tends to allow longer graft survival due to less chance of ischemia and a lower rejection rate.

Transplant centers are developing multidisciplinary approaches to optimize outcomes and minimize the potential risks associated with surgery and hospital stays. Surgical intervention causes tissue injury, pain and a stress response influenced by a combination of endocrine, metabolic and immunological factors. This protective mechanism is associated with the risk of postoperative organ dysfunction, prolonged hospital stays, increased morbidity and mortality.

The surgical approach for kidney transplant surgery is an incision in the right iliac fossa, which extends from the pubic symphysis to the iliac bone. Recently, minimally invasive techniques such as mini-incision, laparoscopic, or robotic surgery have become popular for kidney transplants. Regardless of the approach, kidney transplantation is associated with moderate to severe postoperative pain, which requires effective management. Despite advances in surgical and anesthetic techniques, pain remains an important problem for patients undergoing kidney transplantation and represents a major challenge for anesthesiologists. People are worried about the choice of analgesics because the disease process, coagulopathy, and the risk of hypotension, which affects graft perfusion, change the pharmacokinetics and pharmacodynamics of the drugs. Inadequate pain control is associated with anxiety, delirium and delayed healing. Kidney transplant patients often have multiple comorbidities that, when combined with poorly controlled pain, can lead to cardiovascular, hemodynamic and respiratory complications that in turn impact overall graft recovery and survival. Individuals with kidney disease or poor kidney function should limit their use of analgesics due to potential harm, changes in metabolism and distribution, or slower protein binding and clearance from the body. Pain management in kidney transplant recipients is essential. Based on the available studies, it is necessary to make recommendations and choose the best pain management strategy (4). In recent years, personalized and multimodal approaches have proven to be crucial in perioperative pain management. Using a multimodal approach, along with regional pain relief techniques, is the best way to solve the problem and get rid of pain without using opioids. This allows for early mobilization and the best possible outcome

after surgery. Multimodal analgesia is an approach to pain management that involves the use of different drugs and techniques in order to minimize opioid analgesia. Opioids are the traditional and standard mainstay of therapy for treating surgical pain in the immediate postoperative period. But they have an unfavorable side effect profile that includes respiratory depression, nausea, postoperative ileus, sedation, and pruritus. Furthermore, patients who use high doses of opioids in the first year after transplantation have a higher rate of death and graft failure (5).

The implementation of a multimodal approach, including non-opioid therapy and regional techniques, results in a change in pain management in patients undergoing kidney transplantation (6).

Material and Methods

The main literature search revealed heterogeneity and precluded qualitative systematic reviews or research along Dixon's suggested lines (7). Additionally, Sandelowski's method for theoretical qualitative meta-synthesis was not applicable. A narrative evaluation was conducted for the reasons listed above.

All the data used to construct this paper was found using Medline, IBMS databases, Pubmed and CINAHL Keyword searches. Kidney transplant**,** multimodal analgesia, opioid-free analgesia, were among the search terms used. We also looked up primary article references from our original search. We looked through campus and personal libraries for materials related to the research topic.

Renal Transplant Recipients and Challenges in Analgesia

Opioids are one of the most commonly used groups of analgesics. Most of the research studies that looked at how opioids affected kidney transplant outcomes and success, found that higher opioid use during kidney transplant greatly raises the risk of cardiac arrest, ventricular arrhythmias, changes in mental status, opioid dependence, higher death rates and graft loss (8). Patients with a glomerular filtration rate of less than 50ml/min/ in 1.73m2 also produce morphine-6 glucuronidase and morphine-3 glucuronidase metabolites, which can lead to nausea and vomiting after surgery, as well as unexpected sedation effects, involuntary myoclonus, and decreased breathing. Over a 20-years period in the late 1990s, researchers identified nearly 500,000 opioid overdose deaths. The problem continues, with over 100,000 deaths identified in 2021.

Despite many publications, there is still an absence of recommendations for opioid management in these key patient populations. It is unclear whether and what the direct impact of opioids is on transplant outcomes. Patient evaluation data and the impact of highly controlled chronic opioid exposure on transplant outcomes are scarce.

A systematic review and electronic searches of 25,190 records, including 63 in the survey, assessed the impact of opioid use on transplant outcomes in 19 publications, revealing that patients receiving opioid therapy prior to transplantation. Twenty studies examined opioid minimization strategies in kidney transplant recipients, while 24 studies examined pain management strategies in living donors. In the context of kidney transplant recipients, where careful application of analgesia is critical due to the challenges presented by kidney disease, a multimodal

pain management strategy aims to address the complexity of pain, and the risks associated with overuse opioids in specific patient groups (9). Patients with chronic kidney disease are more specific, which increases the challenges faced by anesthesiologists in the application of multimodal analgesia protocols and could transform pain management methods.

Furthermore, recent literature and the ERAS pathway highlight the efficacy of multimodal analgesia with minimal opioid analgesia, as well as the use and advancement of newer interfacial blocks (10). In addition to optimization of analgesia, ERAS protocols encourage early mobilization, nutrition, early removal of invasive venous and arterial lines, catheters, and reduced hospital stay. During renal transplant surgery, there are number of non-opioid pain relief methods that can be used alone or together to improve pain relief while lowering or eliminating opioid exposure. We have evaluated various interventions and methods of regional anesthesia applied or potentially applied in kidney transplant surgery. We have studied the benefits and adverse effects of each technique from the perspective of the CKD patient population, providing appropriate recommendations and evidence for their safe use.

Nonsteroidal Anti-inflammatory Drugs

It is found that nonsteroidal anti-inflammatory drugs (NSAIDs) and selective cyclooxygenase-2 (COX-2) inhibitors improve analgesia in many surgical patients. Preoperative administration of these drugs has been shown to reduce 24-hours opioid consumption, as well as postoperative nausea and vomiting. It is known that these chemicals can cause more acute kidney injury by narrowing afferent blood vessels and causing acute interstitial nephritis. This is because they stop the enzyme cyclooxygenase from working and stop prostaglandins from being made. Because they stop the prostaglandin pathway from working, there is a chance of bleeding and kidney damage. Therefore, we recommend avoiding these drugs for kidney transplant recipients due to their potential for bleeding and nephrotoxicity. As a result, the simultaneous use of NSAIDs and CNIs in kidney transplant recipients can worsen IG-hemodynamics and cause graft dysfunction. Studies on the use of NSAIDs for pain management in kidney transplantation, however, are insufficient. Nefopam, a non-opioid, non-steroidal anti-inflammatory drug, complements patient-controlled analgesia (PCA) in renal transplantation. It significantly decreased pain intensity in the first 48 hours after surgery and decreased the number of cases of sleepiness and fentanyl use.

Acetaminophen

Multimodal analgesia protocols commonly incorporate acetaminophen (paracetamol) as a fundamental component. Several meta-analyses support this, showing that patients receiving IV paracetamol or propacetamol experienced 50% less pain during the first 4 hours. But patients with end-stage chronic kidney disease are at high risk of infectious blood-borne infections, and the prevalence of chronic hepatitis in this group of patients may be higher than in the general population, complicating the routine use of acetaminophen. Its action occurs by activating descending serotonergic inhibitory pathways in the CNS. Patients with chronic liver disease should reduce the total daily dose to 2 grams.

Lidocaine

Most of the transplant centers use lidocaine as an adjuvant to opioids or as part of multimodal analgesia due to its favorable renal safety profile, which limits mild to moderate pain. Authors Abdelatif and Ibrahim investigated the efficacy of intraoperative infusions of 2% lidocaine in reducing pain in renal transplant recipients. Infusion at a rate of 10ml/h contributed to a significant reduction in pain and fentanyl consumption, as well as the need for analgesia in the first 24 hours postoperatively. During its application, it is necessary to pay attention to possible signs and symptoms of local toxicity, perioral stiffness, metallic taste, tinnitus, dizziness and slurred speech.

GABA analogues

Multimodal analgesia approaches commonly use GABA analogues (gabapentin and pregabalin). Their mechanism of action is the inhibition of calcium channels in the brain, aimed at neuropathic pain. When using them, one should be cautious to avoid potential toxicity, myoclonus, altered mental status and respiratory depression.

Ketamine

It is an NMDA receptor antagonist that causes a dissociative state and analgesia. can lead to altered mental status, hallucinations and hemodynamic changes.

Neuraxial blocks (spinal, epidural, or combined)

These blocks, which have been in use for decades, offer numerous advantages, such as a notable decrease in pain, prompt mobilization, a decreased risk of deep vein thrombosis, early bowel motility mobilization, and a shorter hospital stay. They are also useful for kidney transplant pain control, like all major abdominal procedures. Neuraxial anesthesia techniques help keep the patient's blood pressure stable and protect the graft function more effectively in people with chronic kidney disease. However, the risk of hematoma formation rises dramatically when there is coagulopathy and platelet dysfunction, which can happen to people with chronic kidney disease. Epidural block with local anesthetic, with or without adjuvant, has the dual benefit of being an intraoperative anesthetic technique and an extension of postoperative pain control. Researchers have found that low doses of intrathecal morphine (ITM) effectively provide excellent pain control. In 2022, Ja. El et al. investigated the effects of intrathecally administered morphine on postoperative pain intensity, agitation and delirium, in 296 living donor kidney transplant recipients. They showed that risk factors such as age, smoking and psychotropic drugs have a greater impact than BMI, and they even demonstrated a protective effect. Additionally, it could aid in preventing bladder discomfort following surgery, a common occurrence in CKD patients following transplantation.

Fascial Blocks

Fascial blocks, a recent advancement in regional anesthesia techniques, offer a viable substitute for traditional methods like paravertebral, epidural, or spinal blocks. The primary target of fascial blocks is the deep fascia, a thick membrane of connective tissue that surrounds and encloses muscles, nerves and other structures, including mechanoreceptors and nerve fibers. These blocks prevent direct injection into the nerve or axon, reducing the risk of serious complications such as nerve injury and neuraxial hematoma. Thus, they represent a valid alternative option for high-risk patients. Despite their increasing use even in the context of high-risk operations, there are still no recommendations for their use and management in patients at risk of bleeding. The way local anesthetics work to relieve pain after fascial blocks is by effecting neurons in the area and an effect on the whole body through vascular absorption at faraway sites. Patients with coagulopathy can still benefit from their effective pain control and minimal risk of complications.

Transversus Abdominal Plane Block (TAP)

Renal transplantation has proven these block to be effective techniques for pain control, resulting in a significant reduction in IV opioids and analgesics. Its disadvantage is insufficient coverage of visceral pain and the proximal dermatome (T6-9). In 2001, Rafi first described it. During this block, we apply a local anesthetic in the plane between the internal oblique muscle and the transverse abdominal muscle, thereby blocking the sensorimotor innervations of the anterior abdominal wall, which is innervated by the front part of the spinal segment from T7-11. A catheter can be administered once or repeatedly. This block covers the laparotomy without intraperitoneal extension, eliminating the visceral pain component, making it ideal for kidney transplant recipients. K. Mukhtar et al. first investigated the efficacy of TAP block on renal transplant recipients. Pain, postoperative morphine requirements, nausea, vomiting and sedation were significantly lower in the TAP group. Researchers Jankovich et al., Parikh BK et al., Farag et al., Gopwani SR et al. and Sing et al., looked into continuous TAP block in people who had kidney transplants and found that they had a lot less nausea and vomiting after surgery, as well as less pain and the need for opioid painkillers. In the last two decades, TAP block has become one of the main components of ERAS protocols and multimodal analgesia, but its disadvantages include limited dermatome coverage from T10-L1, lack of visceral analgesia, possible systemic toxicity, colonic hematoma, liver laceration and infections.

Quadratus Lumborum Block (QLB)

Rafael Blanco, an anesthesiologist, first described the QLB block (Quadratus lumborum block) as a variant of the TAP block in 2007. A detailed description of the QLB block emerged much later. This procedure uses the QL muscle (QLM) and pain relief in the thoracolumbar fascia (TLF) as ultrasound landmarks. The thoracolumbar fascia is a tube-shaped connective tissue made up of layers of aponeurosis and fascia that wrap around the back muscles and connects the front of the abdomen to the lower back. We have not fully elucidated the actual mechanism of QLB's analgesia. It is likely that local anesthetics spread along the TLF, and the endothoracic fascia in the paravertebral space is partially responsible for the analgesia. TLF's anatomical-histological features, specifically the surface layer with a dense network of sympathetic neurons, explain an additional mechanism of action for local anesthetics. There are high- and low-threshold mechanoreceptors and pain receptors in the fascia that are sensitive to local anesthetics. These receptors' local anesthetic blockade partially explains QLB analgesia. The most often, it

occurs at the level of T7-L1 dermatomes, but it can also spread to the cranial (T4-5) and caudal (L2-3) regions. Individual anatomical variations and the site of local anesthetic administration influence the height of the block. Sindwani, along with Rahendra R. and his team, conducted research. Al showed that QLB significantly reduced opioid consumption, sedation and pain intensity in kidney transplant recipients. This block has few complications, but like other regional anesthesia techniques, it can lead to systemic toxicity of local anesthetics, infections, femoral nerve block, and quadriceps weakness. In addition, this block is a "deep block" compared to other fascial blocks of the abdominal wall, with a higher risk of hematoma formation, especially in patients with impaired coagulation and platelets. Most of the studies have shown that QLB variations are equal, and in some cases even superior to TAP block after kidney transplant surgery, primarily due to its ability to mask visceral pain (11). However, cited disadvantages include block variation and unpredictable dermatome coverage, which vary depending on the variant and application site.

Erector Spine Plane Block (ESPB)

ESPB (erector spine plane block) is a relatively new technique in regional anesthesia and pain management. Forero first described it in 2016. It has garnered significant attention and sparked debates regarding its mechanism of action. This block provides analgesia for somatic and visceral pain. The local anesthetic diffuses through the channels in the transverse connective tissues, allowing it to reach the ventral and dorsal planes of the thoracic spinal nerves, as well as the sympathetic communications at the level of the intervertebral foramen. Lateral cutaneous branches of the intercostal nerves are also involved, contributing to the block's analgesic effect. When performed at the T9-10 level, it provides analgesia without motor block in the abdominal-pelvic region. For the first time in 2019, Temirov and his colleagues described ESPB in a 36-years-old man undergoing a kidney transplant. In a series of 28 cases, Sharipova and her colleagues demonstrated lower pain, opioid consumption, and an incidence of nausea and vomiting. In 13 patients undergoing renal transplantation, Vishwanath et al. substituted epidural catheter placement with ESPB for postoperative pain management. Paolo Capuano et al. described ESPB in pediatric kidney transplantation for the first time (12). The multimodal approach with ESPB allows optimal pain control without the need for opioids, early mobilization, and rapid recovery of bowel function without constipation and vomiting. If anticoagulant therapy, including heparin, is necessary, ESPB has proven to be a safe and effective strategy without complications, even for patients at high risk of bleeding. Toscano et al. investigated the safety of fascial blocks, especially ESPB, in patients receiving anticoagulant therapy who had coagulopathy. Its location deep in the m. erector muscle plane and superficial to the transverse processes makes the ESPB unique. Compared to other regional anesthesia techniques, this positioning reduces potential risks. Compared to epidural analgesia and paravertebral block, ESPB's distance from major blood vessels and the spinal cord reduces the risk of hypotension and hematoma. The interforaminal spread and injection of the ESPB reduces the risk of pneumothorax compared to a paravertebral block. These anatomical advantages are of particular importance in patients receiving anticoagulant and antiplatelet therapy. Onaj et al. compared QLB and ESPB in open nephrectomy. Both approaches achieved similar results on opioid consumption and pain. QLB is considered a valid option for pain management during kidney surgery, but it has certain limitations in the field of kidney transplantation. First and foremost, QLB is a deeper block with a high risk of bleeding, and secondly, the placement of the ESPB catheter in the postoperative period is more comfortable and has less of an obstacle to early mobilization.

Conclusion

The implementation of a multimodal approach, including non-opioid therapy and regional techniques, has led to a change in the management of pain in patients undergoing kidney transplantation. It is a truly multidisciplinary endeavor that includes extensive pre-transplant evaluation, intensive care during hospitalization and long-term follow-up of the transplant program. Pain management in renal transplantation remains a major challenge despite increased support for opioid minimization protocols and the ERAS pathway. Despite the available literature and evidence on the benefits, safety and efficacy of a multimodal approach to pain management in renal transplantation, there is currently no established strategy or strong procedure-specific recommendations. Also, the studies show a difference in the drug dosage, method of administration, studied group, evaluation system and different time points for pain measurement. Furthermore, there are no studies on an effective acute pain management technique for patients undergoing minimally invasive kidney transplantation, including mini-incision, open, laparoscopic, or robot-assisted kidney transplantation. Current evidence supports that the approach to pain management should be individualized and multimodal. Intravenously administered paracetamol is a well-accepted analgesic by most authors as part of multimodal analgesia. Intrathecal morphine and epidural analgesia are suitable options, and the ERAS guidelines recommend fascial blocks as new safe techniques. Avoid nonsteroidal anti-inflammatory drugs due to the risk of bleeding and renal damage and minimize the use of intravenous opioids. Future studies should further evaluate the safety and efficacy of regional methods to formulate a protocol, construct an algorithm, and develop a strategy for pain management in kidney transplant recipients. We should simplify and individualize this approach, considering available resources, patient's preferences, and anesthetist's experiences.

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BASIC ECHOCARDIOGRAPHY FOR ANESTHESIOLOGISTS: THE TANK, THE PUMP AND THE SURROUNDINGS

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Abstract

Both procedures, transthoracic echocardiography (TTE), as well as transesophageal echocardiography (TEE), in the anesthesiologist's hands could be considered as a must in providing significant data about the hemodynamics while following the beat-to-beat dynamical circulatory changes. Echocardiography as a noninvasive procedure is a real time provider of information about the systolic and diastolic function, valvular structures, fluid status, ventricular contractility and the cardiac output in perioperative setting, as well in critically ill patients. The intention of this article is to elaborate the basic echocardiographic findings which imply the fluid status referred as "The tank", cardiac contractility named as "The pump" and significant findings that involve the pericardium referred as "The surroundings" with the idea of providing the anesthesiologists with enough knowledge to perform basic echocardiographic examination to rule out existence of significant life-threatening conditions in order to provide better patient care while managing complex cases. Here we offer only brief information about the power of echocardiography with the idea to encourage anesthesiologists to start using it as a monitoring tool on a daily basis in a well-selected cases. Detailed and more precise echocardiographic examination is beyond the scope of this article and should be considered for physicians who already pose basic echocardiographic skills.

Key Words: *Echocardiography; Point of Care Ultrasound; Transthoracic Echocardiography.*

Introduction

Modern anesthesiologists and intensivists tend to move borders between specialties in order to provide more accurate patient's care when making prompt decisions on a daily basis. Many years ago, performing perioperative echocardiography as a point of care method, was considered as a procedure which was beyond the anesthesiologist's responsibilities. Rather than that, nowadays, both procedures - transthoracic echocardiography (TTE), as well as transesophageal echocardiography (TEE) in the anesthesiologist's hands could be considered as a must providing significant data about the hemodynamics while following the beat-to-beat dynamical circulatory changes. According to the observational study done by Brian Cowie where performing echocardiography by anesthesiologists was examined, in 98% of the cases the anesthesiologists have obtained a high-quality image for analysis and in 84% of the cases this examination has led to change in therapy in the perioperative period (1). Echocardiographic findings stated by the anesthesiologists corelated with those when echocardiography was performed by cardiologist in

an 87% of the cases (1) which could be considered as an even bigger reason why should echocardiography be part of the standard monitoring in the perioperative period. Echocardiography as a noninvasive procedure is a real time provider of information about the systolic and diastolic function, valvular structures, fluid status, ventricular contractility and the cardiac output (2) in perioperative setting, as well in the critically ill patients. All above mentioned data could lead to significant changes while managing patients with previously established diagnosis of coronary artery disease or stable chronic heart failure who could easily deteriorate perioperatively (2).

In this article we will elaborate the basic echocardiographic findings which imply the fluid status referred as "The tank", cardiac contractility named as "The pump" and significant findings that involve the pericardium referred as "The surroundings" with the idea of providing the anesthesiologists with enough knowledge to perform basic echocardiographic examination to rule out existence of significant life threatening conditions in order to provide better patient's care while managing complex cases. Echocardiographic examination done by intensivists as a point of care tool while monitoring patients in order to assess volume status, myocardial contractility and to detect life threatening conditions was strongly advised and encouraged by the

European Society of Intensive Care Medicine and published back in 2021 (3).

The Tank

Many conditions even in elective patients could result in hypotension and one of them is hypovolemia. Hypovolemia is more frequently met in non-elective emergent cases, where performing TTE could reveal the reason of hypotension and to help us while guiding therapy, when giving volume boluses till reaching homeostasis. There are many static and dynamic ways to assess the volume status and volume responsiveness, but in this article, we will discuss the simplest echocardiographic approaches of volume status assessment, in order to provide the reader with knowledge for gaining simple and basic echocardiographic skills. The quickest and the simplest way to rule out does the reason for hypotension could be hypovolemia, is when we take a look at the heart in parasternal long axis where the left ventricle and Left Ventricular Outflow Tract are seen. Actually in severely hypovolemic patients the heart structures will be looking hyperkinetic, which means left ventricular free wall and interventricular septum will move inwards meeting and "kissing" one another inside the empty ventricle. This sign of a kissing ventricle suggests serious hypovolemia and demands aggressive fluid resuscitation. In situations where hypovolemia is not that severe left ventricular wall movements would be still hyperkinetic but more subtle and not so reliable for diagnosis. In those situations, especially in spontaneously breathing patients, the anesthesiologist must take a look at the Inferior Vena Cava (IVC) diameter and its collapsibility. By placing the probe in the subcostal area, we could find the IVC and see how it enters the right heart. The best place to measure the IVC diameter and evaluate the dynamic changes over respiratory cycle is at 2-3cm before entering the right heart. Measuring IVC over time is possible in M-mode where the movements or venous collapse will be registered. Normal values for the maximal IVC diameter are considered from 12mm to 21mm, where all values below 12mm could suggest hypovolemia (4). Patients could have normal values for maximal IVC diameter and still be hypovolemic which could be demystified with simple measuring the largest and the smallest diameter of IVC in M-mode during the respiratory cycle in spontaneously breathing patients, as well as in mechanically ventilated patients. In spontaneously breathing patients we should measure IVC collapsibility index using the following formula:

dIVCmax-dIVCmin/dIVCmax x100, while in mechanically ventilated patients we should look for IVC distensibility index calculated by the following formula - dIVCmax-dIVCmin/dIVCmin x100. The difference in calculating IVC collapsibility versus distensibility lays in the different physiology of respiration among spontaneously breathing patients versus mechanically ventilated patients. In spontaneously breathing patients IVC collapses during inspiration, because of the negative intrathoracic pressures which facilitate the emptying the IVC into the right atrium. In mechanically ventilated patients due to positive end expiratory pressure during inspiration, IVC dilates. Measuring above mentioned diameters and indexes in seconds could provide us information about the fluid responsiveness of our patients making significant contribution to the diagnosis of the reason of hypotension, but as well in guiding therapy. Therefore, as a bigger the difference of IVC diameter over the respiratory or ventilatory cycle is, the bigger is the volume responsiveness suggesting hypovolemia. IVC collapsibility index has sensitivity of 71% and specificity of 81% in terms of predicting volume responsiveness in spontaneously breathing patients according to 7 studies which had evaluated a total of 395 patients (5). Sensitivity and specificity of IVC distensibility index when predicting volume responsiveness in mechanically ventilated patients is quite similar with 75% and 82% respectively, based on 9 studies which have included 284 patients (5). Blood loss even at 500ml was accompanied with lowering the diameter of IVC for 33-40% from baseline values before the physiological changes of vital signs, as hypotension and tachycardia occur (6). Therefore, dimensions of IVC less than 21mm with IVC collapsibility index greater than 50% in spontaneously breathing patients could suggest slight hypovolemia, but dimensions of IVC lower than 18mm combined with collapsibility index greater than 50% strongly suggest hypovolemia and fluid responsiveness. In mechanically ventilated patients IVC distensibility index greater than 18% implies hypovolemia and fluid responsiveness. However, even more accurate and precise echocardiographic methods for assessment of volume status are available nowadays as measuring the Left Ventricular Outflow Tract Velocity Time Integral with Cardiac output measurement and transmittal flow velocity measurement, but they are considered beyond the basic echocardiographic skills and will not be discussed in this article.

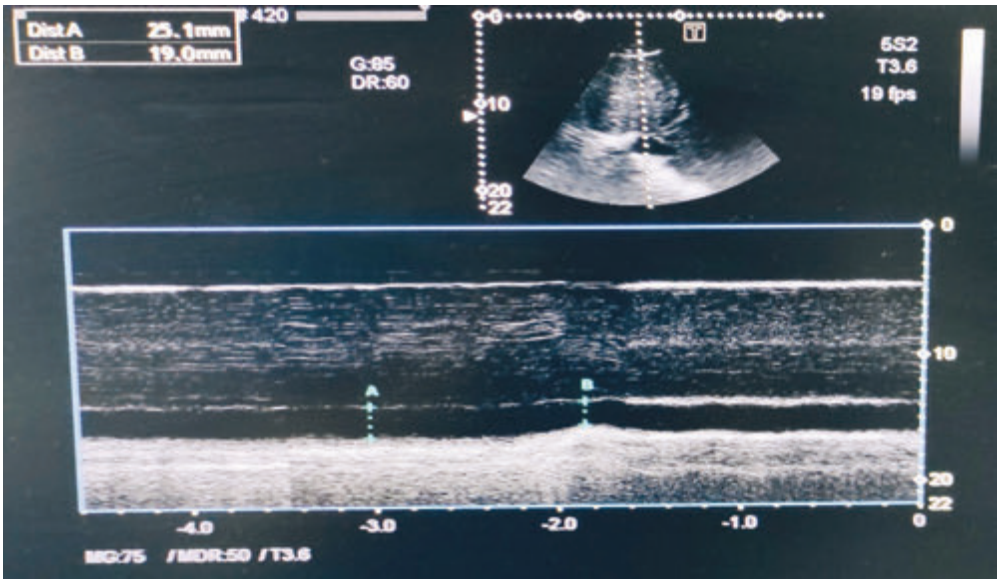


Figure 1. M-mode of dilated Inferior Vena Cava with collapsibility less than 50%.

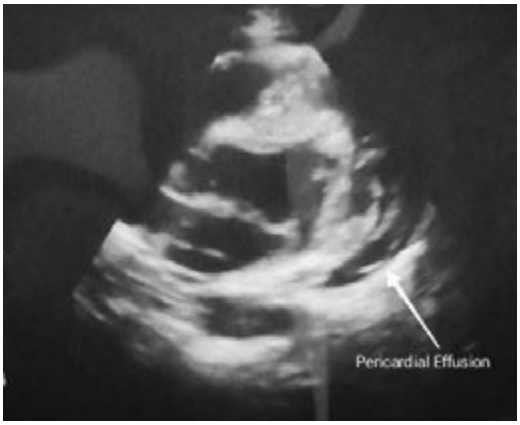
The pump

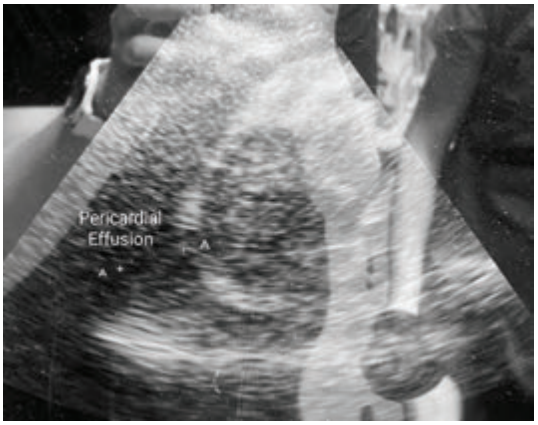
The assessment of cardiac function, precisely the cardiac contractility, is frequently needed before surgery or in shocked patients admitted in the ICU. Elective patients could undergo detailed echocardiographic examination done by cardiologist, but in terms of emergence in complex cases before emergent surgery or during the ICU stay due to resolving acute onset situations, sometimes cardiac contractility should be assessed by the anesthesiologist. Measuring ejection fraction as a surrogate of a cardiac contractility is a mainstay in assessment of cardiac function in elective patients, but it is not a reliable method in shocked patients because ejection fraction is preload and afterload dependent (7). Therefore, other methods should be used when assessing cardiac function in critically ill patients. As a basic skill, the anesthesiologist who will perform point-of-care ultrasound (POCUS), in order to provide quick solution in a deteriorating patient, should use simple eyeballing while assessing cardiac contractility. Nevertheless, eyeballing by itself is not as precise nor objective as expected, but still could help in revealing does cardiac contractility is acutely affected. Eyeballing should be done in parasternal long axis and four chamber view. In parasternal long axis view, one should look after the movements of the left ventricular wall towards the septum, as well as the movement of the mitral valve during opening. Actually if the left ventricular wall moves fine towards the septum and mitral valve while maximally opened is placed near the septum, global cardiac contractility is considered as preserved. When movements of the left ventricular wall are flattened and not easily visible, as well as when the mitral valve during maximally opening is far from the myocardial septum pump, insufficiency should be considered as a significant contributor to the hemodynamic instability. Global systolic function estimation by eyeballing should be made in the 4-chamber apical view, as well as it is considered as a basic skill which is strongly recommended by the ESICM (3). Throughout this window, the left ventricle is better visualized from the apex to the base where radial and longitudinal shortening could be seen and assessed during systole. Based on the simple eyeballing, we could make a conclusion if the cardiac contractility is increased, normal, mildly or severely impaired which in most of the cases could lead to significant changes in therapeutic approach. Increased cardiac contractility in most of the critically ill patients suggests hypovolemia with consequently strongly activated sympathetic response while impaired contractility could be the cause or sometimes even a consequence of the critical illness.

The Surroundings

The most significant condition with a life-threatening property that must not be missed when performing POCUS, is pericardial tamponade. "The surroundings" refers to pericardium and the structures around the heart whose pathologic conditions could lead to impaired hemodynamics. Accumulation of free fluid between the two pericardial layers could be detected in all cardiac windows where pericardial effusion will be visualized as a dark anechoic area around the heart whose dimensions could vary depending on the amount of pericardial fluid (8). In emergent cases where time to treatment is crucial, even only subcostal examination could reveal presence of pericardial effusion with or without hemodynamic compromise leading to fast treatment decision. If the anechoic dark space could be seen in all windows around the heart, then the pericardial effusion is probably big. Essential when deciding if pericardiocentesis is needed or not, is the presence or absence of hemodynamic compromise which by echocardiographic could be identified by detecting collapse of the right atrium in systole or right ventricular collapse in diastole. Right heart collapse could be identified when using subcostal or apical

4-chamber view during the examination where inward movement of the right ventricular free wall is met during diastole. Pericardial tamponade in 92% of the cases is accompanied with dilation of the IVC (8) which becomes larger than 2.5cm and non-collapsible implying impaired anterograde blood flow and should be seen and assessed in subcostal view as it was explained earlier in this article.





Figures 2 & 3. Pericardial Effusion surrounding the heart.

Conclusion

Point of Care Echocardiography in the Anesthesiologists hands when adequately indicated and performed could lead to significantly faster diagnosis of life-threatening conditions demanding immediate treatment. The assessment of the heart function perioperatively by echocardiography should be treated as one more window available to look at the hemodynamics. Echocardiography, even when performed by the very basic skilled Anesthesiologist-Echocardiographer in states of hemodynamic instability could provide answers about the volume status, heart contractility and possible obstructive etiology leading us to decisions based on findings, but rather on assumption while providing the safest possible care for patients.

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CASE REPORT *UDK: 616-089.5:613.25*

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ANESTHETIC CHALLENGES FOR AIRWAY MANAGEMENT IN OBESE PATIENT

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Abstract

Anesthesia management in morbidly obese patients is challenging due to the potential for various complications related to ventilation and airway control. Obesity is associated with an increased risk of perioperative morbidity and mortality. This risk is increased significantly if the BMI Is above 40 kg/m².

This case report is about a 44-years-old morbidly obese patient with predominantly centrally distributed obesity and a Mallampati score of III, who was planned for elective surgical intervention, and it describes the perioperative anesthetic strategies for such patients undergoing general anesthesia and highlights the importance of a comprehensive approach to ensuring their safety.

Key Words: *airway management; general anesthesia; morbid obesity ramp position; obesity; rapid sequence intubation.*

Introduction

According to the World Health Organization, overweight and obesity are defined as abnormal or excessive fat accumulation that poses a health risk. A normal BMI ranges from 18.5kg/m² to 24.9kg/m². A BMI over 25kg/m² is classified as overweight, and a BMI above 30kg/m² is considered obese (1).

Over the world, the prevalence of obesity has increased exponentially (2). Obese patients are a unique group of patients, and each anesthesiologist must know about pathophysiologic changes that occur in these patients, and how to respond if a complication occurs (3). Difficult airway management is a significant challenge in anesthetic practice, particularly in obese patients due to anatomical and physiological alterations. Besides the potential difficulties in securing an airway for these patients, anesthesia management in obese patients is also challenging due to associated comorbidities like sleep-disordered breathing, hypertension, dyslipidemia, ischemic heart disease, diabetes mellitus, osteoarthritis, liver disease, high risk of development of septic shock. Also, obese patients are more prone to gastrointestinal issues, such as gastroesophageal reflux and delayed stomach emptying, which can increase the risk of pulmonary aspiration. Obese patients have altered pharmacodynamics due to physiological changes which include increased cardiac output, fat and muscle mass, increased plasma volume, renal blood flow, and splanchnic blood flow. Therefore, doses of anesthetic medications should be carefully adjusted. Dosing recommendations for patients with normal BMI are usually based on their total body

weight (TBW), because it is similar to their ideal body weight (IBW), but dosing in obese patients is quite different and most of the medications require dosing based on ideal body weight (IBW) to avoid an overdose (3). Obesity is also a major risk factor for developing pulmonary and venous thrombosis. Anticoagulant therapy should be initiated in the preoperative and postoperative period with appropriate dosage to mitigate these risks.

Case Presentation

A 44-years-old man (weight=175 kg, height=180 cm, BMI=54.0 kg/m2) was scheduled for the repair of a ventral hernia, and removal of a suspected metastatic liver deposit. His medical history included hypertension, hyperthyroidism, type II diabetes mellitus, gastroesophageal reflux disease (GERD), and adenocarcinoma of the colon and he was an ex-smoker. The patient had no allergies to medication and food. He was on chronic therapy, including Metformin 1000mg, Lercanidipine 10mg, Levothyroxine 25mg, and Lisinopril/ Hydrochlorothiazide 10/12.5mg. Prior to the intervention, a general physical examination revealed that the patient had morbid obesity, a Mallampati score of III, a neck circumference of 43cm, and slightly limited neck extension. Auscultation showed clear breath sounds, and the chest X-ray indicated no significant changes. The blood glucose level before the intervention was 8mmol/L. Although the patient had not been formally diagnosed with obstructive sleep apnea (OSA), he exhibited symptoms such as daytime sleepiness and snoring. The patient was then monitored using EKG, pulse oximetry, and non-invasive blood pressure measurement. Two intravenous lines were inserted, and the following equipment was prepared: a laryngoscope with both straight and curved spatulas, a McCoy laryngoscope, a tube exchanger, an intubating stylet, a video-laryngoscope, and supraglottic airway devices. Before induction, the vital parameters were as follows: blood pressure 205/120mmHg, heart rate97/min, and SaO2 93%. An epidural block was performed at the Th10-Th11 level, and the epidural catheter was advanced 20cm into the epidural space. After that, the patient was positioned in a ramp-up position. Folded towels were placed under the head and back until the ear was in the same horizontal plane as the sternum, and the patient was positioned in a slightly reverse Trendelenburg position. For premedication, we used Midazolam 1mg. Metoclopramide 20mg also was given. Pre-oxygenation was initiated with 100% oxygen via face mask for about 5 minutes, and rapid sequence intubation with Propofol 200mg and Succinylcholine 120mg was performed. General anesthesia was induced through intravenous administration of Lidocaine 80mg, Fentanyl 100mcg, Ketamine 25mg. The patient was intubated using a video laryngoscope with a D-spatula at the first attempt. A non-depolarizing muscle relaxant Roccuronium Bromide 50mg was used during the procedure. Mechanical ventilation was set on pressure controlled volume guaranteed mode (PCV-VG), with TV of 650ml and RR of 16 per minute, fresh gas flow rate: 3L/min, positive end-expiratory pressure (PEEP) of 6cmH2O, inspired oxygen fraction: 50%; partial pressure of end-tidal carbon dioxide: 37–40mmHg; and peak pressure: 28–30mmHg, I:E ratio of 1:2. Anesthesia was maintained with Sevoflurane 2% vol. Continuous analgesia was provided with the short-acting opioid Remifentanil administered via under target–controlled infusion, TCI 0,05mcg/kg/min. Bupivacaine 0.25% was used through the epidural catheter. During the procedure, Ceftriaxone 2g, MgSO4 1.5g, Famotidine 40mg, and Furosemide 10mg, were administered. The intervention lasted 3 hours and 30 minutes. During the operation, the patient was hemodynamically stable, with blood pressure around 130/80, heart rate around 90/min, and SaO2 around 95-99%. Arterial blood gas analyses were taken as well, and they were normal, Ph=7.38; pCo2=39.3mmHg; pO2=84.5mmHg; HCO3=23.2mmol/l; BE (ecf)=-1.8mmol/l. After the surgical procedure was done, the patient

was positioned in a slightly reverse Trendelenburg position, and when he started breathing on his own, Neostigmine 3mg and Atropine 1mg were administered. Extubating was done when the patient was fully awake to reduce the possibility of obstruction of his airway. Following extubating, 100% oxygen was given for about 2 minutes. The patient was then taken to the recovery room for further observation. During the entire stay in the recovery room, the patient had stable vital parameters, he was put on an oxygen mask 4L/min, his blood pressure was around 150/90mmHg, and SaO2 was around 97%. After 1 hour and 30 minutes of stay in the recovery room, the patient was successfully transferred to the Clinic of Abdominal Surgery.

Discussion

Perioperative management of obese patients is challenging, and the management of the airway in these patients requires careful planning. Patients suffering from obesity develop anatomical changes due to redundant adipose tissue in the upper airway and the head and neck areas, shoulder and back. The increased adipose tissue deposition in the upper airway leads to airway narrowing (3). A larger tongue is more difficult to displace in the submental space during laryngoscopy. Excessive soft tissue around the cheeks and face leads to difficult bag and mask ventilation. Because of their poor respiratory mechanisms, difficulty with bag-mask ventilation, and difficulty with tracheal intubation, patients with morbid obesity are considered high-risk candidates for airway manipulation (3). These include early airway closure, micro-atelectasis, decreased chest wall compliance, decreased functional residual capacity (FRC), and increased requirements for oxygen. Because the supine position leads to accelerated desaturation in patients with morbid obesity by aggravating early airway closure and atelectasis and further lowering FRC, certain modifications are needed in these patients during intubation. To facilitate intubation in these patients, the "ramp" position is recommended. In this position, the external auditory meatus must be positioned in the same horizontal position as the sternum of the patient. This position will improve mask ventilation, lung capacity, pulmonary compliance, better visualization of vocal cords, and offer a longer safe apnea period. Pre-oxygenation of these patients is very important. Due to lower FRC, high-quality pre-oxygenation is essential. When compared to patients with a normal BMI, these patients have a shorter safe apnea time and a faster time to desaturation (3). At least 5 to 10 minutes of pre-oxygenation with 100% oxygen is recommended. The ODEPHI trial (2021), a multicenter randomized study, demonstrated that high-flow nasal oxygen (HFNO) during gastrointestinal endoscopy reduces the incidence of desaturation compared to traditional oxygen therapy (4). HFNO is an advanced oxygenation technique that provides a higher fraction of inspired oxygen (FiO2) than standard systems, with flow rates reaching up to 70L/minute (5). Since we don't have HFNO in our department, we used 5 minutes of pre-oxygenation with 10L/min of oxygen via face mask and successfully increased the oxygen saturation in the patient from 93% to 99% before induction. Our initial plan for anesthesia was to perform awake intubation, but because our patient had GERD, we decided to use rapid sequence intubation versus awake intubation. We were fully aware of all the complications that can come with securing the airway in morbidly obese patients, we were prepared in advance, and we managed to avoid any complications during intubation. Our patient underwent the planned surgical procedure successfully without major complications.

Conclusion

Obesity is a condition that can have negative impacts on all organs and organic systems. Since the prevalence of obesity is increasing, anesthesiologists should adjust to the needs of these patients. With careful planning and preparation, obese patients can be successfully managed. Anesthetic management of these patients is challenging and requires a multidisciplinary approach to assure their safety. Before the intervention, the proper position of obese patients is very crucial. "Ramp position", as previously discussed, is very beneficial. This posture allows gravity to assist in the downward displacement of the diaphragm, improving lung capacity and chest wall expansion (3). Additionally, since the period of apnea can lead to rapid desaturation, it is essential to maximize oxygen reserves through effective pre-oxygenation before induction. This case report emphasizes the critical importance of proper positioning of obese patients, and pre-oxygenation, and demonstrates that with proper planning and preoperative assessment, these patients can be managed safely.

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CASE REPORT *UDK: 617.7-007.681-073.756.8*

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THE ROLE OF THE ANTERIOR SEGMENT OPTICAL COHERENCE TOMOGRAPHY IN THE DETECTION OF ANGLE RECESSION GLAUCOMA

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Abstract

Angle recession glaucoma is classified as a type of traumatic secondary open-angle glaucoma. Angular resection is strongly associated with traumatic hyphema. As many as 60% of nonpenetrating or consecutive ocular trauma will develop some degree of angle resection. The most commonly associated conditions are sports injuries (boxing, paintball), traffic accidents (impact from an airbag, other ocular trauma), physical attacks, falls from a height.

We present a case of a 27-years-old patient injured in a traffic accident in whom we diagnosed secondary glaucoma with a recession of the iridocorneal angle after blunt trauma to the eyeball.

Regression of symptoms and normalization of the condition of the left eye were monitored for one week. At the first control, the visual acuity has improved significantly. When measuring the eye's pressure of the left eye, an increase in intraocular pressure with a value of 27mmHg was observed. Asymmetry of different sectors of the angle was determined gonioscopically. Subsequently, anterior-segment optical coherence tomography was performed once again, which confirmed the presumed diagnosis.

Key Words: *angle resection; anterior-segment optical coherence tomography; glaucoma; ocular trauma.*

Introduction

Angle recession glaucoma (ARG) is classified as a type of traumatic secondary open-angle glaucoma. Traumatic glaucoma refer to a heterogeneous group of post-traumatic ocular disorders that, by a different mechanism, lead to an abnormal elevation of intraocular pressure and have an increased risk of developing optic neuropathy (1).

It has been reported that up to 60% of non-penetrating or consecutive ocular trauma will develop some degree of angle resection. The most commonly associated conditions are sports injuries (boxing, paintball), traffic accidents (impact from an air bag, other ocular trauma), physical attacks, falls from a height (1).

Angular resection is strongly associated with traumatic hyphema. As many as 60% of nonpenetrating or consecutive ocular trauma will develop some degree of angle resection. The most

commonly associated conditions are sports injuries (boxing, paintball), traffic accidents (impact from an airbag, other ocular trauma), physical attacks, falls from a height (2,3).

ARG was first described by Collins in 1892. The association between ocular trauma and unilateral glaucoma was described by D'Ombrain in 1949 (1).

Case Presentation

In this paper, we describe a case of a 27-years-old patient in whom we diagnosed secondary glaucoma with recession of iridocorneal angle after blunt trauma to the eyeball. Namely, the patient was injured in a traffic accident.

During inspection, a periocular hematoma was observed on the left eye. The best-corrected visual acuity according to Snellen optotype was 0.16. Eye pressure was digital/ normal.

The motility of the left eye was normal in all directions, without the appearance of double images.

During examination with a biomicroscope, diffuse edema of the cornea, folds of Descemet, slightly dilated pupil temporally and the presence of hyphema in the anterior chamber of the eye were observed. The posterior segment was without ability to trace details. Echography was done, without the presence of pathological content in the vitreous.

The patient was hospitalized, placed on resorptive, antibiotic therapy. Regression of symptoms and normalization of the condition of the left eye were monitored for one week, after which the patient was sent for home treatment.

At the first control, the visual acuity has improved significantly, and at the time the best corrected visual acuity was 1.0. When measuring the eye pressure of the left eye, an increase in intraocular pressure was observed with a value of 27mmHg NCT (pachymetry: 489). Biomicroscopically, the cornea was neat, transparent, anterior chamber was without side contents, pupil slightly mydriatic, temporally at 4h irregular (synechiae), lens neat. Next, gonioscopy with a Goldman lens was approached. Asymmetry of different sectors of the angle was determined gonioscopically. A large area of the ciliary body was visible especially with retrograde depression of the iris (indentation) including the ciliary processes and the circular ciliary muscle. Characteristic deepening and clefting of the angle were noted, which were expected to become more prominent with time due to atrophy and fibrosis of the ciliary muscle.

Subsequently, anterior-segment optical coherence tomography was performed once again, which confirmed the presumed diagnosis.

The patient was placed on anti-glaucomatous therapy (beta-blocker), with which the eye pressure normalized, and it continued to be normal during subsequent control examinations.

Figure 1. AS-OCT

Discussion

Angular recession is an important clinical sign of previous contusion injury. It is not responsible for glaucoma by itself. Secondary angle-recession glaucoma occurs due to more subtle changes in the trabecular meshwork.

The pathohistological mechanisms that lead to an increase in intraocular pressure are multifactorial. Five key processes are described:

First, blunt force at the time of eyeball injury causes the pupil to be pushed laterally and posteriorly toward the iris and angle. These hydrodynamic forces deepen the iridocorneal angle and increase the diameter of the corneoscleral limbal ring.

A split is caused between the longitudinal and connecting circular and oblique muscles. The tear is usually peripheral to the ciliary body circulus arteriosus and may tear the branches - the anterior and posterior ciliary arteries, the end result of which is bleeding into the anterior chamber. An eye that physiologically has a wider iridocorneal angle has a greater tendency to develop ARG than an eye that has a normal or narrow angle.

Muscles can atrophy years later after the trauma. Degenerative changes resulting in fibrosis and obliteration of the intertrabecular space and Schlemm's canal have been observed on biomicroscopic examinations. Some studies indicate that the formation of a hyaline membrane that covers the angle and is centrally connected to Descemet's membrane, may cause posterior expansion of this membrane (4,5,6).

Diagnosing angle recession is not difficult at all. As the surface of the iris is traced to its root, widening of the angle is noted. The rupture occurs in the ciliary body, between the plane of the circular and longitudinal muscle fibers. The iris and circular muscle fibers are seen posteriorly. Longitudinal muscle fibers remain attached to the scleral spur. The gap between the two is clear, and bending of the beam of the cut lamp in the region of the gap is also present. Angle recession differs from cyclodialysis in that the ciliary body detaches from the scleral spur exposing the surface of the sclera in the angle (7).

Ocular trauma is a significant cause of blindness worldwide, especially if associated with glaucoma. Direct damage from blunt or penetrating trauma, hemorrhage, inflammation, lens-related

problems, trauma-related orbital and cerebrovascular pathologies, and chemical injuries can increase intraocular pressure, and lead to traumatic glaucoma. Loss of vision can occur due to eye trauma itself or due to its complications. Glaucoma can develop over time due to significant ocular hypertension, which is a major complication of an eye that has had trauma. According to Girkin and colleagues, blunt trauma is more likely to cause glaucoma than penetrating trauma. Cession of the angle of the anterior chamber and its association with monocular chronic simple glaucoma has not been fully appreciated. Ocular hypertension can occur in the short or long term after trauma (7,8).

In clinical practice, assessment of the iridocorneal angle is done using traditional or high-tech methods. Gonioscopy is the traditional method, where a gonio lens are used to examine the angular structures in detail. In addition to being an inexpensive method, gonioscopy allows the evaluation of pigmentation and provides a dynamic assessment of the structures of the indentation angle. However, it is a method that relies heavily on the experience of the operator and the patient's cooperation, and it requires local anesthesia and careful disinfection to avoid infection. By revolutionizing ophthalmic practice, high-tech methods of diagnosis are used today, such as anterior segment optical coherence tomography (AS-OCT) (9).

Managing ARGs can be challenging. The initial treatment is medical therapy, eventually followed by surgical intervention. The treatment of this secondary glaucoma is in many ways similar to that of primary open-angle glaucoma, although miotic drugs and argon laser trabeculoplasty are controversial therapies for this condition. The only precaution is to avoid the use of prostaglandin analogues in the immediate post-traumatic period, due to their possible pro-inflammatory effect. Surgical treatment is necessary when post-traumatic glaucoma is resistant to medical therapy. In filtration surgery, mitomycin-C is recommended to prevent filtration fibrosis, which is common in eyes with prior trauma (10,11,12).

Conclusion

Following ocular trauma, it is not uncommon for many patients to develop some form of secondary glaucoma. Severe blunt ocular trauma (an ocular contusion) can lead to a glaucomatous state by producing a hyphema, angle recession and inflammation. Despite the gonioscopy in the diagnosis of ARG, AS-OCT plays a significant role as a non-invasive method. Screening for ocular hypertonia must be regular and systematic after ocular trauma involving lesion of the iridocorneal angle.

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CASE REPORT *UDK: 616.133.3-007.64-089.844*

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ONE PATIENT - TWO INTERVENTIONS: SACCULAR ANEURYSM FLOW DIVERTER AND STENT - ASSISTED ANEURYSM EMBOLIZATION

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Abstract

We present a case of a 40-years-old patient treated for brain aneurysms using a flow diverter stent for a wide-necked saccular aneurysm in the right internal carotid artery and stent-assisted embolization for a small wide-necked aneurysm in the anterior communicating artery. The intervention was executed seamlessly, showcasing a promising approach to complex aneurysm management.

Key Words: *Advanced imaging modalities; Cerebral aneurysm; Endovascular techniques; High-resolution imaging; Stent-assisted embolization.*

Introduction

Cerebral aneurysms are abnormal bulges in the wall of a blood vessel in the brain. Saccular aneurysms, also known as "berry aneurysms", are the most common type, accounting for 70-80% of the cases (1, 2). These aneurysms pose a significant risk due to the possibility of rupture, which can lead to hemorrhagic stroke and other severe neurological outcomes (3).

The management of cerebral aneurysms has evolved significantly over the years, with endovascular techniques becoming prominent due to their minimally invasive nature and favorable outcomes (4). The traditional approach of surgical clipping, although effective, is associated with higher morbidity and longer recovery times (5). In contrast, endovascular techniques offer a safer and more efficient alternative. Flow diverter stents and stent-assisted embolization are among the advanced techniques used to treat complex and wide-necked aneurysms. Flow diverter stents work by redirecting blood flow away from the aneurysm sac, promoting thrombosis within the aneurysm while preserving flow in the parent vessel (6). Stent-assisted embolization combines the use of a stent with coil embolization, providing structural support to prevent coil migration and ensuring effective occlusion of the aneurysm (7).

Recent advancements in imaging, such as high-resolution CT angiography and MRI, have further enhanced precision and effectiveness of endovascular interventions (8). These imaging modalities allow for detailed visualization of aneurysm anatomy, facilitating accurate planning and execution of complex procedures. The integration of these advanced techniques has significantly improved patients' outcomes, reducing the risk of aneurysm rupture and minimizing procedural complications (9).

This case report presents a 40-years-old male patient diagnosed with two brain aneurysms: a wide-neck aneurysm in the cavernous segment of the internal carotid artery (ACI) and a small wide-necked aneurysm in the anterior communicating artery (AcomA). What makes this case particularly interesting is the patient's complex medical history, which posed significant challenges for treatment. The decision to employ a combined endovascular approach using a flow diverter stent and stent-assisted embolization in a single session demonstrates the versatility and efficacy of these advanced techniques in managing difficult aneurysms.

This report details the decision-making process, the procedural steps and the successful outcome, contributing valuable insights to the growing body of literature on the management of complex cerebral aneurysms.

Case Presentation

The patient is a 40-years-old male with a notable medical history of uncontrolled hypertension, borderline cholesterol and triglyceride levels and class II obesity. The patient presented with neurological symptoms characterized by retrobulbar pressure, blurred vision and diplopia. An initial ophthalmologic examination revealed extensive vascular changes, prompting further evaluation through advanced neuroimaging.

Computed tomography (CT) angiography and magnetic resonance imaging (MRI) were performed, revealing the presence of two aneurysms: a wide-necked aneurysm in the cavernous segment of the right internal carotid artery (ACI) and a small wide-necked aneurysm in the anterior communicating artery (AcomA) (*Figures 1-2*).

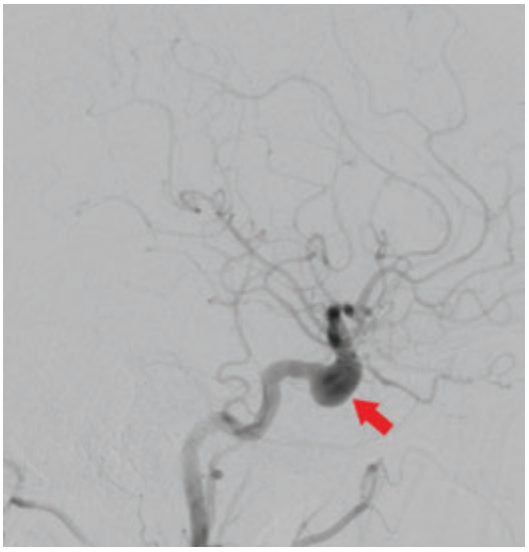

Figure 1: Saccular aneurysm in the cavernous segment of the right ACI**.**

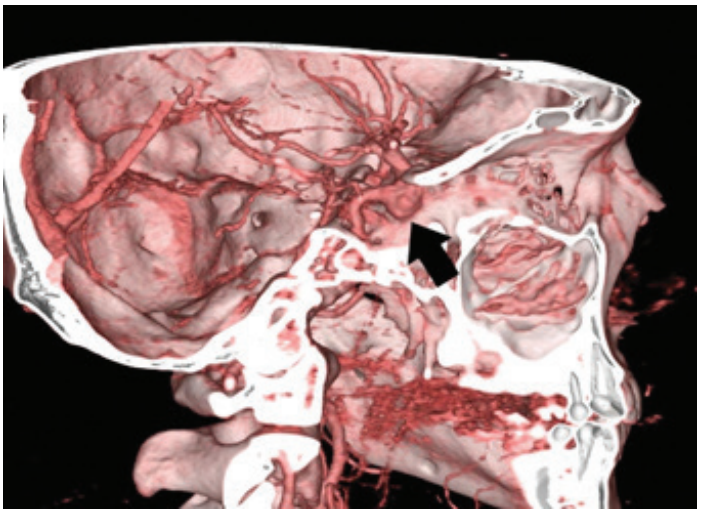

Figure 2: Wide-necked saccular aneurysm in the cavernous segment of the right ACI.

Given the complexity of the aneurysms and the patient's medical history, a multidisciplinary team decision was made to proceed with a combined endovascular approach. The procedural plan included the implantation of a flow diverter stent for the right ACI aneurysm and stent-assisted embolization for the AcomA aneurysm, executed within a single session.

Under general anesthesia, a retrograde puncture of the right common femoral artery was performed following the Seldinger technique. A long introducer sheath was advanced to the right internal carotid artery (ACI), and an access catheter was positioned. The A2 segment of the cerebral artery (ACA) was catheterized first, and a braided self-expanding stent was deployed from A2 to A1, covering the neck of the AcomA aneurysm. Immediate stasis of the aneurysm was achieved upon placement of the stent.

Subsequently, the M1 segment of the right middle cerebral artery (MCA) was catheterized, and a flow diverter stent was used to bridge the neck of the cavernous aneurysm (*Figures 3*). This resulted in the successful redirection of blood flow and subsequent stasis within the aneurysm sac. Throughout the procedure, 7500 I.U. of Heparin was administered intravenously to maintain anticoagulation. Post-procedurally, the patient was transitioned to a regimen of antihypertensive medications, nonsteroidal anti-inflammatory drugs, and dual antiplatelet therapy to prevent thromboembolic complications. Hemostasis was achieved using an AngioSeal device at the femoral artery puncture site. The intervention was completed without any immediate complications, and the patient was monitored in the intensive care unit for 24 hours post-operatively. Follow-up imaging demonstrated proper placement of the stents and successful occlusion of both aneurysms. The patient was discharged on postoperative day three, with instructions for regular follow-up and adherence to the prescribed medication regimen. At the one-month follow-up, the patient reported significant improvement in vision and no recurrence of neurological symptoms.

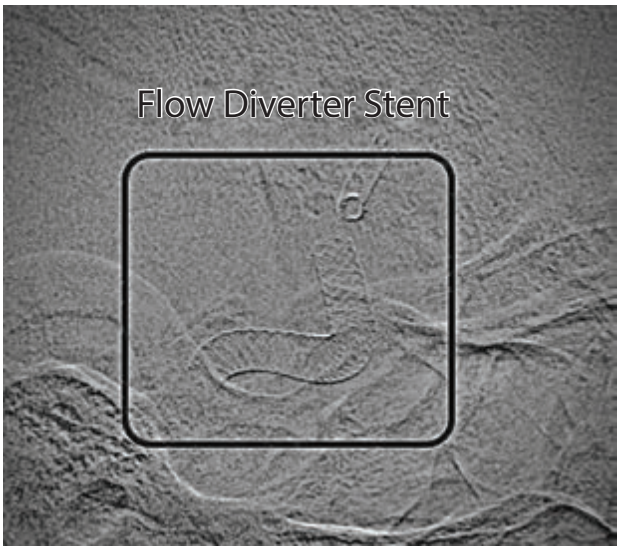

Figure 3. Flow divert stent in the right MCA.

Discussion

The treatment of complex cerebral aneurysms requires meticulous planning and execution, particularly when multiple aneurysms are present. In this case, the combination of a flow diverter stent and stent-assisted embolization provided a successful outcome without complications.

Flow diverter stents have revolutionized the treatment of wide-necked saccular aneurysms by redirecting blood flow away from the aneurysm sac, promoting thrombosis within the aneurysm while preserving flow in the parent vessel (6, 9, 10, 11). This modality was effectively employed for the right internal carotid artery (ACI) aneurysm in our patient. Stent-assisted embolization, on the other hand, involves the placement of a stent across the aneurysm neck to provide a scaffold for coil embolization (4, 7). This technique was suitable for the wide-necked aneurysm in the anterior communicating artery (AcomA), ensuring immediate stasis within the aneurysm sac (7).

This approach is backed by the latest criteria, including the 2021 updated guidelines from the American Heart Association/ American Stroke Association (AHA/ASA) for the management of patients with unruptured intracranial aneurysms (8). These emphasize the benefits of using flow diversion and stent-assisted coiling for complex aneurysms that are not amenable to simple coiling or clipping.

When comparing this case to similar cases in the literature, our findings are consistent with studies such as those by Brinjikji et al. (2020) and Cagnazzo et al. (2018), which demonstrate the efficacy and safety of using a combination of flow diverters and stents in managing multiple aneurysms (6,7).

The decision-making process for choosing these specific interventions involved evaluating the size, shape and neck morphology of the aneurysms, along with the patient's overall health status and risk factors such as uncontrolled hypertension and obesity. Alternative treatment options, such as microsurgical clipping or standalone coiling, were considered. However, these options

were deemed less favorable due to the patient's medical history and the anatomical challenges presented by the wide-necked aneurysms. Endovascular approaches offered a minimally invasive solution with a lower risk profile and faster recovery (12).

The outcomes of this case underscore the potential for improved patient's prognosis through integrated treatment. The seamless execution of both interventions in a single session not only minimized the procedural risks, but also facilitated an efficient recovery process. This successful case contributes to the growing body of evidence supporting the use of advanced endovascular techniques for complex aneurysm management.

Conclusion

The successful treatment of a 40-years-old male with complex cerebral aneurysms using a combination of flow diverter stenting and stent-assisted embolization, underscores the efficacy and safety of these advanced endovascular techniques. This case highlights the importance of a multidisciplinary approach and personalized treatment plans in managing challenging aneurysms, particularly in patients with significant comorbidities.

High-resolution imaging facilitated precise diagnosis planning, leading to a seamless intervention without complications. The patient's significant postoperative improvement underscores the advantages of minimally invasive endovascular strategies over traditional surgical methods. This case contributes to the growing body of evidence supporting flow diverter stents and stent-assisted embolization for wide-necked and complex aneurysms. It emphasizes the necessity of preventive healthcare and adherence to medical advice in managing cerebrovascular conditions.

In conclusion, the innovative use of advanced endovascular techniques in this case exemplifies the potential for achieving excellent clinical outcomes and the evolving landscape of cerebral aneurysm management.

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PREGNANCY IN A PATIENT WITH A CONGENITAL UNICORN UTERUS AND CONIZATION DUE TO CERVICAL CANCER

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Abstract

Introduction: A unicornuate uterus can cause gynecological and obstetrical complications, such as hematometra, infertility, miscarriage and premature births. However, in some cases, despite the small capacity of unicornuate uterus, a successful pregnancy with the birth of a healthy and viable fetus is still possible, as in this case.

Case Report: We present a case of a 39-years-old patient, who delivered a fetus prematurely at 32 weeks of pregnancy, conceived by IVF. What is important about this case is that the patient had a congenital unicornuate uterus with a small capacity, and in which 18 months before conception, a conization was performed, due to a diagnosed carcinoma of the cervix. After conization and two negative Pap smears, after 8 months, the patient was suggested to start trying to get pregnant. Since there was no success with spontaneous pregnancy in the next 10 months, it was decided that the patient would become pregnant with an IVF procedure. The patient became pregnant during the first IVF attempt and after the first embryo transfer, the pregnancy began to develop successfully. At the beginning of pregnancy, the length of the cervix was 25mm. and the first shortening on the cervix was observed at 21st week of pregnancy, when the measured length was 20mm. Strict rest, progestogens and tocolytic therapy were indicated, with which the first contractions were delayed and appeared for the first time at 26th week of gestation. Two maturations of the fetal lung of the fetus with corticosteroids were carried out at 28 and 31 weeks of pregnancy, and due to increased contractions, the process of delivery began at 32nd week of pregnancy, when it was decided to end the birth by Caesarean section. The patient gave birth by caesarean section to a live male fetus weighing 1,345 grams and 40cm length and with APGAR score 6/7/7 at 32.2 gestational weeks. The caesarean section went without complications and the patient left the hospital three days after the operation. The newborn had a proper adaptation after delivery and was placed in the NICU, where he spent 29 days, without major complications, with spontaneous respirations only on the support of diffused oxygen in the first ten days.

Conclusion: Despite the fact that it is difficult to achieve a successful pregnancy with the birth of a live and healthy fetus in patients with congenital unicornuate uterus, and in this case complicated by shortening of the cervix before pregnancy due to conization, however, with good pregnancy management, delivery of a healthy fetus is possible in such cases as well. Even though the pregnancy in such cases cannot last until the due date, with timely prescription of corticosteroids and termination of the pregnancy to the maximum gestational week, a healthy and vital fetus can still be obtained.

Key Words: *caesarean section; conization; microinvasive carcinoma; preterm delivery; unicorn uterus.*

Introduction

Unicorn uteri account for 2-13% of all genital Müller duct anomalies occurring in women. Anomalies of the Müllerian ducts, such as a unicornuate, bicornuate, or septate uterus, occur in 5-10% of women of reproductive age who have had a miscarriage (1). Uterine anomalies lead to spontaneous abortions, preterm births, fetal malpresentation, rupture of the amniotic fluid, placental abruption, increased number of caesarean sections and intrauterine fetal growth retardation (2, 3). Only 29% of women with a unicornuate uterus give birth, and 44% end up giving birth prematurely (4, 5). 24% of these pregnancies end with spontaneous abortion in the first trimester, and about 20% in the second trimester with the birth of immature fetuses (4-6,7). In these pregnancies with a unicornuate uterus, there is a risk that a rupture of the horn may occur in over 50% of the patients, mostly at the end of the second trimester (8).

The use of progesterone in these pregnancies has been shown to be an important factor in maintaining these pregnancies, despite the fact that its effectiveness decreases with increasing of the gestational age (5).

Case Presentation

This is a case of pregnancy in a patient after conization and with a congenital unicornuate uterus with a small capacity, who carried the pregnancy and gave birth prematurely at 32 weeks of pregnancy.

A 37-year-old patient, without previous conception and childbirth, came for a consultation about getting pregnant, after two years of marriage. At the first consultation, a routine gynecological examination was performed, during which a Pap smear was taken, and an ultrasound of the genitals was performed, which detected a uterus with a smaller capacity and two ovaries of normal size and morphology.

The result of the Pap smear after one week showed a suspicion of squamous cell carcinoma, after which a colposcopy of the cervix was performed with a positive finding for a cancerous process on the posterior lip of the cervix, after which a biopsy of the cervix was indicated.

After a certain preparation of the patient, in the middle of the menstrual cycle and after the end of the patient's menstruation, a biopsy of the cervix and endocervical curettage was performed and the obtained material was sent for histopathological analysis. The biopsy result showed squamous cell microinvasive carcinoma (T1A1). The obtained result of the biopsy indicated to make a diagnostic conization, as the next step.

The patient was prepared and the following month, conization with an ultrasound knife was performed, after which the histopathological diagnosis was confirmed for microinvasive squamous carcinoma of the cervix on the posterior lip, with the greatest depth of invasion up to 1mm, (PT1A1), and lines of the operative incision endo and exocervical passed through healthy tissue.

The patient's condition was monitored postoperatively and after two Pap smears with good results and a colposcopy with good results, the patient was advised to try to get pregnant.

Next, an HSG (Figure 1) was performed, and it was confirmed that it was a congenital unicornuate uterus with only the right horn developed, with a normal right tube and agenesis of the left tube and with one cervix.

There were also two unsuccessful inseminations after one year of conization of the patient.

After 18 months without successful conception, it was decided to implement a stimulation protocol for the patient and IVF. After the stimulation protocol was performed, the patient's follicles were punctured, 3 oocytes were obtained, two of which were fertilized, and it was decided to return only one embryo with embryo transfer to the right horn of the patient's uterus.

After two weeks of the embryo transfer, we received a positive pregnancy test and after 4 weeks of the embryo transfer, a vaginal ultrasound detected a fetus in the uterus, with a positive heartbeat (Figure 2).

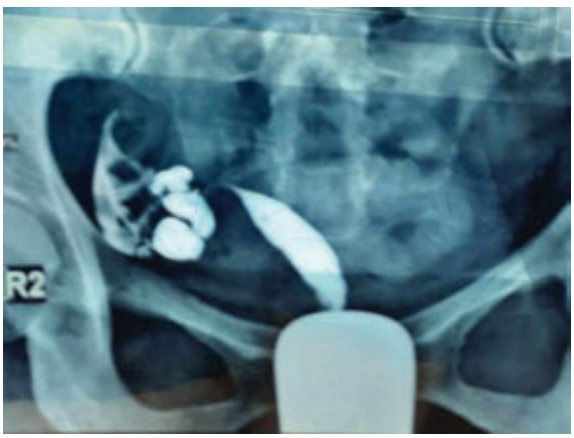

Figure 1. HSG- hysterosalpingography

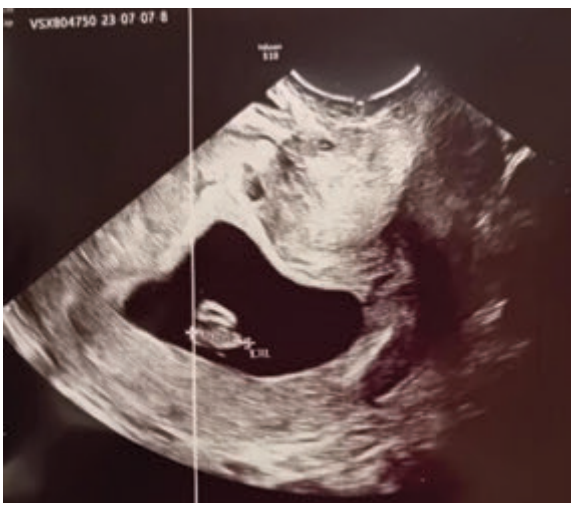

Figure2. Pregnancy detection with US

The pregnancy was managed actively, with frequent controls and monitoring of the growth and progress of the fetus, as well as with measurements of the cervix, which was shortened and 25mm long from the beginning of the pregnancy, due to a previous conization of the patient.

The pregnancy was monitored by protocol with all: ultrasound, biochemical, infectious and genetic screenings. During the entire pregnancy, progesterone was administered orally and vaginally to the patient, as well as magnesium and with a recommendation for strict rest.

Ultrasound examinations monitoring of fetal growth and development and cervical length were performed every 2-3 weeks. Detailed ultrasound screenings of the fetus were performed in the first (Figure 3) and second trimesters (Figure 4) of pregnancy, infectious screenings by taking microbiological smears and serological analyzes at the end of the first trimester in the 12th week of gestation, biochemical investigations and genetic screening due to the mother's age - 39 years were performed, and were with normal finding.

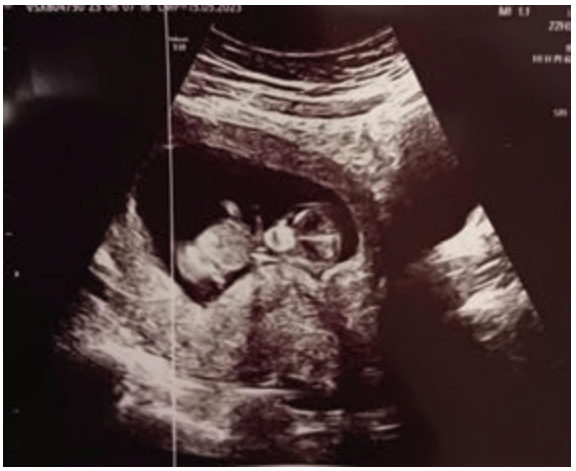

Figure 3. US screening in 1st trimester

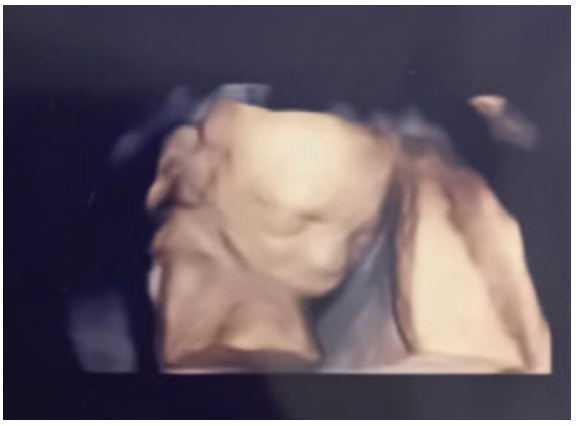

Figure 4. US screening in 2nd trimester

The patient was also monitored for laboratory analyses, glycemia and blood pressure measurement during pregnancy, which fortunately were normal all the time and were not a factor in complicating the pregnancy.

In the 15th week of pregnancy, the cervix was 25mm long, it had not been further shortened since the beginning of pregnancy, and therefore it was decided not to place a cerclage, but to intensively monitor and treat infections during pregnancy, which can lead to shortening of the cervix and also to prevent its shortening of the cervix by local and systematic use of progestogens.

At 21st week of pregnancy, the first shortening of the cervix by 5mm was observed, and the cervix was 20mm long. The patient was advised to have further therapy with progestogens, tocolytics and strict rest.

The first mild contractions of the uterus appeared in the 26th week of pregnancy, and the first ripening with corticosteroids, for pulmonary ripening due to the risk of premature birth, was carried out in the 28th week of pregnancy.

Measurements of the length of the cervix showed 15mm, and further strict rest, progestogen therapy and tocolytics were advised. The contractions continued and the second ripening was carried out at 31st week and due to the strong contractions and the opening of the cervix of 3cm, it was decided to end the delivery by Caesarean section at 32.2 weeks of pregnancy.

The patient gave birth by caesarean section at Gynecology and Obstetrics Clinic in Skopje, to a live male fetus with weight 1,345 grams and 40cm length and with APGAR score 6/7/7. The caesarean section went without complications and the patient left the hospital three days after the operation. The newborn had a proper adaptation after delivery and was placed in the NICU, where he spent 29 days, without major complications, with spontaneous respirations only on the support of diffused oxygen inthe first ten days.

The newborn developed a neonatal infection that was treated with an antibiotic and jaundice that was treated with hydration and ultraviolet lamp tanning. The newborn at discharge from the hospital, after spending 29 days in the OINT after delivery, had a developed sucking reflex and weighed 1,850g, with advised regular neonatological controls.

Discussion

This is a successful pregnancy story, in a mother with congenitally small uterine capacity – a unicorn uterus and a shortened cervix due to a conization performed before pregnancy. With good preparation of the patient, despite the small capacity of the uterus and short cervix, as well as good management during pregnancy, with appropriate examinations, therapy and rest during pregnancy, all led to a successful end of pregnancy, with premature delivery of a healthy newborn (4, 5).

With a small capacity of the uterus and a shortened cervix and with the entire regime that was imposed on the patient during the pregnancy by the doctors who managed the pregnancy, with timely maturation with corticosteroids for pulmonary maturity, the maximum delay of the pregnancy was reached until 32nd gestational week and finished with premature delivery with viable fetus.

In these patients, spontaneous abortions and premature termination of pregnancies even before the end of the second trimester, with the birth of immature fetuses, which are not capable of life, are common (2, 3).

Ultrasound and imaging techniques in such cases are essential as diagnostic methods in pregnancy planning and management, as well as for monitoring the growth and development of the fetus in the uterus, as well as for measuring the cervix.

Conclusion

Despite the fact that it is difficult to achieve a successful pregnancy with the birth of a live and healthy fetus, in patients with congenital unicorn uterus, and in this case complicated by shortening of the cervix before pregnancy due to conization, however, with good pregnancy management, delivery of a healthy fetus is possible in such cases as well. Even though the pregnancy in such cases cannot last until the due date, with timely prescription of corticosteroids and termination of the pregnancy to the maximum gestational week, a healthy and vital fetus can still be obtained.

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CASE REPORT *UDK: 616.056.7:618.5-089.888.61*

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SUCCESSFULLY COMPLETED PREGNANCY IN A PATIENT WITH KLIPPEL FEIL SYNDROME (KFS)

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Abstract

Klippel-Feil syndrome is a congenital anomaly characterized by fusion of two or more cerebral vertebrae. The three main manifestations are a low hairline, a short neck and limited neck movement. This syndrome can cause chronic headaches and neck and back pain.

Klippel-Feil syndrome is diagnosed by clinical evaluation, identification of characteristic physical findings and specialized tests. Diagnosis begins with X-rays or other advanced imaging techniques, such as Magnetic Resonance, which shows the fusion of the cervical vertebrae and the open spaces (interspaces) between the vertebrae. Treatment: Therapy is symptomatic and supportive. Careful evaluation, continuous follow-up, and coordination of multiple specialists are required to improve the outcome.

The patient is thirty years old, with a fixed diagnosis of Klippel-Feil syndrome, thoracis scoliosis, pre-existential hypertension, deafness. During the examination, it was established that it is a eutrophic fetus, without major anomalies, orderly fetoplacental flow, orderly fetal movements. A recommendation was given to do control examinations at the Clinic for Pulmonology, Orthopedics, Cardiology and Nephrology. The next two controls were on a weekly basis until the 27th gestational week, when, due to malignant hypertension, admission was done to PHI GAK. During hospitalization, high values of the angiogenic factors sFLT/PLGF up to 793.05, proteinuria 0.79g/L and malignant hypertension regulated by double antihypertensive therapy were determined. NST was reactive. The ultrasound finding was normal, the fetus had a normal fetoplacental flow. After detailed anesthetic preparation, the patient was delivered by elective caesarean section at 28.5 weeks of gestation and a live female fetus was obtained with RTM=920g/35cm and AS=6/7/7. The intervention went smoothly.

Key Words: congenital anomaly, *Klippel-Feil syndrome, pregnancy.*

Introduction

Klippel-Feil syndrome (KFS) is a congenital anomaly characterized by fusion of two or more cervical vertebrae. The main three manifestations are a low hairline, a short neck and limited neck movement. This syndrome can cause chronic headache and neck and back pain (1).

It was described by Maurice Klippel and Andre Feil separately. The exact incidence of this disorder is unknown. It is assumed to be around 42,000-50,000 livebirths. It occurs more often in female individuals (about 65%). KFS type 2 (Figure 1.) is the most common one (2).

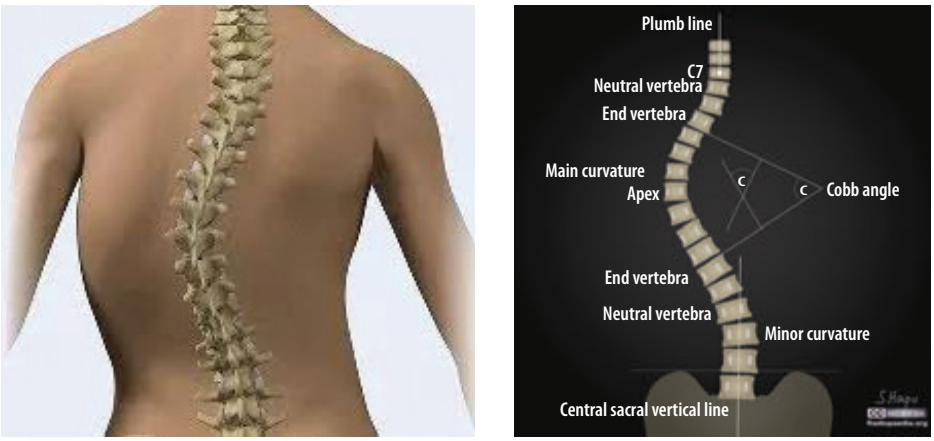

Figure 1

In KFS, it may be accompanied by other conditions and abnormalities:

- Scoliosis,
- Cervical dystonia,
- Genitourinary abnormalities,
- Sprengel deformity (small and not lowered scapula),
- Heart deformities,
- Pulmonary abnormalities and respiratory problems,
- Hearing problems,
- Facial asymmetry,
- Torticollis,
- Central nervous system abnormalities,
- Other skeletal abnormalities,
- Situs inversus,
- Synkinesis (movements of one hand involuntarily imitate the intentional movement of the other hand).

The exact cause and mechanism of KFS is not exactly known. Medical research believes that KFS occurs when embryonic tissue that normally develops into individual vertebrae does not divide correctly (3).

Isolated KFS may be sporadic or hereditary. KFS can sometimes occur as a combination of genetic and environmental factors, mutations, and at least 3 genes are associated with the onset of KFS.

Sometimes, KFS occurs randomly, and sometimes it is genetic and runs in several family members. Autosomal dominant and autosomal recessive inheritance, with different genes (4).

When KFS is caused by mutations in GDF6 or GDF3, it is inherited in an autosomal dominant manner.

When KFS is caused by mutations in the MEOX1 gene, it is inherited in an autosomal recessive manner (4,5).

KFS is diagnosed by clinical evaluation, identification of characteristic physical findings and specialized tests. Diagnosis begins with X-rays or other advanced imaging techniques, such as Magnetic Resonance, which shows fusion of the cervical vertebrae, open spaces (interspaces) between the vertebrae and possible pressure on the spinal cord. X-rays of the entire spine are performed to detect other spinal abnormalities. KFS can be associated with a wide range of abnormalities involving other parts of the body. Therefore, it is necessary to do:

- Examination of the chest to determine the disorder of the heart and lungs.
- Examination of the chest to detect abnormalities of the ribs.
- MRI for spinal stenosis or neurological deficit.
- Ultrasound of the kidneys or renal anomalies.
- Hearing evaluation due to high incidence of hearing loss.
- Various laboratory tests to determine the functioning of the organs (5).

Treatment**:** There is no cure for this syndrome. Therapy is symptomatic and supportive. Careful evaluation, continuous follow-up, and coordination of multiple specialists are required to improve outcome, and additional scans may be needed to determine the exact abnormality (6).

Neck collar, traction, physical therapy, non-steroidal anti-inflammatory drugs, analgesics can be used. In most people, the symptoms are progressive due to the degenerative changes that occur in the spine.

Surgical intervention may be indicated for various reasons, such as persistent pain, neurological deficit, neck instability, spinal cord constriction or to correct severe scoliosis. Sometimes surgical intervention is needed to improve other skeletal anomalies, or those associated with the heart, kidneys, etc.

Those with an increased risk of neurological complications should be regularly monitored by health professionals and advised to avoid activities that may lead to trauma or injury to the cervical vertebrae.

The prognosis for people with CFS varies depending on the specific characteristics and severity of the affected person. People with minimal fusion of the cervical vertebrae can lead a normal, active life and may not have significant restrictions. People with severe forms of CFS require close monitoring but may have a good prognosis if symptoms and complications are properly treated (7).

Case Presentation

Our patient is thirty years old, with a fixed diagnosis of Klippel-Feil syndrome, thoracis scoliosis, pre-existential hypertension, deafness. At the age of one year, cheilognathopalatoschisis was corrected, nephrolithiasis was present.

At the University Clinic of Gynecology and Obstetrics, the patient appears for the first time at 24.3 weeks of gestation, in an outpatient clinic where she has a scheduled screening examination in the second trimester Figure 2.

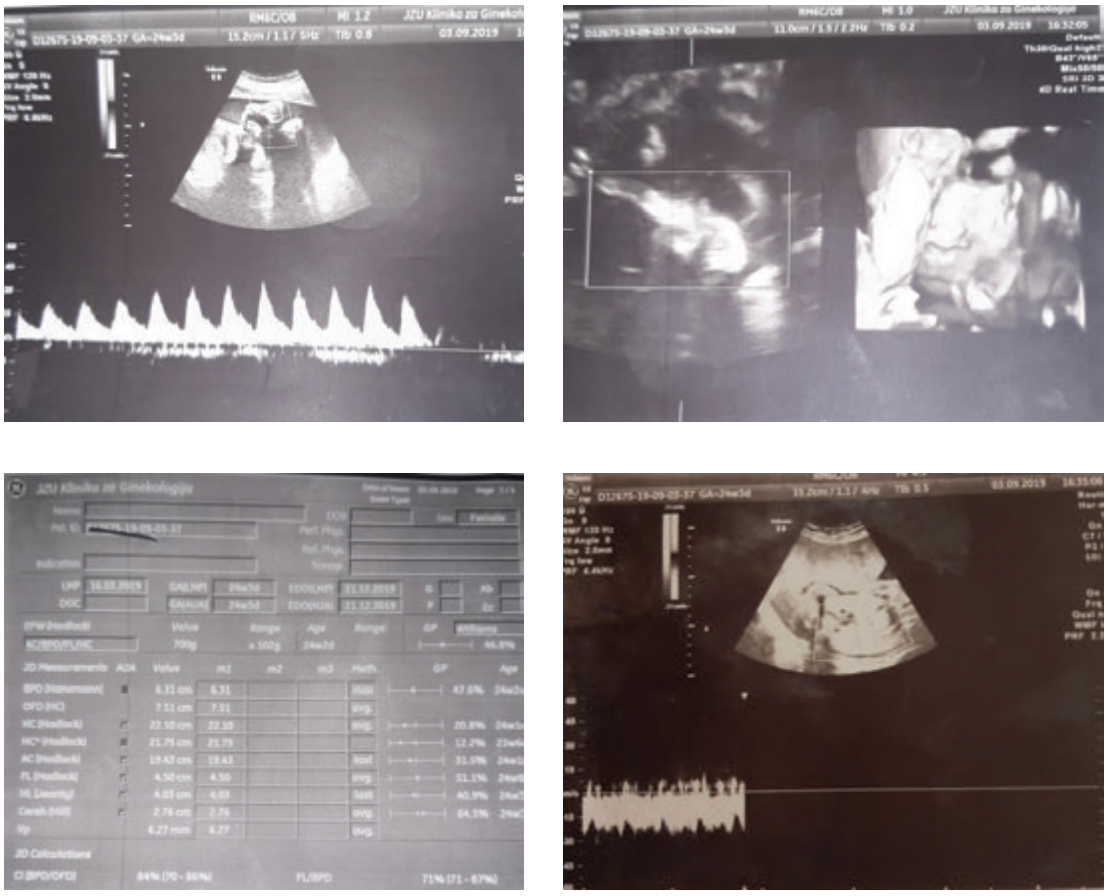

Figure 2

During the examination, it was established that it was a eutrophic fetus, without major anomalies, normal fetoplacental flow, normal fetal movements. A recommendation was given to do control examinations at the Clinic for Pulmonology, Orthopedics, Cardiology and Nephrology. At the control examination after 1 week, the patient had an examination only at the Pulmonology and Orthopedics Clinic, where appropriate therapy was prescribed. Laboratory analyzes were in reference values. Blood pressure was regulated by antihypertensive therapy.

The next two controls were on a weekly basis until the 27th gestational week, when, due to malignant hypertension, she was initially admitted to the Department of Pathological Pregnancy, and then transferred to the Department of Peripartum Intensive Care. During the hospitalization, therapy for fetal lung maturation, antihypertensive and neuroprotective therapy was prescribed. A series of council examinations were performed by a nephrologist, cardiologist (correct findings), pulmonologist and otorhinolaryngologist. It was communicated with the patient with a sign language professional.

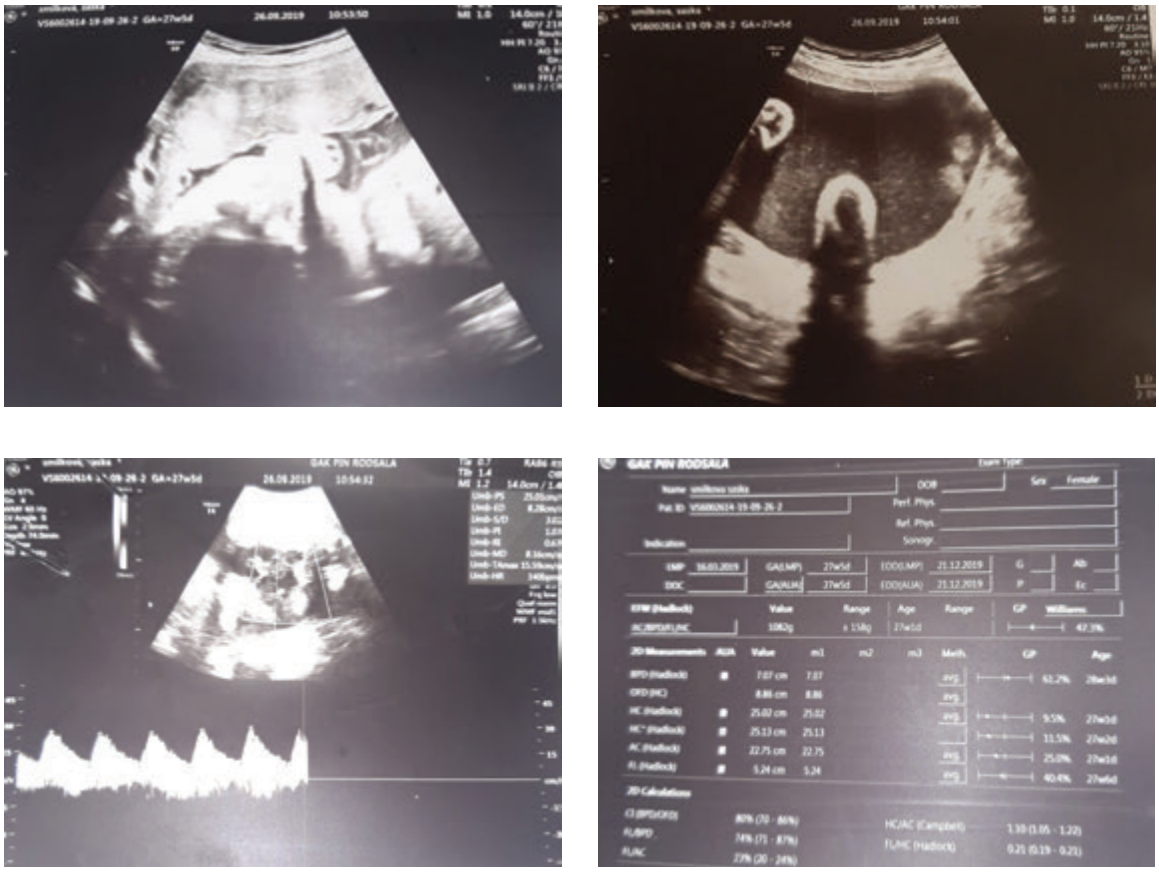

Figure 3

During hospitalization, high values of the angiogenic factors sFLT/PLGF up to 793.05, proteinuria 0.79g/L and malignant hypertension regulated by double antihypertensive therapy were determined. NST was reactive. The ultrasound finding was normal, the fetus had a normal fetoplacental flow.

After detailed anesthetic preparation, the patient was delivered by elective caesarean section at 28.5 weeks of gestation and a live female fetus was obtained with RTM=920g/35cm and AS=6/7/7. The intervention went smoothly. Postoperatively, the hypertension was regulated, the wound healed per primam, and she was discharged from the clinic on the third postoperative day. After 82 days of stay in the Department of Intensive Care and Therapy, the newborn was discharged in a stable condition and current weight of 1920g.

A few years later, it can be seen that the newborn is developing normally. I am happy that the girl has normal growth and development and does not lag behind her peers. A mother is filled with love and has a purpose in life. A beautiful picture of a happy family.

Conclusion

Although the Klippel-Feil syndrome is rare and described disorders make treatment difficult, with careful preparation, the pregnancy can be successfully terminated. Difficulties can be successfully overcome with a multidisciplinary approach.

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CASE REPORT *UDK 616.831-002-073.763.5:618.3*

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WERNICKE`S ENCEPHALOPATHY AS A RARE COMPLICATION OF HYPEREMESIS GRAVIDARUM

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Abstract

Wernicke's encephalopathy (WE) is a neurological condition caused by thiamine deficiency (vitamin B1) and it is the most commonly seen in chronic alcoholics. Other etiologies, connected to this pathology, are malnutrition, hemodialysis, gastrointestinal surgery, hyperemesis gravidarum (HG), etc. Clinical criteria of WE are altered mental status or memory impairment, oculomotor dysfunction and cerebellar dysfunction. Cerebral magnetic resonance is the diagnostic of choice. Wernicke's encephalopathy in pregnancy is a result as a complication of HG.

We present a case of pregnant women in her 16th gestational week who was presented with consciousness impairment, nystagmus and ataxia, and suffered for a month before receiving her initial WE. As a diagnostic method, magnetic resonance of brain was performed with characteristic signs of WE.

Key Words: *Case report; Hyperemesis gravidarum; Magnetic resonance; Radiology; Wernicke encephalopathy.*

Introduction

Wernicke's encephalopathy (WE) is a reversible rare neurological condition caused by hyperemesis gravidarum (HG) due to thiamine (vitamin B1) deficiency.(1,2)

Chronic alcoholism (the most common), Hyperemesis gravidarum, malnutrition, inflammatory bowel disease, etc., can lead to WE. (3)

Clinical criteria of WE are characterized by mental status alteration, ophthalmoplegia, and ataxia triad. If there is one or two of the previous symptoms in correlation with clinical, laboratory and diagnostic findings, the diagnosis of WE can be confirmed.(4) This case is to present the importance of MRI in early diagnosis of WE in pregnant women.(5,6)

This is a case of women in her 2nd trimester of pregnancy with HG that developed the typical symptoms of WE and characteristic imaging findings on the brain imaging. On MRI, there are distinct pattern of alterations that include symmetrical alteration in the mamillary bodies, thalami, Tectal plate and periaqueductal area.

Case Presentation

A 38-years-old pregnant patient at 15 weeks and 6 days of gestational age, in her third pregnancy, presented with symptoms of weakness, spontaneous nystagmus, ataxia, mental confusion and amnesia.

One month before this visit, she was hospitalized for a week for extreme vomiting due to the Hyperemesis gravidarum.

Laboratory tests showed the following changes: thiamine level (50nmol/L), drop in hemoglobin levels (103mg/dl, reference: 120-180g/l), albumin (28g/l, reference: 35-52mg/dl), CRP (34 reference level <5) and increased liver enzymes AST (332U/L, reference 5-34U/L), ALT(523U/L, reference 9-55U/L) and LDH (363U/L, reference 125-220U/L).The other performed exams, did not show significant deviations. The ultrasound exam showed a live fetus.

MRI of brain was obtained using postcontrast sequences with sagittal and axial T1, axial T2 and FLAIR and diffusion weighted imaging (DWI). On T2/FLAIR sequences there were hyperintensities in the medial part of both thalami and periaqueductal areas (Figure 1), which also showed DWI restriction - highly suggestive for of Wernicke´s encephalopathy (Figure 2).

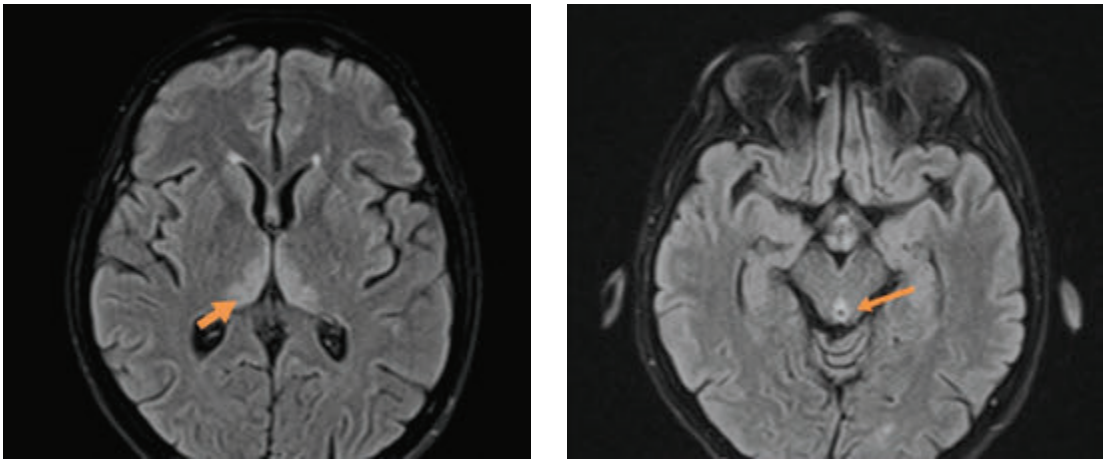

Figure 1. Presentation of hyperintensities in thalami and periaqueductal areas on MRI brain in T2/FLAIR sequence.

As a result of the clinical symptoms, laboratory analyses and the findings from the magnetic resonance, the diagnosis was in favor of WE, and intravenous administration of thiamine was initiated.

For the safety of the patient induced abortion was suggested and with consent of the mother, the abortion was performed.

During the time of hospitalization, an improvement in the patient`s condition was observed.

Control MRI of the brain was performed. This follow-up showed a resolution of previously bilateral hyper intense signals regions on T2/FLAIR sequence, with progressive reduction of hypersignal changes of bilateral thalamic regions of restricted diffusion (Figure 3).

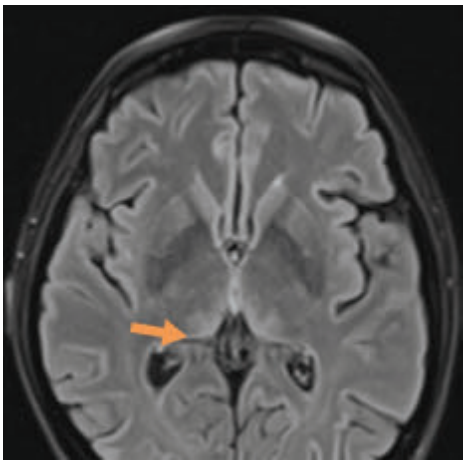

Figure 3. Presentation of reduction of hypersignal changes of bilateral thalamic regions on T2 FLAIR on MRI.

Discussion

Hyperemesis gravidarum is a condition that occurs very frequently in early pregnancies and can lead to weight loss, malnutrition, dehydration, but in very rare cases can cause rare neurological complications as WE.(7)

The patient in this case, presented with the triad of symptoms typical for WE: ataxia, spontaneous nystagmus, mental confusion, and previous history of hyperemesis gravidarum.(2,8)

The laboratory results showed low levels of vitamin B1 and obtained MRI showed characteristic findings for WE.

The diagnosis of WE is based by clinical presentation, but the definitive diagnosis can be accomplished with MRI which shows bilateral symmetrical low T1, high T2 and FLAIR signal intensity with restricted diffusion of the medial thalami, periaqueductal area, mamillary bodies, etc.(9)

The treatment should include a high dose of thiamine replacement.(10)

Conclusion

WE as a complication of HG is rare neurological condition.

Small possibility of WE at pregnant patients should be treated immediately with thiamine iv administration. Undiagnosed WE could cause neurological morbidity and mortality.

The complementary approach of clinical exam, laboratory results and typical MRI findings lead to early recognition and better outcomes for the patients.

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RISK OF TRANSMISSION OF HIV INFECTION DURING PROFESSIONAL EXPOSURE AT DENTISTS

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Abstract

The transmission of blood-borne diseases, such as HIV infection, hepatitis B and hepatitis C virus infection, still represents a risk for professional exposure among healthcare workers today.

We present the case of a 39-years-old female patient, first diagnosed with HIV infection in November 2021. As a result of antiretroviral therapy efficiency, undetectable values of HIV RNA viral load in serum and immune reconstitution were achieved.

In December 2023, the patient was presented to the University Dental Clinical Center due to tooth pain for a dental examination. A diagnosis of chronic apical periodontitis of the tooth (VI lower right) was made, after which the patient was advised to continue treatment at the Clinic of Oral and Periodontal Diseases. After the examination, presence of dental plaque cleaning was done, and a drain was placed in the periodontal pocket after curettage. During the examination and dental interventions, the medical staff used standard protective equipment, protective gloves, a mask and protective glasses. Examination and treatment procedures were carried out in compliance with the appropriate protocols of evidence-based medicine, and the correct disposition of the used medical material was made.

Key Words: *chronic apical periodontitis; HIV infection; professional exposure.*

Introduction

The transmission of blood-borne diseases, such as HIV infection, hepatitis B and hepatitis C virus infection, still represents a risk for professional exposure among healthcare workers today. Based on data from the World Health Organization (WHO), it is estimated that approximately 2.5% of HIV infections, 40% of hepatitis B and hepatitis C virus infections among health workers are the result of professional exposure (1).

HIV infection is transmitted through direct contact with body fluids containing the HIV virus from an HIV-infected person, as blood, breast milk, seminal fluid and vaginal secretions. Also, HIV can be transmitted by vertical transmission from mother to child during pregnancy and childbirth (2).

Professional exposure to HIV infection in healthcare workers is the most often through percutaneous injuries involving needlesticks or cuts from sharp objects, contact with mucous membranes or skin (especially if the skin is damaged due to injuries or dermatitis, or if the contact is prolonged or larger areas of skin surfaces are affected), with HIV-infected body fluids. Many factors influence the risk of professional transmission of HIV infection, such as the use of personal protective equipment, the type of injury, the prevalence of HIV infection in the country, the frequency and number of exposures, and of course the level of HIV RNA viral load at the source of HIV infection (3). It is important to note that persons with HIV infection who regularly receive antiretroviral therapy (ART) and have undetectable values of HIV RNA viral load in serum determined by polymerase chain reaction (PCR-polymerase chain reaction), cannot transmit the virus to their sexual partners (2). According to the data from the Centers for diseases control and prevention (CDC) the risk of professional transmission of HIV varies by the type of exposure and it is almost equal to zero in the case of splashing body fluids containing the HIV virus even in cases where there is presence of blood, extremely low in cases of splashing of HIV-infected body fluids on intact skin or mucous membranes and less than 1% in case of percutaneous injuries (needle stick) (4).

The estimated risk of transmission of HIV infection from percutaneous exposure to HIV-infected blood is approximately 0.3%, from exposure to mucous membranes approximately 0.09%, and the risk from eye, nose or mouth exposure to HIV-infected blood is estimated to be approximately 0.1% (1 in 1000) (1).

Dentists play an important role in ensuring the oral health of patients with HIV infection. More than 40 types of oral manifestations are present as clinical manifestations in people with HIV infection, and between 70 and 90% of people living with HIV will have at least one oral manifestation of the disease during their lifetime. Therefore, people with HIV infection need dental care (5).

Some oral manifestations of HIV infection have important diagnostic significance and show the progression of the disease, some cause pain and discomfort, and sometimes they can be life-threatening. The available information is that the risk of transmission of HIV infection in dental offices is very low. The risk of transmission of HIV infection during dental interventions for health professionals is low, due to the fact that saliva does not contain the HIV virus unless it is contaminated with blood (5).

In dentistry, accidental contact with blood occurs when closing syringe needles, during surgical interventions, biopsies, sutures, when disposing of used needles in containers or during transportation of medical waste (1). The specific nature of interventions in dental health care requires the existence of specific strategies and protocols in order to prevent the transmission of HIV infection at dental offices (5).

Prevention of occupational exposure to HIV according to CDC recommendations, is the application of standard protective measures at all times during work with patients, assuming that all blood and body fluids are potentially infected. It is also recommended to use protective gloves, protective glasses, masks and clothing when in contact with body fluids or blood, wash hands

and other skin surfaces immediately after contact with blood or body fluids, careful handling and disposal of sharp objects during and after the interventions, use of safe equipment for the prevention of needlesticks, correct disposition of medical waste and sharp objects in containers, reporting the exposure to an appropriate medical person, application of post-exposure prophylaxis (PEP) after an assessment by the medical person (4).

Today, the highly effective ART used in the treatment of HIV infection enables the suppression of viral replication and the drop of the viral load in HIV-infected persons to undetectable values, so that at the same time these persons cannot transmit the infection. WHO recommends the use of ART as PEP in order to prevent the occurrence of HIV infection during professional exposure (2). HIV PEP reduces the possibility of transmission of HIV infection if given within a maximum period of 72 hours after exposure to HIV. The earlier HIV PEP is started, it is better, every hour after exposure is important and counts (4).

In June 2021, in the Republic of North Macedonia an instruction for the application of PEP after professional exposure to HIV was adopted (6). Through the presentation of this case, the importance of informing health personnel about the existence of preventive measures in case of risk exposure to body fluids from an HIV-infected person will be emphasized, which will contribute to reducing the possibility of transmission of HIV infection among health workers, as well as reducing discrimination and stigma for working with people living with HIV.

Case Presentation

We present a patient aged 39 years, female, single, smoker, one pack of cigarettes per day, employed in the food industry, first diagnosed with HIV infection in November 2021.

According to the epidemiological data obtained from the history of the disease, the transmission of HIV infection occurred through heterosexual way. The patient was tested for HIV infection at the Institute for Transfusion Medicine in Skopje, when donating blood according to the rules for criteria and procedures for assessment and testing of blood or blood component donors, in accordance with the principles of good transfusion practice published in the official paper in 2009. As part of the blood testing protocol for voluntary blood donors, in addition to testing for blood group and Rh factor, tests for antibody detection, testing for syphilis, testing for hepatitis B and C, the presence of antibodies to the cause of the syndrome was also tested of acquired immunodeficiency (AIDS)-HIV virus. After receiving a positive result for HIV antibodies, the patient was referred to the PHO University Clinic for Infectious Diseases and Febrile Conditions in Skopje as a reference institution, in order to confirm the diagnosis of HIV infection. At the clinic, confirmatory tests of the fourth generation Enzyme linked immunoassay (ELISA) were performed for the detection of antibodies to HIV and p24 antigen, as well as the detection of antibodies by Western blot. The combination of these two tests to confirm the diagnosis of HIV infection has an accuracy of 99.9% (7). The patient was without subjective symptoms and has no history of other past diseases.

After confirming the patient's HIV infection, a procedure of investigations was started, which included a set of laboratory biochemical and serological investigations, screening for tuberculosis and determination of the degree of immunodeficiency caused by the HIV virus according to the recommendations of the European AIDS Clinical Society (EACS) in order to start ART treatment as soon as possible (Table 1).

Table 1. Laboratory biochemical investigations

parameter	25.11.2021	28.12.2021	03.08.2022	08.03.2023	04.12.2023
Total bilirubin	6	4	6	4	4
Dir./ind. bilirubin	2/4	1/3	2/4	1/3	1/3
ALT	20	11	18	26	31
AST	22	17	19	31	24
Gama-GT	30	32	36	83	74
glycemia	5.7	5.5	5.3	6.4	5.7
Urea	4.0	2.6	2.9	2.7	2.4
creatinine	45	55	55	54	50
cholesterol	4.0	4.19	4.3	4.5	4.9
triglycerides	0.67	0.8	1.15	1.42	0.98
HDL cholesterol				1.4	1.5
LDL cholesterol				2.46	2.9
Hgb	144	145	153	145	159
Er	5190	5200	5020	4740	5.20
Le	4.1	3.9	4.8	4.7	6.0
Tr	271	234	277	243	268

Serological tests performed during the initial screening of the patient were: HBsAg negative, anti HBc tot negative, anti HBs negative, anti HCV negative, anti-Treponema pallidum IgM and IgG negative, anti -oxoplasma IgM negative, anti EBV IgM negative IgG positive, anti-Cytomegalovirus IgM negative IgG positive.

According to the EACS recommendations for the treatment of patients with HIV infection, the patient's initial combined ART included two nucleoside reverse transcriptase inhibitors (NRTI) - Tenofovir disoproxil/ Emtricitabine and one non-nucleoside reverse transcriptase inhibitor (NNRTI) - Efavirenz. As a result of ART efficiency, undetectable values of HIV RNA viral load in serum and immune reconstitution were achieved (Figure 1) (Figure 2).

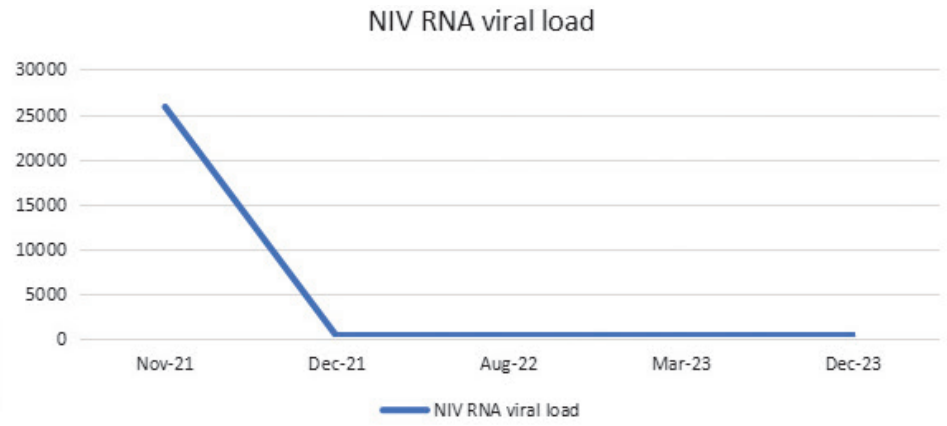

Figure 1. Presentation of reduction of HIV RNA viral load in human plasma.

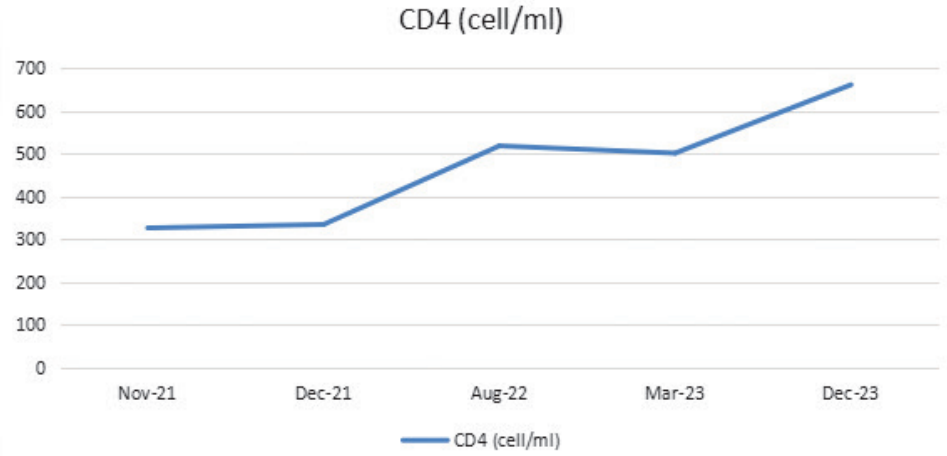

Figure 2. Presentation of immune reconstitution and increase in CD4 cell count.

The quantification of HIV RNA in human plasma was performed using real time polymerase chain reaction RT-PCR Abbot System m2000sp/m2000rt with a lower limit of detection <40 cop/ml, while the determination of immune deficiency using absolute photo-microscopy and light absorption detection on a multicolor platform (Facs Presto-BD) for absolute and percentage detection of CD4 lymphocytes, expressed in the number of cells per milliliter (cell/ml).

In December 2023, the patient was presented to the University Dental Clinical Center due to tooth pain for a dental examination. A diagnosis of chronic apical periodontitis of the tooth (VI lower right) was made, after which the patient was advised to continue treatment at the Clinic of Oral and Periodontal Diseases. After the examination, presence of dental plaque cleaning was done, and a drain was placed in the periodontal pocket after curettage. During the examination and dental interventions, the medical staff used standard protective equipment, protective gloves, a mask and protective glasses. Examination and treatment procedures were carried out in compliance with the appropriate protocols of evidence-based medicine and the correct disposition of the used medical material was made.

After the medical procedures, a consultation was done with an appropriate medical doctor/ person at the Department for HIV infections at the PHO University Clinic for Infectious Diseases and Febrile Conditions to assess the risk of professional exposure and the need for additional preventive measures. An assessment of the risk of transmission of HIV infection was made, taking into consideration all risk factors, including the patient's current HIV status, and no additional preventive measures were taken.

Discussion

The effectiveness of ART allows the life expectancy of people living with HIV infection to be extended, which in the next period will result in a greater number of patients with HIV infection who will need dental care. Also, certain oral diseases are a frequent clinical manifestation in certain stages of HIV infection, which increases the need for dental interventions and treatment. Therefore, it is necessary to have awareness and knowledge of the risks of professional exposure and transmission of HIV infection when performing dental procedures (8).

A study in Ethiopia showed that professional exposure to HIV infection and the risk of transmission have a significant association with the education and awareness of the health personnel (3). The role of educational training for the prevention of infection transmission is an effective strategy for acquiring skills with which health workers can protect themselves and their colleagues (3).

When assessing the risk of professional exposure to HIV infection in the patient, several risk factors were taken into consideration. One of them was an assessment of the source of HIV infection, where it was established that the patient received ART regularly and had undetectable HIV RNA viral load values in human plasma. The risk of transmission of HIV infection in such cases is extremely low, because the presence of the virus in the blood is not detected, it is present in small amounts in the form of latent infection in certain cell reservoirs (4).

During the dental interventions, the standard measures for protection against professional exposure to HIV infection were applied in accordance with the guidelines for the application of PEP against the transmission of HIV infection from the Ministry of Health of the Republic of North Macedonia (6). The correct disposition of the infectious material was implemented and no exposure to body fluids containing the HIV virus during patient care has been reported. Based on the estimated risk, the need for additional preventive measures such as the use of PEP among health workers was not indicated (6).

Application of HIV PEP shortly after exposure has been shown to reduce the risk of developing HIV infection by 81%. A study in Ethiopia found that 81.6% of exposed health workers did not use HIV PEP. Another study in Kenya also found that less than 45% of health workers did not request HIV PEP due to lack of information, while a study in Cameroon showed nurses' lack of knowledge about HIV PEP in 73.7% (8). In a study conducted in Cameroon of 312 participants, 63.5% had a professional injury, 51% had adequate knowledge of the existence of HIV PEP recommendations, while 30.3% used HIV PEP (8).

Conclusion

The implementation of standard protection measures, the effectiveness of ART in preventing the transmission of HIV infection, the possibility of applying PEP as prevention in case of professional exposure significantly reduce the risk of transmission of HIV infection. Education of health workers about the risks of transmission during professional exposure to HIV infection will improve the reduction of discrimination and stigma of people who are living with HIV when providing appropriate medical care.

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CASE REPORT *UDK: 616-006.441-085.277-073.763.5*

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MRI SIGNS IN METHOTREXATE - RELATED LEUKOENCEPHALOPATHY IN CHILDREN WITH BURKITT LYMPHOMA - ABDOMINAL MANIFESTATION

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Abstract

Burkitt lymphoma, classified as a subtype of non-Hodgkin lymphoma, primarily targets children. It frequently presents with extranodal involvement, often manifesting as an abdominal or pelvic mass upon initial presentation. Treatment regimen commonly incorporates chemotherapy, wherein the prognosis, particularly in pediatric cases, is notably favorable, with survival rates exceeding 90%. However, the utilization of methotrexate, a chemotherapy agent employed in hematological malignancies and other neoplasms, warrants careful consideration due to its propensity for neurotoxicity. Methotrexate-induced neurotoxicity may be presented across a spectrum of acute and chronic leukoencephalopathies. One significant manifestation is toxic encephalopathy, characterized by its predominant affliction of subcortical white matter. Additionally, notable findings include confluent hyperintensities observable on T2 and FLAIR imaging, particularly evident in the centrum semiovale region. Magnetic resonance imaging (MRI) stands as the preferred diagnostic modality. This non-invasive and sophisticated imaging technique holds immense clinical and research utility. Leveraging MRI enables early detection of neurological conditions, facilitates ongoing monitoring of treatment outcomes, and supports timely interventions, thereby offering significant benefits in patient's care.

We report the case of a 4-years-old patient diagnosed with Burkitt lymphoma, who underwent an MRI scan following symptoms of blindness and convulsions. Initial CT scans showed no discernible pathology. Subsequent MRI findings revealed signal abnormalities, typical of methotrexate-related leukoencephalopathy. Notably, convulsions ensued shortly after initiating methotrexate treatment. These MRI findings are characteristic of toxic encephalopathy, highlighting the importance of vigilant monitoring in patients undergoing methotrexate therapy.

Key Words: *Burkitt lymphoma, MRI, Methotrexate leukoencephalopathy, toxic leukoencephalopathy.*

Introduction

Burkitt lymphoma is recognized for its aggressive nature and can be manifested in various anatomical locations, including the head and neck, pleural space, gastrointestinal tract, retroperitoneum, peritoneum, kidneys and gonads. The radiographic features of Burkitt lymphoma vary depending on the organ involved. Abdominal presentations may or may not include a palpable

mass. In our case, a palpable abdominal mass led to a CT-guided biopsy, confirming the diagnosis of Burkitt lymphoma via histopathology.

Upon hospitalization, the prescribed therapy involved the administration of methotrexate. However, shortly after initiating methotrexate treatment, the patient exhibited symptoms including convulsions. Methotrexate, a potent anticancer drug, can induce neurotoxicity, particularly in high doses. Its mechanism of action involves competitive inhibition of dihydrofolate reductase, thereby depleting DNA precursors. The exact mechanism underlying methotrexate-induced leukoencephalopathy remains unclear, though it is proposed to involve the release of adenosine, resulting in cerebral blood vessel dilation, neuronal dysfunction and cytotoxic edema.

Methotrexate can be administered orally, intravenously or intrathecally. MRI serves as the preferred diagnostic imaging modality, with neurotoxic side effects, such as leukoencephalopathy, manifesting as transient hyperintense regions on T2-weighted imaging (T2WI), diffusion restriction, and abnormal or absent contrast enhancement (1, 2, 3). Sequential MRI examinations enable the detection of leukoencephalopathy in symptomatic patients and may reveal abnormal findings in asymptomatic individuals following methotrexate treatment (4).

In some cases, discontinuation of methotrexate therapy may be necessary, as the brain abnormalities associated with the acute toxic leukoencephalopathy can potentially reverse with therapy or removal of the offending agent during the early phase of onset.

Case Presentation

We present an intriguing case involving a four-years-old child exhibiting abdominal manifestations of Burkitt lymphoma alongside methotrexate-related leukoencephalopathy. The patient's initial presentation occurred in April 2024, when she was presented to the emergency department with a distended abdomen persisting for one week, accompanied by the presence of a palpable solid mass in the abdominal region. Subsequently, the patient underwent a CT scan of the abdomen with intravenous contrast for further evaluation.

CT Findings

The CT scan showed a large, expanding mass in the abdominal cavity, involving the mesentery and displacing bowel loops without causing obstruction. The mass extended from below the pancreas to the suprapubic region and surrounded the uterus, making the ovaries indistinguishable. There were also enlarged lymph nodes near the aorta and below the diaphragm. The findings suggested a potentially aggressive process requiring further investigation and multidisciplinary management. The patient, diagnosed with Burkitt lymphoma through clinical, biochemical and molecular assessments by the pediatric hemato-oncology team, was hospitalized.

Due to the exacerbation of symptoms and onset of convulsions, a brain CT was conducted, which revealed no significant abnormalities.

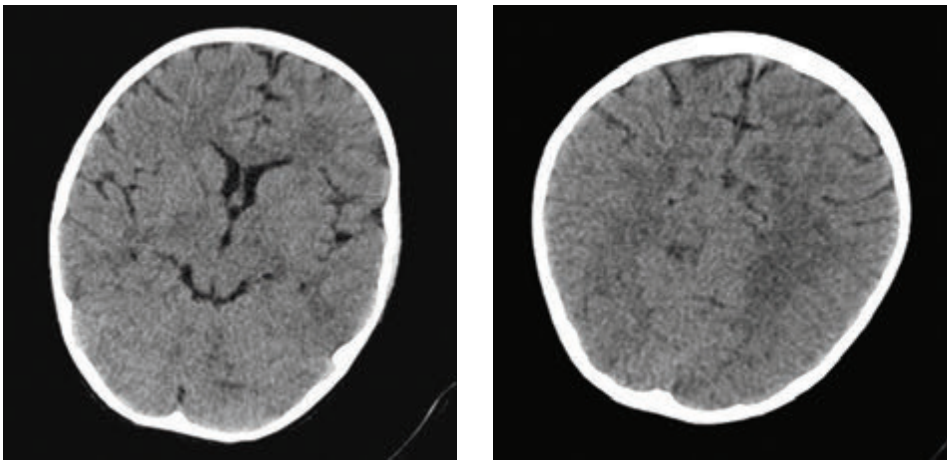

Figure 1.

Subsequently, an MRI of the brain was performed, which demonstrated: Bilateral diffuse high signal changes in the cerebellum on T2 and FLAIR sequences, as well as areas of restricted diffusion, indicating focal zones of cytotoxic edema.

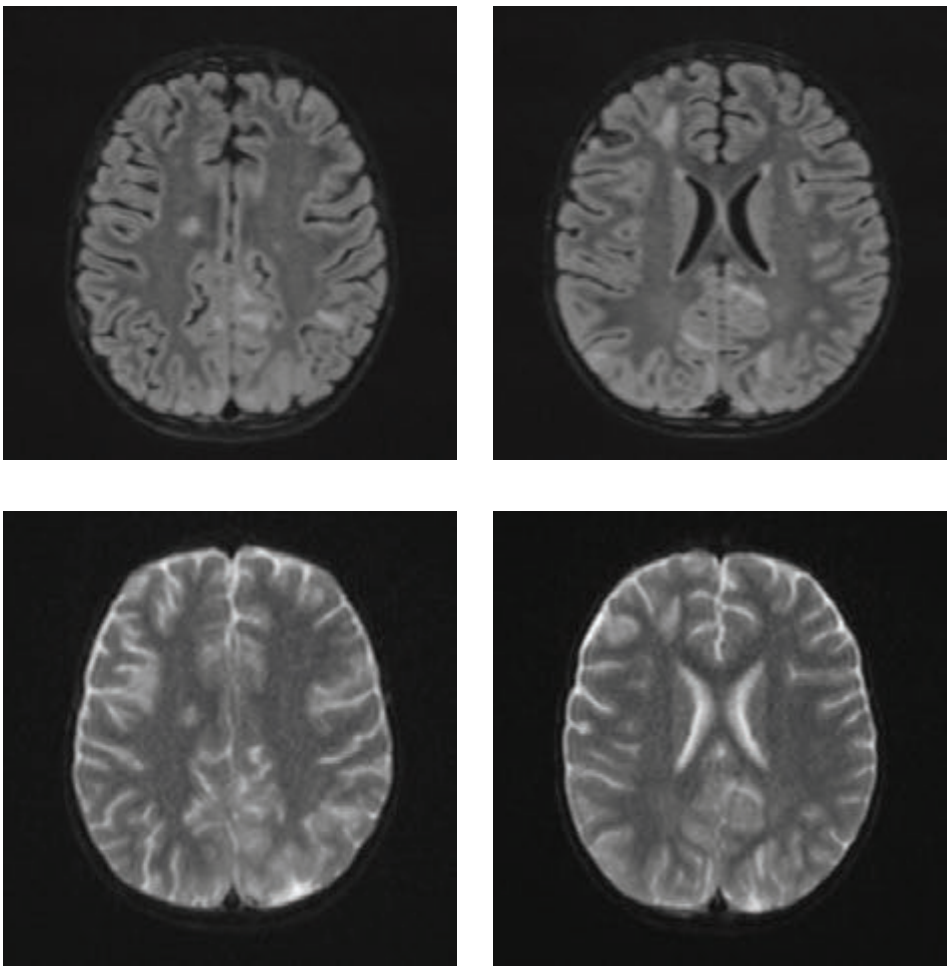

Figure 2.

The MRI of the brain revealed the following findings:

- Bilateral subcortical zones, predominantly in the occipital region, exhibiting confluent hyperintense signals on T2 and FLAIR sequences, accompanied by edema.
- A suspected area of cytotoxic edema in the superior parietal lobe.
- High signal intensities on T2 and FLAIR sequences observed in the centrum semiovale, right of the corpus callosum body, and bilaterally in the frontal gyrus, without diffusion restriction.
- In the supraventricular region, extending inferiorly from the projection of the postcentral gyrus into the subcortical white matter to the posterior part of the corpus callosum body (excluding it), and in the left superior temporal lobe, there was a cortico-subcortical lesion characterized by cytotoxic edema and restricted diffusion.

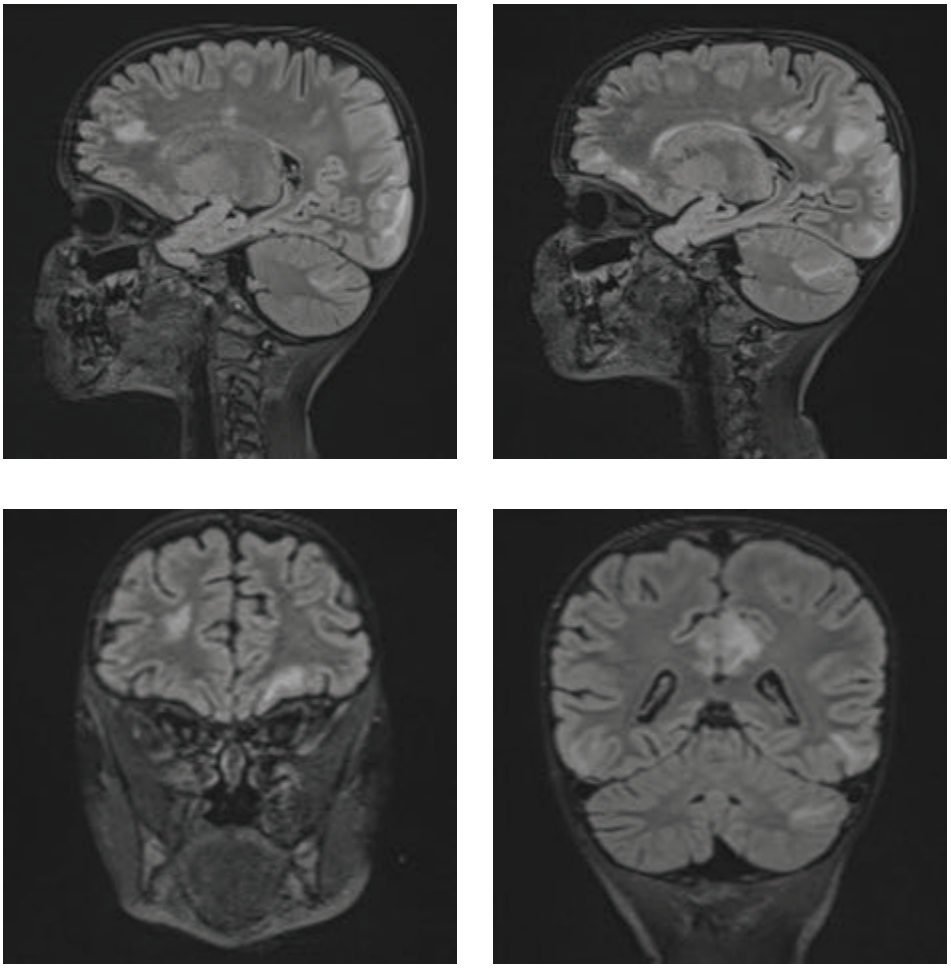

Figure 3.

The changes observed are characteristic radiological markers appreciated on DWI, indicative of cytotoxic edema. The DWI changes are considered reliable early signs of acute toxic encephalopathy, specifically methotrexate-related leukoencephalopathy. Post-contrast MR images did not show any abnormal contrast enhancement.

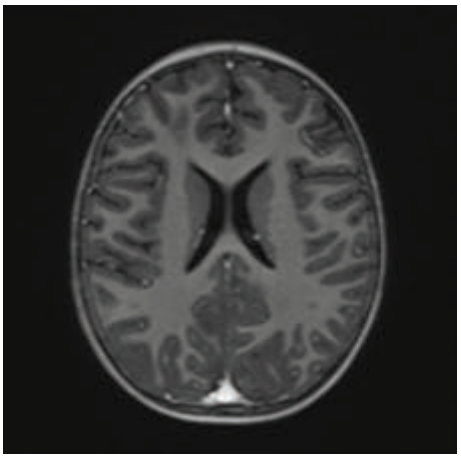

Figure 4.

Discussion

Methotrexate (MTX) is a cornerstone chemotherapeutic agent used in the treatment of various malignancies, including Burkitt lymphoma. While effective, MTX is associated with several adverse effects, one of the most severe being methotrexate-related leukoencephalopathy (MTX-LE) (5). This case report highlights the radiological findings of MTX-LE in a pediatric patient diagnosed with Burkitt lymphoma, presenting with an abdominal manifestation and subsequently developing neurological symptoms.

Radiological Findings

MRI is instrumental in the early detection and evaluation of MTX-LE. In our case, MRI of the brain revealed the following key features:

Bilateral Occipital Dominant Subcortical Hyperintense Zones: These areas were evident on T2-weighted and FLAIR sequences, indicating diffuse cerebral involvement. The predilection for the occipital region was consistent with reported cases of MTX-LE, which often presents with symmetric white matter changes.

Edema and Cytotoxic Edema: The superior parietal lobes showed suspected zones of cytotoxic edema. This was further supported by the presence of diffusion-weighted imaging (DWI) changes, characterized by restricted diffusion, a hallmark of cytotoxic edema. These findings align with the pathophysiology of MTX-LE, where MTX-induced neuronal damage leads to cellular swelling and subsequent restricted diffusion.

Supraventricular and Frontal Gyrus Involvement: High signal intensities on T2 and FLAIR sequences were noted in the centrum semiovale, right of the corpus callosum body, and bilaterally in the frontal gyrus, without diffusion restriction. This suggests early involvement before the development of significant cytotoxic damage.

Cortico-Subcortical Lesion in the Left Superior Temporal Lobe: This region exhibited cytotoxic edema with restricted diffusion, underscoring the multifocal nature of MTX-LE. The involvement of both cortical and subcortical areas is a typical feature in severe cases of MTX-LE.

When encountering MRI findings suggestive of methotrexate-related leukoencephalopathy (MTX-LE), it's essential to consider a broad range of differential diagnoses to ensure accurate diagnosis and appropriate management. Potential alternative explanation for similar radiological findings is Posterior Reversible Encephalopathy Syndrome (PRES). Although PRES typically manifests with posterior cerebral involvement, an atypical presentation may involve predominantly anterior regions. Awareness of these uncommon presentations is crucial for accurate diagnosis and appropriate management of PRES (6).

Clinical Implications

The early identification of MTX-LE is critical for timely intervention. The presence of characteristic DWI changes, even in the absence of clinical symptoms, should prompt consideration of MTX-LE (7). In this case, the patient's neurological deterioration and convulsions underscored the need for immediate imaging and clinical intervention. The absence of abnormal contrast enhancement on post-contrast MR images suggests that MTX-LE can present without blood-brain barrier disruption, further complicating diagnosis without advanced imaging modalities.

Pathophysiology

MTX-LE is believed to result from direct toxic effects on oligodendrocytes and myelin sheaths, disruption of folate metabolism, and excitotoxicity mediated by homocysteine accumulation. The resultant demyelination and white matter necrosis lead to the observed radiological changes. The predilection for the periventricular white matter, as seen in this case, is characteristic of MTX-induced neurotoxicity.

Management and Prognosis

Upon diagnosis of MTX-LE, the immediate cessation of MTX is recommended, along with supportive care and consideration of alternative chemotherapeutic regimens (8). The prognosis of MTX-LE varies, with some patients experiencing partial or complete recovery, while others may suffer from persistent neurological deficits (9). Early detection, as highlighted in this case, is crucial for improving outcomes. The timing of a follow-up MRI is crucial for monitoring the progression or resolution of neurotoxicity and for guiding further treatment. Here are the general recommendations for follow-up MRI:

Immediate Follow-Up

Initial Follow-Up MRI: Typically recommended within 2 to 4 weeks after the initial diagnosis of MTX-LE. This helps to assess the progression or improvement of the lesions observed in the initial MRI and to evaluate the effectiveness of any interventions that have been initiated.

Mid-Term Follow-Up

Subsequent MRI: Depending on the findings of the initial follow-up MRI, a subsequent MRI might be performed every 1 to 3 months. The exact interval can be adjusted based on clinical symptoms, changes observed in previous imaging and the patient's overall neurological status.

Long-Term Follow-Up

Long-Term Monitoring: After stabilization or improvement of the acute phase, MRI may be recommended every 6 to 12 months to monitor for any late-onset neurotoxicity or chronic chang-

es, especially if the patient continues to receive chemotherapy or other neurotoxic treatments.

Clinical Triggers for MRI

Worsening Symptoms: Any new or worsening neurological symptoms, such as seizures, cognitive changes or motor deficits, should prompt an immediate MRI to rule out new or worsening leukoencephalopathy.

Reinitiation of MTX: If methotrexate therapy is reinitiated or modified, it may be prudent to perform an MRI before restarting and then at intervals during treatment to monitor for recurrence of neurotoxicity.

Conclusion

This case underscores the importance of vigilance for neurological symptoms in pediatric patients undergoing MTX therapy for Burkitt lymphoma. MRI, particularly DWI, plays a pivotal role in the early detection of MTX-LE. Recognizing the characteristic radiological markers can facilitate prompt diagnosis and intervention, potentially mitigating the severe neurological sequelae associated with this condition. Future studies are needed to further elucidate the pathophysiology of MTX-LE, and optimize management strategies for affected patients.

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PATHOPHYSIOLOGY AND CLINICAL IMPACT OF HEART - LUNG BINOMEN IN ICU

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The heart-lung relationship represents a critical duality in the intensive care unit (ICU). This interrelationship gives rise to several "conflicts," such as reno-cardiac, renal, reno-pulmonary syndromes, mechanical ventilation-brain issues, and anticoagulants for cardiac reasons causing hemorrhages (gastrointestinal, cerebral). Recent literature provides valuable insights into the heart-lung duality, helping to understand the primary problems and side effects on each system during therapeutic interventions targeting the other system (1). The heart-lung circulation interconnects these organs, necessitating consideration of one organ's effects on the other to prevent decompensation of related chronic diseases.

Chronic pulmonary diseases (asthma, emphysema, chronic obstructive pulmonary disease) increase pulmonary resistance, leading to pulmonary hypertension (2). Pulmonary hypertension raises right ventricular afterload and pressure in the pulmonary artery, which can decompensate the right ventricle. During asthma, forced inspiratory pressure generates a significant negative intrathoracic pressure, enhancing venous return and overfilling the right ventricle. Right ventricular failure and increased filling pressures shift the interventricular septum leftward, reducing left ventricular filling volumes, leading to low cardiac output and pulmonary congestion. Spontaneous tachypneic respiration results in increased respiratory effort, fatigue and hypoxia (3). Hypoxia disrupts myocardial oxygen balance, negatively impacting cardiac output, arterial pressure and systemic organ perfusion.

Mechanical ventilation traps the heart between the lungs, which can increase diastolic filling pressures, decrease end-diastolic filling volumes, cause significant diastolic dysfunction, and further reduce stroke volume and cardiac output. Mechanical ventilation disrupts normal physiology, affecting heart function and hemodynamics (4). Under normal conditions, diaphragmatic movements during inspiration create negative pressure, enhancing the pressure difference between the mean systemic pressure and right atrial pressure. This pressure difference determines preload and venous return, which are components of cardiac output. Negative intrathoracic pressure directs venous blood into the heart, increasing end-diastolic filling. However, mechanical ventilation can overload and dilate the right ventricle, compressing the left ventricle. Under mechanical ventilation/PEEP/recruitment maneuvers, abnormal positive pressure inspiration reduces venous return, cardiac output, and causes hypotension/ hypoperfusion. These phenomena are more pronounced under preexisting hypovolemia.

Lung hyperinflation increases right ventricular afterload and decreases right ventricular stroke volume, predisposing to hypotension via intraventricular septum shift and reduced left ventricular preload (5). Mechanical ventilation also stretches pulmonary vasculature, contributing to pulmonary hypertension.

During the weaning process, spontaneous breathing-induced negative intrathoracic pressure increases left ventricular afterload, left ventricular overfilling, left ventricular ischemia, and pulmonary edema, especially in patients with impaired left ventricular function.

Therapeutic maneuvers involve several strategies. Strict hemodynamic monitoring is essential, particularly in ventilated patients with septic shock and/ or ARDS. TEE, TTE, Doppler examination, PICCO, and pulmonary artery catheterization provide valuable information about hemodynamic changes during mechanical ventilation. Monitoring right ventricular filling is crucial. Excessive ventilation stretches pulmonary vessels, causing pulmonary hypertension and further reducing right ventricular afterload and ejection. Right ventricular overfilling leads to right ventricular ischemia and failure, reducing diastolic filling of the left ventricle. Right ventricular function can be supported by optimizing volume, inotropism, and reducing afterload. Drugs that reduce afterload include inodilators (dobutamine, milrinone) and pure dilators such as NO. ECMO can help mitigate the side effects of mechanical ventilation.

In conclusion, intensive care physicians must possess a thorough understanding of the interrelated adverse effects of the heart-lung pathophysiological relationship to optimize patient's outcomes (6).

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LETTER TO THE EDITOR *UDK: 616.98:579.852.13]:614.253.5*

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THE ROLE OF THE NURSE IN THE CONTROL AND MANAGEMENT OF PATIENTS WITH CLOSTRIDIUM DIFFICILE

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Abstract

Clostridioides Difficile is one of the most important intrahospital pathogens. This sporogenous anaerobic bacterium is increasingly isolated from feces, primarily in older hospital patients on antibiotic therapy, and is associated with several clinical manifestations, starting with diarrhea and ending with pseudomembranous colitis. The main emphasis in this paper is the prevention of these bacterial infections, and the initial protection of patients who are suspected of CDI (Clostridium Difficile Infection) mandates that they should be immediately isolated from other patients. In hospital settings where the existence of CDI has been detected, special wards must be opened in order to isolate a larger group of patients. Practically, the isolation of both individual patients and groups of patients has a major role in reducing transmission and bringing the epidemic under control.

The role of the nurse in the prevention, control and therapy of patients who have Clostridioides Difficile Infection is crucial. It certainly implies that education and knowledge about this problem is essential.

Key Words: *Antibiotic treatment, Clostridioides Difficile infection, nurse, role.*

Introduction

Clostridium, a term that comes from the Greek word (klōstēr) meaning "spindle" are gram positive, anaerobic bacteria from the family Clostridiaceae, that have the ability to form spores and the most of them are pathogenic. According to the pathogenesis, clostridia endospores are resistant to heat and can survive several hours in boiling water, and some of them can survive even a heat of 110°C for a period of one hour. Some of the clostridia can move by means of peritrichously arranged flagella. They can be found in the soil and the digestive system of animals.

Clostridium Difficile, by definition, is the cause of antibiotic-induced inflammation in the intestines. As one of the most important intrahospital pathogens, this sporogenous anaerobic bacterium is detected in feces, primarily in elderly patients who are kept on antibiotic therapy and is manifested with several clinical disorders, starting from diarrhea, and ending with pseudomembranous colitis.

Aim of the Research

The aims of this specialist paper are to examine the representation of Clostridioides Difficile in samples from suspected patients, to determine the toxicity of the strains directly from the samples and from the grown cultures, to determine the genotypic affiliation of the isolates, to determine their antibiotic sensitivity, as well as the possible association of these phenotypic and genotypic characteristics in the isolates. Finally, nurses' role in control and management of these affected patients is emphasized.

Material and Methods

In general, all fecal samples received were taken in the period 2020-2023 at the Institute of Microbiology and Parasitology, at the Faculty of Medicine in Skopje, as well as from the Microbiological Department at the Clinic for Infectious and Febrile Conditions, also in Skopje, with the aim of diagnoses CDI, where they are practically examined for immune chromatographic proof of glutamate dehydrogenase antigen (GDH) and toxins A and B of Clostridioides Difficile.

Results

The highest percentage of resistance to the investigated antibiotics was observed among isolates of Clostridioides Difficile originating from patients hospitalized in surgical clinics. The highest percentages of resistance to the tested antibiotics were observed in the isolates belonging to the dominant rib type 001/072 and in the hyper virulent rib types 017 and 027. Namely, the number of fecal samples sent from different clinics and outpatient clinics with a request for a laboratory diagnosis of CDI does not correspond to the number of positive findings, and the greatest discrepancy was detected in surgical clinics.

Conclusions and Discussion

In general, the laboratory diagnosis of CDI should be based on a two-part algorithm that includes the detection of GDH and Clostridioides Difficile toxins A and B, directly in fecal samples. Further additional testing of Clostridioides Difficile culture toxins also slightly reduces the false-negative rate (%). Vancomycin and metronidazole are the starting point here as the first option for CDI therapy. Therapy with clindamycin, erythromycin, imipenem, ciprofloxacin and moxifloxacin, may be considered a risk factor for CDI. There is a particularly high risk in patients receiving ciprofloxacin. The obtained results indicate the existence of a connection between ribotypes and antibiotic resistance in Clostridioides Difficile, and the acquisition of resistance to antibiotics is one of the main factors for the distribution and movement of ribotypes, mostly in hospital conditions, as well as the further emergence of new types. Monitoring these genotypic and phenotypic characteristics of the isolates can be of great epidemiological importance.

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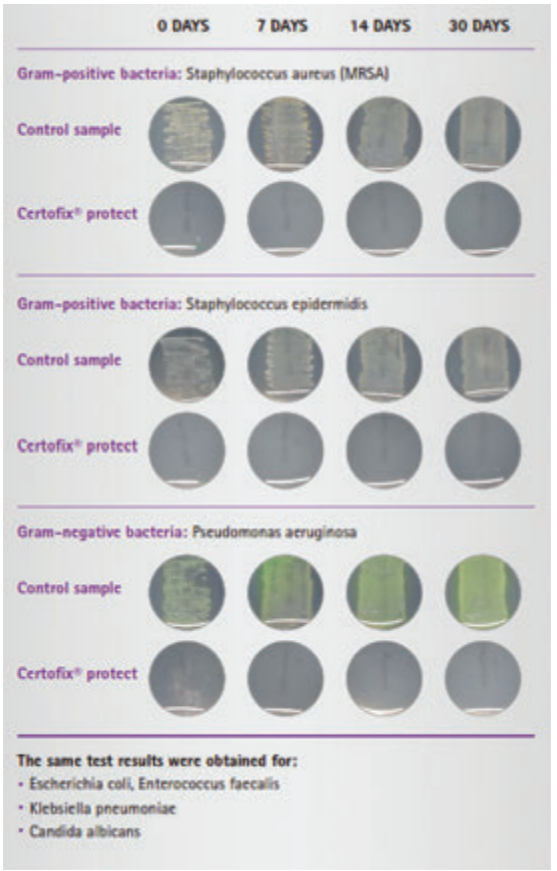

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