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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 аналгезија 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 аналгезија** за умерена до средна болка при оперативни зафати.

Голем број на клинички студии ја докажуваат ефикасноста на **i.v. paracetamol** како **предоперативна и интраоперативна аналгезија**.

КЛИНИЧКА СТУДИЈА:

Ефект од **предоперативен i.v. paracetamol** за постоперативни аналгетски потреби кај пациенти кои се подложни на оперативни зафати. ASreenivasulu, RPrabhavathi, 2015

Цел: Да се утврди ефикасноста на **предоперативната употреба на 1000mg i.v. paracetamol** кај постоперативните болки и аналгетски потреби кај пациенти подложни на хируршки зафати.

Метод: 60 пациенти беа поделени во две рандомизирани групи од по 30 пациенти.

На I. Група им беше администрирано **ампула од 1000mg i.v. paracetamol** разредена **0,9%NaCl** р-ор 30 минути пред индукција (**ГРУПА П**),

На II. Група им беше администрирано **i.v. 0,9% NaCl** р-ор **100мл** 30 минути пред индукција (**ГРУПА НС**)

Сите пациенти беа индуцирани со **i.v. thiopentone 5mg/kg**, **i.v. fentanyl 2µg/kg**, **i.v. vecuronium 0.1mg/kg**

Постоперативниот резултат на болка беше мерен со **Визуелна Аналогна Скала (ВАС) од "0-10"**. Исто така беше забележувана и **постоперативната употреба на tramadol** како спасувачки аналгетик. Инциденцата на **постоперативно гадење и повраќање (ПОПГ)** 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.

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

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

Табела 3: Споредба на ПОПГ помеѓу двете групи

ПОПГ	
I Група П	II Група НС
0	4

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 мултимодално 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**

Baxter

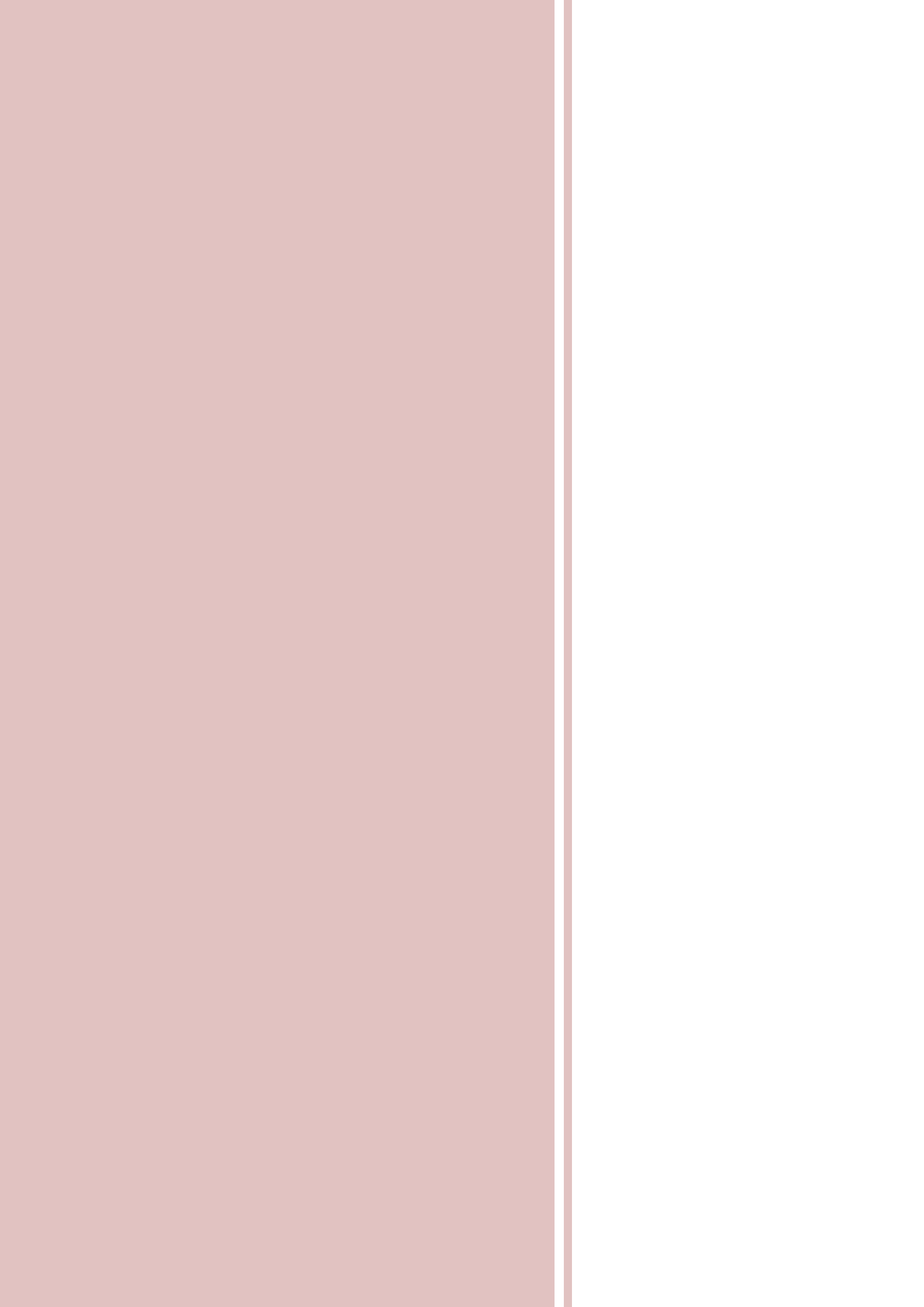
WHEN EARLY RECOVERY REALLY MATTERS



Дистрибутер за Македонија



FARMA TREJD



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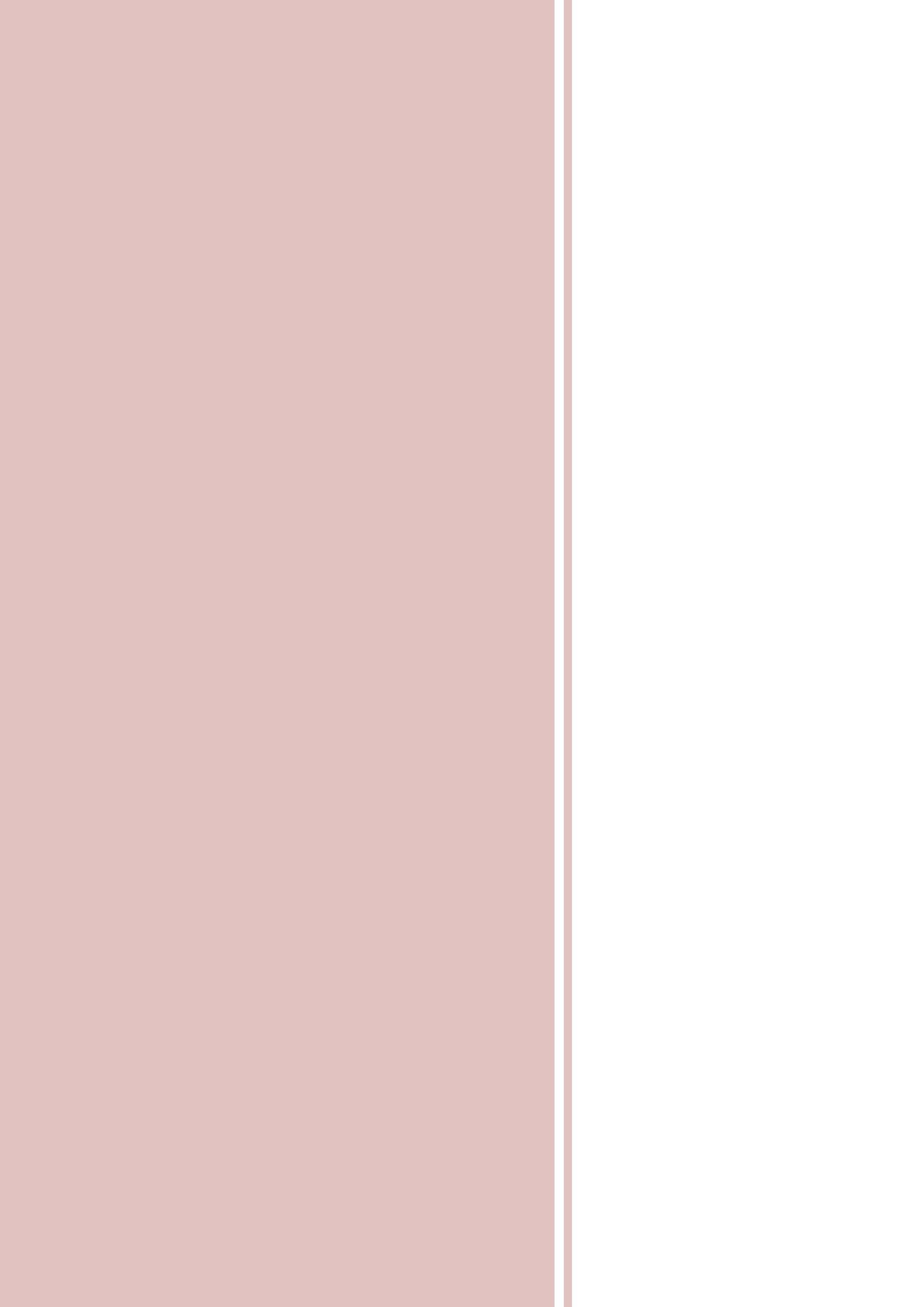
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THE ROLE OF ANESTHESIOLOGISTS AND REGIONAL ANESTHESIA AT DISASTERS

Prof. Dr. Fatma Sarıcaoğlu

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Ankara -TURKIYE*

There will always be a frontier where there is an open mind and a willing hand.

Charles F. Kettering

According to the World Health Organization, a disaster is "a sudden event involving substantial loss of infrastructure, people, and the economy and which overwhelms the resources of that country, area, or community" (1). Both man-made and natural catastrophes, such as war and industrial accidents, as well as natural disasters like earthquakes, tsunamis, and disease epidemics, may be to blame. Although the frequency of earthquake incidents appears to be unchanged, the number of people affected has increased as a result of earthquakes occurring in highly populated areas.

Disasters can be classified as either natural or man-made. According to the timing of their formation, the natural group is divided into catastrophes that emerge gradually (extreme cold, drought, starvation) and suddenly (earthquake, flood, landslide, avalanche, hurricane, hose, volcano, fire). Human catastrophes include terrorist, nuclear, biological, and chemical attacks, as well as transit, industrial, and overpopulation mishaps, as well as attacks on migrants and internally displaced people (1).

Earthquakes are one of the most powerful and destructive natural phenomena that occur on our planet. They can cause widespread devastation, loss of lives, and economic damage, making them a significant threat to human societies. Throughout history, the Earth has experienced many powerful earthquakes that have left a lasting impact on the affected regions. These seismic events can vary in magnitude, with the most severe earthquakes reaching levels that are hard to comprehend (1,2).

The devastating 7.8-magnitude earthquake near the Türkiye-Syria border in the early hours on Monday, 6th of February 2023, was followed by another one nearly as strong. The earthquakes that struck Türkiye and Syria caused one of the biggest disasters impacting the region in recent times. Tens of thousands of people have been killed, and many more have been injured. Thousands of buildings have collapsed, leaving countless people exposed to severe winter conditions. Schools and hospitals have been destroyed. We have had many field hospitals and many transferred victims from the region. We have not received the exact numbers of victims from the Ministry of Health yet.

Disaster medicine is made up of many different specialties, but anesthesia is one of the most crucial ones. During emergencies, anesthesiologists can use information from the field to gather quick choices and manage a routine rescue operation. Anesthesia crisis managers need to be skilled at disaster management. In times of tragedy, anesthesiologists play a critical role in helping injured patients with prompt and effective care (3).

The first hour of treatment after a disaster is the "golden hour," and it is the most crucial. It is crucial in determining whether or not the patient will survive. One of the most crucial challenges at that time is the triage. Stabilizing the patient, preparing appropriate fluid therapies, establishing vascular access, performing resuscitation, providing transport, and establishing communication between hospitals are all necessary (4).

The anesthesiologist has many difficulties managing patients' anesthesia during disasters. Patient knowledge is restricted, past medical history, drugs used, allergy status, genetic abnormalities, and stomach fullness are unknown, and the existence of various traumas may result in challenging breathing issues. Considerations for selecting anesthesia methods include the type of surgical procedure, the patient's vital signs, the availability of resources as equipment, medicine, personnel, the benefits and drawbacks of the anesthesia technique, the physical conditions of the environment and transportation options (5).

Regional Anesthesia Benefits

Regional anesthetic treatments provide advantages over general anesthesia in field settings, including pain relief while maintaining general function, reduced resource use, and an overall improved recovery. The capacity to alleviate pain or carry out procedures while keeping patients aware and physically functional is a significant advantage (5).

In both civilian and military in-a-field hospital settings, regional anesthesia has been utilized extensively with positive outcomes in resource-constrained and austere environments, and it has been recognized to be an important tool in the wake of several natural disasters (6,7). Four main factors led to the selection of regional anesthesia: the first, the relative simplicity of the techniques makes them safer in the absence of advanced monitoring and with limited patient history and laboratory facilities; the second, recovery from general anesthesia would require the use of an ICU/post-anesthesia care unit bed, a limited resource in the disaster setting that may limit operating room turnover or access to ICU beds by other patients; the third, the absence of advanced monitoring makes the techniques safer in the absence of advanced monitoring and with limited patient history and laboratory facilities; the fourth, an anesthetic approach that minimizes postoperative pain and narcotic requirements is necessary due to the shortage of medical and nursing staff as well as communication issues with patients throughout the recovery phase. Finally, the patient is easier to transfer in case an emergency evacuation due to aftershocks would be necessary during operation (7, 8).

Regional anesthesia provides good surgical conditions and effective pain relief, but also makes patient transfers between hospitals and within hospitals easier. Future disaster relief force planners should think about putting anesthesiologists with strong regional anesthesia skills on board, as well as to confirm the availability of suitable portable ultrasound equipment, particular short bevel block needles of various lengths, and suitable local anesthetics in various concentrations (9). Regional anesthesia is practicable and secure, and its application in disaster relief scenarios can save resources.

Natural disasters are a fact of life as long as humans are on the planet. It is obvious that our professional team must adjust and be ready. Making an accurate risk assessment is the first step to being prepared for emergencies. The emergency plan thereafter contains this risk assessment.

REFERENCES:

1. WHO. Humanitarian Health Action. Glossary of humanitarian terms. Available from <http://www.who.int/hac/about/definitions/en/> (accessed 18 August 2017).
2. Schultz CH, Koenig KL, Noji EK (1996) A Medical Disaster Response to Reduce Immediate Mortality after an Earthquake. *N Engl J Med* 334: 438-444. Link: <https://bit.ly/3civr2r>.
3. Missair A, Gebhard R, Pierre E, et al. Surgery under extreme conditions in the aftermath of the 2010 Haiti earthquake: the importance of regional anaesthesia. *Prehosp Disaster Med* 2010; 25: 487-93.
4. Traumaesthesia (2008) ASA refreshercourses in anesthesiology. American Society of Anesthesiologists.
5. Missair A, Pretto EA, Visan A, et al. (2013) A matter of life or limb? A review of traumatic injury patterns and anesthesia techniques for disaster relief after major earthquakes. *Anesth Analg* 117: 934-941. Link: <https://bit.ly/3fuijJL>.
6. Rossler B, Marhofer P, Hupfle M, et al. Preparedness of anaesthesiologists working in humanitarian disasters. *Disaster Med Public Health Prep* 2013; 7: 408-12.
7. Buckenmaier CC, Lee EH, Shields CH, Sampson JB, Chiles JH (2003) Regional anesthesia in austere environments. *Reg Anesth Pain Med* 28: 321-327. Link: <https://bit.ly/3bpR3ZK>.
8. Sumartono CS, Sulistiawan SS, Semedi BP, et al. (2020) The role of anesthesiologist and selection of effective anesthesia techniques in lombok's earthquake victims' management. Preprints. Link: <https://bit.ly/35NIMxy>.
9. Amat Camacho N, Hughes A, Burkle FM, et al. Education and Training of Emergency Medical Teams: recommendations for a global operational learning framework. *PLoS Curr Disasters* 2016; doi:10.1371/currents.dis.292033689209611ad 5e4a7a3e61520d0 (accessed 18 August 2017).

STENTING OR NOT PRIOR TO SHOCK WAVE LITHOTRIPSY FOR UPPER AND MIDDLE POLE RENAL STONE OF 10-20MM

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Abstract

Objective: To evaluate the impact of routine ureteral stenting before SWL treatment for upper and middle pole stone of 10-20mm in size, on the prevention of post-SWL complications and to confirm whether this procedure affects the improvement of the success rate.

Methods: Our study was retrospective study, carried out in GH "8th of September" - Skopje in the period from March 2022 to November 2022 with an analysis of the medical data of 41 patients treated with extracorporeal shock wave lithotripsy (SWL) for stones in the upper and the middle pole of 10 to 20mm in size. The first group included 13 patients treated with SWL, with a ureteral JJ stent placed before treatment, and the second group included 28 patients without a ureteral JJ stent. Patients were treated with an extracorporeal lithotripter of the third generation of electromagnetic lithotripters (Lithoskop®, Siemens Medical Systems, Erlangen, Germany). Both groups were compared in stone size, stone clearance pain, steinstrasse, UTI, lower urinary tract symptoms (LUTS), hematuria and number of SWL sessions.

Results: The mean size of the stone in the group of patients with ureteral JJ stent was statistically significantly greater compared to the non-stented group ($p=0.000012$). The average number of sessions and re-treatment rate was significantly higher in patients with a ureteral JJ stent ($p=0.006$). There was a statistically significant difference in the energy used for stone disintegration in both groups ($p=0.0028$). Stone clearance occurred in 76.92% patients in stented group and 85.71% in non-stented group. In stented group lower urinary tract symptoms were found in 33.7 versus 0% in a non-stented group. "Steinstrasse" developed in 7.69% of the patients with JJ stent and in 7.14% patients without JJ stent. Regarding pain, lower urinary tract infections and hematuria, there was no statistically significant correlation between the two groups ($p=0.84$ $p=0.14$ $p=0.17$).

Conclusion: Routine stenting for upper and middle pole stone of 10-20mm in size before SWL should not be recommended because it does not prevent the formation of a "steinstrasse", does not improve the success rate and causes irritative symptoms of the lower urinary tract.

Key Words: pre-stenting, steinstrasse, SWL, ureteral JJ stent.

Introduction

The development of minimally invasive surgical techniques in the last three decades has significantly changed the approach of modern medicine in the treatment of kidney stones. These changes redefined modern kidney stone treatment techniques, including SWL, RIRS and PCNL, which became much less invasive and easily performed methods with few complications and almost completely have replaced the open surgical approach. In the European Urological Association (EAU) guideline, percutaneous nephrolithotomy (PCNL) is recommended as the method of choice for the treatment of the kidney stones larger than 20 mm, while extracorporeal shock wave lithotripsy (SWL) is recommended for kidney stones smaller than 10mm, while SWL, RIRS and PCNL are recommended as the methods of choice in the treatment of kidney stones between 10 and 20mm (1). The main argument in favor of endourological techniques was the fact that the stone can be removed in one session with little consequences, in contrast

to SWL, which has a retreatment rate of 20 to 30%, and problems related to the elimination of stones (2). But, still SWL is widely used in the treatment of stones smaller than 20mm, primarily due to its higher efficiency in selected cases and the low morbidity rate, which are some of the most important advantages of this method, which today makes it the first choice for treatment in many cases, despite other available treatment alternatives (3). However, there are factors that limit the use of SWL and influence its success such as: the type of lithotripter, stone-related factors such as size, structure, number and location, renal anatomy and patient-specific structural features (4,5).

With SWL, the stone is not removed completely, but it is broken into smaller fragments of different sizes, which must be spontaneously eliminated from the urinary tract. The duration of fragment elimination is highly variable, and fragments can obstruct the ureter, leading to post-SWL complications such as renal colic, hydronephrosis and renal failure (6). This especially applies to the SWL treatment of larger stones, when large number of fragments are created, which can be impacted in the ureter and form a stone road or “steinstrasse”. To prevent the formation of “steinstrasse” and other post-SWL complications, some studies highlight the benefit of stenting the ureter with a ureteral JJ stent before the intervention (7). On the other hand, there are studies that indicate that the use of ureteral JJ stents can reduce post-SWL complications such as obstruction and renal colic but does not prevent the formation of “steinstrasse”, does not reduce the rate of infectious complications and does not increase success rates (8, 9). The use of ureteral JJ stent is associated to stent-related symptoms (SRSs) such as patient discomfort, bladder pain and lower urinary tract symptoms (LUTS) such as: frequency, urgency, dysuria, hematuria, and lumbar pain that reduce the patient’s quality of life. Therefore, the routine use of a ureteral JJ stent before SWL is a controversial issue, especially in the treatment of stones up to 20mm in size.

The aim of this study was to evaluate the impact of routine ureteral stenting with a JJ stent before SWL treatment for upper and middle stone of 10-20mm in size, on the prevention of post-SWL complications and to confirm whether this procedure affects the improvement of the success rate.

Materials and Methods

This study is a retrospective study, carried out in GH “8th of September” - Skopje in the period from March 2022 to November 2022 with an analysis of the medical data of 41 patients treated with extracorporeal shock wave lithotripsy (SWL) for stones in the upper and the middle pole of 10 to 20mm in size. The first group included 13 patients treated with SWL, with a ureteral JJ stent placed before treatment, and the second group included 28 patients treated with SWL, without a ureteral JJ stent. The study included: patients aged 18 to 70 years with an isolated solitary stones with a size of 10 to 20mm in the middle or upper pole, body mass index (BMI) $<30\text{kg/m}^2$, without anatomical abnormalities, with normal renal function. Patients with staghorn stones, multiple stones, stones smaller than 10mm and stones larger than 20mm, untreated urinary tract infection, congenital anomalies of the kidneys, solitary kidney, presence of uncorrected coagulopathies, patients with radiolucent stones and pregnant women were excluded. For each of the subjects included in the study, laboratory tests, urine culture, coagulation tests, EKG, ultrasonographic examination of the urinary tract and computerized tomographic urography (KT-urography) were carried out preoperatively. The stones’ width and length were calculated based on the widest perpendicular diameters of the native CT-urography series. The surface of the stone was determined according to the formula of Tiselius and Anderson: The surface of the stone = length x width x 3.14 x 0.25.

All patients were treated with an extracorporeal lithotripter of the third generation of electromagnetic lithotripters (Lithoskop®, Siemens Medical Systems, Erlangen, Germany). Preoperatively, patients from both groups were given a single dose of antibiotic prophylaxis with a third-generation cephalosporin. Immediately before the intervention, each patient was given intravenous sedoanalgesia with amp. fentanyl i.v. (1mg/kg) and amp. midazolam i.v. (0.05-0.1mg/kg).

Postoperatively, the patients were monitored according to the following protocol: on the first postoperative day, complete blood analysis, ultrasonography of the urinary tract and KUB imaging were performed, after 3 months, ultrasonography of the urinary tract and non-contrast CT imaging were performed.

The efficiency of the method in both groups was assessed by determining the absence of residual fragments of the concretion or the presence of clinically insignificant fragments <4mm on control radiological examinations after the 90th postoperative day. The safety of the method in both groups was determined in terms of the frequency and severity of intra- and postoperative complications.

Results

In our analysis, no statistically significant difference was detected in terms of age, gender and stone location in both groups. Out of total 41 patients, 65.8% (27/41) were men and 34.1% (14/41) were women. In 31.7% (13/41) of patients, a ureteral JJ stent was placed before SWL while in 68.2% (28/41) a ureteral JJ stent was not placed. The mean age of patients treated with a ureteral JJ stent was 53.5 ± 7.0 years, and of patients treated without a ureteral JJ stent was 50.9 ± 10.4 years ($p=0.41$). Patients from both groups were homogeneous in terms of gender structure ($p=0.69$). In both groups, the majority were male versus female, namely 8/13 (61.54%) versus 5/13 (38.46%) in the stented group and 19/28 (67.86%) versus 9/28 (32.14%) in the non-stented group. The male-to-female ratio in the stented and non-stented groups was 1.6:1 and 2.1:1, respectively. Stones in both groups were equally present in the left and the right kidney ($p=0.84$). There was no significant difference in the topographical distribution of the stones ($p=0.68$). In the group of patients with a ureteral JJ stent, 7/13 (53.85%) of the stones were located in the upper calyces and 6/13 (46.15%) in the middle calyces, while in the group of patients without a ureteral JJ stent 17/28 (60.71%) of the stones were located in the upper calyces and 11/28 (39.29%) in the middle calyces. The comparison of the two groups regarding the dimensions of the stones showed that stones with a significantly different surface area were treated in both groups ($p=0.000012$). The mean size of the stone in the group of patients with ureteral JJ stent was statistically significantly greater compared to the non-stented group and was $245.40 \pm 22.99\text{mm}^3$ versus $156.18 \pm 47.0\text{mm}^3$ respectively (Table 1).

Table 1. Demographic characteristics of patient and stone

Patient and stone characteristic	Stent	No stent	p-value
No if patient	13	28	
Age			
mean \pm SD	53.5 \pm 7.0	50.9 \pm 10.4	t=0.8 p=0.41
min – max	45 – 65	28 – 70	
Sex			
Female	5/13 (38.46%)	9/28 (32.14%)	X ² =0.16 p=0.69
Male	8/13 (61.54%)	19/28 (67.86%)	
Stone			
left	7/13 (53.85%)	16/28 (57.14%)	X ² =0.04 p=0.84
right	6/13 (46.15%)	12/28 (42.86%)	
Stone			
upper pole	7/13 (53.85%)	17/28 (60.71%)	X ² =0.17 p=0.68
middle pole	6/13 (46.15%)	11/28 (39.29%)	
stone volume(mm3)			
mean \pm SD	245.40 \pm 22.99	156.18 \pm 47.0	Z=4.38 ***p=0.000012
median (IQR)	240.2(226.08–253.55)	142.08(122.46–200.96)	

t (Student t-test), X² (Pearson Chi-square test), Z (Mann-Whitney test)

p<0.01, *p<0.0001

No statistically significant difference was detected regarding the number of applied shock waves required for stone disintegration in both groups (p=0.082). On the other hand, there was a statistically significant difference in the energy used for stone disintegration in both groups (p=0.0028). In the group of patients with a ureteral JJ stent, the average energy used for stone disintegration was 241190.8 \pm 123468 J versus 144119.9 \pm 74288.5 J in the group of patients without a ureteral JJ stent. It was shown that the average number of sessions was significantly higher in patients with a ureteral JJ stent (p=0.006). A statistically higher number of patients in the stented group had re-treatment after the failed first treatment (p=0.0069). In fact, 9/13 of the stented patients (69.2%) and 7/28 of non-stented patients (25.0%) underwent an additional second or third treatment for stone disintegration. The success rate of SWL after 3 months, in the group of patients without a ureteral JJ stent was 85.71% (24/28) and was higher in relation to the success rate in patients with a ureteral JJ stent which was 76.92% (10/13). Despite the significant percentage difference between the two groups, no statistically significant difference was detected (p=0.66). In the stented group, the average time of the procedure was 49.15 \pm 1.7 minutes, while in the non-stented group it was 46.14 \pm 3.5 minutes. The difference of 3.01 minutes was statistically significant (p<0.0026) (Table 2).

Table 2. Treatment parameters and success rate

Treatment Parameters	Stent	No stent	p-value
No of SW			
mean \pm SD	1302.85 \pm 1871.5	2926.57 \pm 1673.4	Z=1.7 p=0.082
median (IQR)	105(103-4000)	4000(1578.5-4000)	
Energy (J)			
mean \pm SD	241190.8 \pm 123468	144119.9 \pm 74288.5	Z=2.98 **p=0.0028
median (IQR)	326726(115932-342470)	114669.5(106029-171445.5)	

No of session			
1-session	4/13 (30.77%)	21/28 (75%)	Fisher's exact **p=0.006
2-session	3/13 (23.08%)	5/28 (17.86%)	
3-session	6/13 (46.15%)	2/28 (7.14%)	
Re-Treatment			
yes	9/13 (69.23%)	7/28 (25%)	X ² =7.3 **p=0.0069
no	4/13 (30.77%)	21/28 (75%)	
Treatment duration(min)			
mean ± SD	49.15 ± 1.7	46.14 ± 3.5	Z=3.01 **=0.0026
median (IQR)	50 (48 – 50)	46 (44.5 – 49)	
Success rate	10/13 (76.92%)	24/28 (85.71%)	Fisher's exact p=0.66
Unsuccessful	3/13 (23.08%)	4/28 (14.29%)	

t(Student t-test),X²(Pearson Chi-square test),Z (Mann-Whitney test)
****p<0.01, ***p<0.0001**

Various morbidities such as “stainstrasse”, pain, lower urinary tract infection, hematuria and lower urinary tract symptoms (LUTS), were studied among stented and non-stented patients. Regarding pain, lower urinary tract infections and hematuria, there was no statistically significant correlation between the two groups (p=0.84 p=0.14 p=0.17). Regarding the post-SWL complications, a statistically significant difference was observed regarding the total number of complications, which in the group of patients with a ureteral JJ stent was 76.92% versus 28.57% in the non-stented group (p=0.0069). A statistically significant correlation between both groups was observed in the presence of a ureteral stent and the presence of lower urinary tract symptoms (LUTS) such as frequency, urgency and dysuria (P=0.002), which were more significant in the stented group as seen in Table 3. A total of 7.69% patients in the stented group and 7.14% patients in the non-stented group had “stainstrasse”. There was no statistically significant difference in the formation of “stainstrasse” in both groups (p=0.95).

Table 3. Complication

Complication	Stent	No Stent	P value
Overall	10/13 (76.92%)	8/28 (28.57%)	X ² =7.3 **p=0.0069
LUTS	4/13 (30.77%)	0	**p=0.002
Hematuria	2/13 (15.38%)	1/28 (3.57%)	p=0.17
Pain	2/13 (15.38%)	5/28 (17.86%)	p=0.84
UT infection	1/13 (7.69%)	0	p=0.14
Stainstrasse	1/13 (7.69%)	2/28 (7.14%)	p=0.95

t (Student t-test),X²(Pearson Chi-square test),Z (Mann-Whitney test)
*** *p<0.01, ***p<0.0001**

Discussion

Ureteral stents are commonly used to allow drainage of the kidney in the presence of obstruction between the kidney and the bladder, usually caused by a stone or stone fragments produced during the treatment of kidney stones with SWL. This condition is significantly related to the size of the stone. In our study, there was a significant difference in stone surface area between the two groups. In the group of patients with a ureteral JJ stent, the surface of the stone was significantly larger compared to the group of patients without a ureteral JJ stent ($p=0.000012$). This result corresponds to the research done by Hollowell at all in which it was determined that the most urologists use a ureteral JJ stent in the case of stones larger than 2cm^2 (10). We believe that urologists desire to prevent obstruction and consequent hydronephrosis and pain during SWL treatment of larger stones that play a role in the preference for using a ureteral JJ stent as in our study. A survey of American urologists on the use of ureteral stents before SWL showed a rate of 28% for 10mm stones, 57% for 15mm stones, and 87% for 20mm stones (11). The use of a ureteral JJ stent before SWL treatment is a rather undefined process, and numerous studies have shown that it is unbeneficial. In the study by Musa at all. it was shown that the use of a ureteral JJ stent before SWL, does not improve the outcome of the treatment (12). The authors reported a three-months success rate of 88% in the group of patients with a ureteral JJ stent and 91% in the group without a ureteral JJ stent. Similar results were shown in the study by Argyropoulos at all., where the success rate in patients with a ureteral JJ stent was 78% compared to those without a ureteral JJ stent, where it was 93% (13). And in the study by Mohayuddin at all. the success rate in patients with a ureteral JJ stent and those without it was 77.5% versus 82.5% respectively (14). It was observed that placement of a ureteral JJ stent before SWL for renal stones of $2\text{cm} \pm 2\text{mm}$ reduces the risk of renal colic and obstruction but does not reduce the formation of a "stainstrasse" or infectious complications. Our study is consistent with the findings of those studies. In our study, a worse outcome of SWL was also observed in patients with ureteral JJ stent. The overall success rate of the SWL method was higher in patients without a ureteral JJ stent compared to the patients in whom a ureteral JJ stent was placed preoperatively, and was 85.71% vs. 76.92%, respectively, but without confirmed statistical significance ($p=0.66$). The lower success rate of SWL in patients with a ureteral JJ stent may be due to the effect of the JJ stent on ureteral peristalsis, leading to reduced elimination of fragments.

Stainstrasse is a radiological finding that occurs after SWL. Although there are suggestions that ureteral JJ stents have a contribution to the elimination of fragments after SWL and the prevention of "stainstrasse", as in the study of Shen et al., Bierkens et all. found no difference in the rate of occurrence of "stainstrasse" with or without a ureteral JJ stent (15,16). And in the study by Kato et al. no difference was found between patients with and without a ureteral JJ stent in terms of "stainstrasse" formation (17). The results in our study were correlated to these results. In our study, no statistically significant difference was observed between patients with and without ureteral JJ stent regarding the formation of "steinstrasse" ($p=0.95$). We believe that the edema created by the ureteral JJ stent on the mucosa of the ureter and the reduced lumen of the ureter are the most likely reasons for the appearance of "stainstrasse" despite the presence of the ureteral JJ stent.

Ureteral JJ stent use is also associated to lower urinary tract symptoms (LUTS) such as frequent and urgent urination with dysuria. In the study by Musa A. at all. as many as 85% of stented patients had LUTS (11). Joshi et all. reported that 60% of the patients with a JJ stent had symptoms of overactive bladder, such as increased frequency of urination and urge incontinence (18). A study by Ozkan B at all. showed a LUTS rate of 38% (19). The results in our study are consistent with the results of Ozkan B at all. (19). In our series, about 30.77% of the patients had frequent and urgent urination with dysuria. In our study, a statistically significant difference was observed between patients with and without placed ureteral JJ stent in terms of LUTS ($p=0.002$). These symptoms were generally controlled by symptomatic therapy, and there was no need to remove the ureteral stent because of these symptoms in any of the patients.

In our study, we did not find a statistically significant difference in the occurrence of pain, lower urinary tract infections and hematuria between the two groups ($p=0.84$ $p=0.14$ $p=0.17$). These results are consistent with the most of results published in the literature such as those in the study by Shen et al. (15). In the study of Mobasher Saeed et al. (20), also, there was no statistically significant difference in terms of the same parameters between the two groups ($p=0.06$, $p=0.8$, $p=1$) (20).

In this research, we did not find a significant difference regarding the number of Shock wave use for stone disintegration in both groups ($p=0.082$). This result is consistent with the most of results published in the literature including those published in the study by Musa et al. who showed an identical number of SW strokes in the group of patients with and without a ureteral JJ stent (11). On the other hand, in our study there was a significant difference regarding the energy used for stone disintegration in the group of patients with a ureteral JJ stent versus the group of patients without a ureteral JJ stent ($p=0.0028$). This finding was correlated with the study of Preminger et al. which showed the use of significantly higher energy and a higher incidence of re-treatment in the group of patients with a ureteral JJ stent compared to those without a ureteral JJ stent ($p<0.005$) (21). Also, in the study of Wagar et al. significantly higher energy was used for the disintegration of stones in the patients with a ureteral JJ stent compared to those without a ureteral JJ stent ($p<0.005$) (22). Contrary to this, in the study of Ozkan et al. there was no significant difference in the energy used in patients with and without a JJ stent placed ($p=0.627$) (19). The reason for this difference is the different types of lithotripters during the intervention, as well as the difference in the experience of the physician. In our study, the mean number of sessions, as well as the retreatment rate were significantly higher in the group of patients with a ureteral JJ stent versus those without a ureteral JJ stent ($p=0.006$, $p=0.006$). These results were correlated with the results of Sfoungaristos et al. who reported that patients with a ureteral JJ stent needed more SWL sessions for stone disintegration compared to patients without a ureteral JJ stent ($p=0.019$) (23). Also, in the study of Ozkan et al. the average number of sessions was significantly higher in the group of stented patients compared to non-stented patients ($p=0.000$) (19).

Conclusion

Routine stenting of renal stones of 10-20mm in size before SWL should not be recommended because it does not prevent the formation of a “stainstrasse”, does not improve the success rate and causes irritative symptoms of the lower urinary tract. However, it can be used in cases of sepsis and in patients with worsening renal function due to obstruction or with unbearable pain.

References

1. Türk C, Petřík A, Sarica K, et al. Guidelines on Interventional Treatment for Urolithiasis. *Eur Urol.* 2016 Mar;69(3):475-82. doi: 10.1016/j.eururo.2015.07.041. Epub 2015 Sep 4. PMID: 26344917.
2. Rosa M, Usai P, Miano R, et al. Recent finding and new technologies in nephrolithiasis: A review of the recent literature. *BMC Urology.* 2013; 13:10–35.
3. Drach GW, Dretler S, Fair W, et al. Report of the United States cooperative study of extracorporeal shockwave lithotripsy. *J Urol.* 1986; 135: 1127-1133.
4. Obek C, Onal B, Kantay K, et al. The efficacy of extracorporeal shock wave lithotripsy for isolated lower pole calculi in comparison with isolated middle and upper caliceal calculi. *J Urol.* 2001; 166: 2081-2084.

5. Gillenwater JY. Extracorporeal shockwave lithotripsy for the treatment of urinary calculi, in: Gillenwater JY, Grayhack JT, Howards SS, and Duckett JW (Eds). *Adult and Pediatric Urology*, St Louis, Mosby Year Book, 1991, vol 1, pp 695-710.
6. Buchholz NP, Meier-Padel S, Rutishauser G (1997) Minor residual fragments after extracorporeal shock wave lithotripsy: spontaneous clearance or risk for recurrent stone formation? *J Endourol* 11:225–232.
7. Kirkali Z, Esen AA, Akan G (1993) Place of double-J stents in extracorporeal shock wave lithotripsy. *Eur Urol* 23:460–462.
8. Musa AA. Use of double J stents prior to extracorporeal shock wave lithotripsy is not beneficial: results of a prospective randomized study. *Int Urol Nephrol*. 2008; 40: 19-22.
9. Mohayuddin N, Malik HA, Hussain M, et al. The outcome of extracorporeal shockwave lithotripsy for renal pelvic stone with and without JJ stent – a comparative study. *J Pak Med Assoc*. 2009; 59: 143-146.
10. Hollowell CM, Patel RV, Bales GT, et al. Internet and postal survey of endourologic practice patterns among american urologists. *J Urol*. 2000; 163: 1779-1782.
11. Drach GW, Dretler S, Fair W, et al. Report of the United States cooperative study of extracorporeal shockwave lithotripsy. *J Urol*. 1986; 135: 1127-1133.
12. Musa AA. Use of double-J stents prior to extracorporeal shock wave lithotripsy is not beneficial: results of a prospective randomized study. *Int Urol Nephrol* 2008;40(1):19-22.
13. Argyropoulos AN, Tolley DA. Ureteric stents compromise stone clearance after shockwave lithotripsy for ureteric stones: results of a matched-pair analysis. *BJU Int*. 2009 Jan;103(1):76-80. doi: 10.1111/j.1464-410X.2008.07886.x. Epub 2008 Aug 14. PMID: 18710453.
14. Mohayuddin N, Malik HA, Hussain M, et al. The outcome of extracorporeal shockwave lithotripsy for renal pelvic stone with and without JJ stent--a comparative study. *J Pak Med Assoc*. 2009 Mar;59(3):143-6. PMID: 19288938.
15. Shen P, Jiang M, Yang J, et al. Use of ureteral stent in extracorporeal shock wave lithotripsy for upper urinary calculi: a systematic review and meta-analysis. *J Urol* 2011; 186:1328-35.
16. Bierkens AF, Hendrikx AJ, Lemmens WA, et al. Extracorporeal shock wave lithotripsy for large renal calculi: the role of ureteral stents. A randomized trial. *J Urol* 1991; 145:699-702.
17. Kato Y, Yamaguchi S, Hori J, et al. Utility of ureteral stent for stone street after extracorporeal shock wave lithotripsy. *Hinyokika Kiyo*. 2005; 51: 309-314.
18. Joshi HB, Okeke A, Newns N, et al. Characterization of urinary symptoms in patients with ureteral stents. *Urology*. 2002; 59: 511-516.
19. Ozkan B, Dogan C, Can GE, et al. Does ureteral stenting matter for stone size? A retrospective analyses of 1361 extracorporeal shock wave lithotripsy patients. *Cent European J Urol*. 2015;68(3):358-64. doi: 10.5173/ceju.2015.611. Epub 2015 Oct 15. PMID: 26568882; PMCID: PMC4643708.

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20. Mobasher Ahmed Saeed, Mohammad Ali Sajid, Abdullah, Syed Majid Waseem, et al. Outcome of Extracorporeal Shock Wave Lithotripsy for renal pelvic stone with and without double J stent. JSZMC. 2019 Vol.10 No.02 1682-86.
 21. Preminger GM, et al: Ureteral stenting during extracorporeal shock wave lithotripsy: help or hindrance? J Urol 142: 32 (1989).
 22. Waqar Ahmed Memon¹, Salman El Khalid², Imran Sharif², et al. The Efficacy of JJ Stent on Stone Free Rate After Extracorporeal Shock Wave Lithotripsy: A Retrospective Study PJMD 2021, VOL. 10 (02):22-27.
 23. Sfoungaristos S, Polimeros N, Kavouras A, et al. Stenting or not prior to extracorporeal shockwave lithotripsy for ureteral stones? Results of a prospective randomized study. Int Urol Nephrol. 2012 Jun;44(3):731-7. doi: 10.1007/s11255-011-0062-3. Epub 2011 Sep 30. PMID: 21960371.

SPECIFIC ANESTHETIC APPROACHES IN PATIENTS WITH BREAST CANCER

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ABSTRACT

Objectives: The latest research shows an influence of some anesthetics and anesthetic techniques on patient's outcome who underwent breast cancer surgery. Surgery remains a golden standard in breast cancer therapy. The proper choice of type of anesthesia is crucial for a patient's safety and outcome.

Aim: To analyze which type of anesthesia for patients undergoing breast cancer surgery was the most preferable during 3-years period and to compare data with those in literature. **Material and Methods.** A three-years retrospective analysis (2019-2021) at Thoraco-vascular Surgery Clinic was done. Out of 1304 patients hospitalized for breast cancer surgery, a group of 60 patients were selected for analysis, divided into two groups according to the type of anesthesia (total intravenous anesthesia (TIVA) or TIVA + lidocaine). The effects of types of anesthesia on hemodynamic parameters, respiration and postoperative comfort were analyzed. Data were discussed with data from PubMed, Cochrane database. **Results:** All 1304 patients received TIVA. There was increasing use of TIVA over the years. TIVA + intravenous lidocaine 60mg was used in 25% of all patients in year 2020 and 30.4% in 2021. Blood pressure showed a significant decrease in both groups, without change in the heart rate. There was a significant reduction in postoperative respiratory rate ($12,7\pm 1,1$ vs $13,7\pm 1,6$; $P=0,04$) and better postoperative comfort ($2\pm 0,38$ vs $1,56\pm 0,62$; $P=0,01$) in the lidocaine group. The TIVA patients were more tachypneic and less satisfied. **Conclusion:** Using less harmful anesthetics and anesthetic techniques in everyday practice is imperative. TIVA+ lidocaine is a safe anesthesia in breast cancer surgery and can increase a patient's survival.

Key Words: anesthesia, breast surgery, immune function, local anesthetics.

Introduction

The Breast cancer remains as a leading cause for morbidity and mortality among the female population in the world and in our country. The annual incidence of Breast Cancer in the world depends on the level of development of the country (1). During 2020 in EU 13.3% of all newly diagnosed malignancies belonged to the breast cancer. The data obtained from the Institute for Public Health of Republic of North Macedonia shows 1200 new cases per year, with a mortality rate of 26.4 on 100000 (2).

Surgery and modified radical mastectomy remain the gold standard of treatment of the breast cancer. The anesthesiologic approach is delicate because the patients with malignancy are female, vulnerable population, under psychological stress, and can undergo repetitive operations. Unfortunately, surgical manipulation over the tumor inevitably provokes dissemination of the tumor cells through blood in the lymphatic system, with an impact to the outcome of the patients

with breast carcinoma. Recent research shows that some anesthetics and anesthetic techniques contribute to the outcome (3, 4). This knowledge increased the interest of anesthesiologists to discover more data about the anti-stress effects of anesthetic agents and its effects in breast surgery. Until today there is no present ideal anesthesia or anesthetic technique for breast surgery, the most of them have advantages or some unwanted effect (5).

During surgery the surgical trauma provokes a stress response of the body with an increase in the catecholamines, prostaglandins, cortisol, cytokines and others. Those products produce immunosuppression with decreased cells immunity. The dissemination of the tumor cells, inflammation, growth factors and impaired immunity are the key factors responsible for the long-time prognoses of the patients with breast tumor (6). The operative stress and the anesthetic agents activate a state of molecular mechanisms which reflects the genetic transcription of the patients with breast carcinoma (7). Current references show that volatile anesthetics and opioids suppress the immune function and play a role in the dissemination of the tumors. Otherwise, several new randomized studies affirm that the use of Propofol, local anesthetics, NSAID-analgesics and tramadol have either positive effect or no effect on the immune function (8). This problem is still under scope and additional research is needed. Those data motivated us to make a retrospective study to find out what anesthetic protocol is used for breast surgery in our department and to discuss if it is safe for the patients or something should be changed.

Goal

The main aim of this study was to find out which type of anesthesia was the most likely and preferable for patients undergoing breast surgery in our department and to compare the obtained data with those in the literature. To complete the secondary outcome, an overview of the medical literature was made. The obtained data were compared to those from the literature and the last data about the unwanted effects of anesthetics on tumor growth, as well as which possible markers are the most appropriate for use were discussed.

Results

The data of the given anesthesia in a three-years period is demonstrated below in Table 1. In this period 4035 patients were anesthetized for operations in thoraco-vascular surgery, and out of them 1304 cases were anesthetized for mastectomy. The type of anesthesia was general: total intravenous anesthesia (TIVA) with propofol, Fentanyl/ remifentanil and pancuronium/ rocuronium. It was obvious that in 2020, with the aim of decreasing the perioperative stress, during the introduction to anesthesia to TIVA, i.v. bolus of 60mg lidocaine 1% was added. In 2021 in order to prevent postoperative pain, preoperatively were added “dorsal rectus plane” block and Pectoralis major and minor blocks (Pictures 1&2).

Table 1. The total number of anesthesia and anesthesia of Ca mammae at a three-years period (n=4035).

Year	2019	2020	2021	N
Total N/%	1798/44.5	1009/25	1228/30.4	4035
Ca mammae /Year	530 (29.4%)	368 (36.47%)	406 (33.06%)	1304
Type of anesthesia for Ca mammae	General TIVA	TIVA + iv lidocaine	TIVA + Lid + blocks	

The data show that in 2019, 29.4% of all surgical interventions in the UC for thoraco-vascular surgery, were modified radical mastectomies. This number increases in 2020 and 2021 to 36.4 and 33.06 respectively.

The data of 60 representative patients in demographics and hemodynamic response anesthetized with TIVA and TIVA with lidocaine are presented in Tables 2 and 3.

Table 2. Demographics of the Groups (N, %, M±SD)

Groups	N	Sex (N/%)		Ages (Years)	Weight (kg)
		Female	Male		
TIVA	30	29 (96.66%)	1 (3.34%)	60.47±6.12	72.29±11.79
TIVA +lidocaine	30	30 (100 %)	0 (0%)	60.43±8.59	73.82±17.25
p		>0.05	>0.05	0.51	0.000

Demographic data show that most of the patients were female, in good condition, and approximately of same age @60 year. The differences between the groups were insignificant >0.005.

Blood pressure (BP) and heart rate (HR) in the two groups were noted in 5 times periods (T₀-T₅), where Mean BP was used as the most accurate. The times of measurement were as follows: T₀ – before the induction to anesthesia. T₁ after the induction to anesthesia, and T₂, T₃, T₄, T₅ every ten minutes after surgical incision. The approximate time of anesthesia was from 40 to 60 minutes. The values of BP and HR in the time T₀, were similar in both groups without significant differences.

Table 3. Hemodynamic disorders according to the type of anesthesia.

Variables	N	Mean BP		N	HR	
		TIVA	TIVA + Lido		L	TIVA
Groups/Timing	R			L		
T₀	30	101.43±16.89	106.43±15.73	30	83.63±15.80	84.13±12.88
T₁	30	91.77±15.58	96.90±14.31	30	79.80±14.52	80.87±10.87
T₂	30	88.87±14.15	94.47±15.27	30	77.93±13.38	80.97±11.65
T₃	30	85.87±16.33	94.40±13.69	30	78.40±15.13	80.77±13.29
T₄	28	83.43±13.60	92.83±10.36	23	78.43±14.74	80.26±12.90
T₅	20	91.55±12.63	94.09±14.94	11	74.45±14.84	78.09±13.85
p		p = 0.001	p = 0.01		p = 0.42	p = 0.75

Kruskal-Wallis test: H (% , N= 154) =14.89 и p<0.05(p = 0.01)

The analysis of the BP in the studied periods shows a significant decrease in the TIVA group (p=0.001), and in the TIVA +Lidocaine group (p=0.01). The heart rate was not significantly changed in the groups (p=0.42 Vs p=0.75).

The effect of applied anesthesia on postoperative respiration was evaluated by the values pSO₂ and the respiratory rate, for postoperative pain visual analogue scale (VAS) was used, and the comfort was measured by three digits (1 - uncomfortable; 2 - mild comfort; 3 - comfort). The results are presented in the table below (Table 4.).

Table 4. Postoperative respiration, pain, and comfort in the studied groups (M±SD)

Anest	Resp/min	SpO ₂	Pain	Comfort
TIVA	13.7 ± 1.6	96.1 ± 1.5	7.3 ± 1.1	2 ± 0.38
TIVA + lidocaine	12.7 ± 1.1	96.8 ± 1.3	6.8 ± 1.08	1.56 ± 0.62
p	P=0.04	P=0.19	P=0.18	P=0.01

There was a significant difference in postoperative respiration/ minute and postoperative comfort (P<0.05). The TIVA patients were more tachypneic and less satisfied. The values of SpO₂ and postoperative pain were similar, but with lower VAS scores in the TIVA + Lidocaine group.

Discussion

According to the data from the recent literature, it appeared that volatile anesthetics and opioids suppress the immune function and could affect the long-term prognosis of patients with breast cancer (5). But other studies show that the use of Propofol, local anesthetics, NSAID-analgesics and tramadol have benefits, either positive effect or no effect on the immune function (8). The data from this study show a continuous improvement in the type of anesthesia, without the use of volatile anesthetics for breast surgery. Propofol with its beneficial properties was used in all anesthetized patients. The involvement of i.v. lidocaine is an unpretending beginning of the use of multimodal anesthesia as an opioid sparing technique. All of them with the main goal of achieving a safe anesthesia for patients with cancer.

It is known that surgery as a surgical trauma produces a severe stress response of the body, which is complex including the release of catecholamines, inflammation and growth cells (9). For this reason, less invasive surgical techniques are developed and new anesthetic techniques, such as: balanced anesthesia, multimodal anesthesia, regional and combined anesthesia. In all those surgical and anesthesiologic technics the patients are in the first line, using the multidisciplinary teams, whose main goal is to decrease the surgical stress, to optimize the physiological functions and to facilitate the postoperative recovery.

The surgery for breast carcinoma - partial or radical mastectomy, has a direct influence on the stress response and cells immunity, producing immunosuppression. Therefore, the activity of natural Killer Cells (NKC's) which are the main defense mechanism against the spread of tumor cells, is decreased, the relation of T2/T1 is impaired, and the activity of cytotoxic lymphocytes (CTL's) is suppressed (15-10).

The data in the literature about the effects of some Anesthetics on the tumor growth are still controversial (11).

In 2020, it was referred that volatile anesthetics, as isoflurane and sevoflurane, decrease the cytotoxicity NKC's, CTL's and the relation of T1/T2 cells, and they have tumorigenic effects because they inhibit the cellular apoptosis and stimulate the cells proliferation and migration (12). Other authors show that those attributes are dose dependent (13). Contrary to these findings are the results of some in vitro studies, where the authors assure that there are not significant differences and without invasive characteristics (14,15).

The situation about the agents used for total intravenous anesthesia (TIVA) is less alarming. The use of propofol for anesthesia in breast surgery shows several beneficial effects. It has limited influence on the immune function and NKC's, it can inhibit the systemic inflammatory response (SIRS) and the activity of hypoxia induced factor 1 alfa (HIF1α) (23,24). Propofol helps the

cellular apoptosis of tumors, what makes it to be one of the preferable agents in anesthesia of breast surgery (16).

Dexmedetomidine, a selective α_2 agonist with simpaticoliticos and anti-inflammatory effects used still in anesthesia for sedation, is not convenient agent for cancer surgery. Experimental studies confirm that it stimulates the appearance of metastasis (17).

Opioids such as fentanyl, remifentanyl, alfentanil or sufentanil have immunosuppressive effects. They decrease the activity of the NKC's, cytokines production, phagocyte's activity, and the release of antibodies (18). Those effects are decreased if they are used in combination with propofol, what was used as a preferred TIVA anesthesia in this studied material (19,20)

Conclusion

The ideal anesthesia does not exist, but the tendency in everyday practice should be to use the less harmful agents. With this study was shown that the most preferable anesthesia was general anesthesia (TIVA) where induction was done with propofol. The combination with local anesthetics (i.v. lidocaine) or regional techniques confirmed its benefits for patients with breast cancer. It is expected that such combinations could suppress the changes in immune function and can increase the survival of the patients with breast carcinoma. Further research in this field is necessary.

References:

1. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Akinyemiju TF, Al Lami FH, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2016: A Systematic Analysis for the Global Burden of Disease Study. *JAMA Oncol.* 2018;4 (11):1553.
2. Институт за јавно здравје на Република Северна Македонија: Извештај за реализирани активности во врска со скрининг на ракот на дојка кај жените на возраст од 50-69 години, во Република Северна Македонија за 2019 година, Скопје, 2020.
3. Schreiber RD, Old LJ, and Smyth MJ (2011) Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion *Science* 331 1565-1570 <https://doi.org/10.1126/science.1203486> PMID: 21436444.
4. Ponferradaa RA, Ruiz JCM , MolinaSR , et al. Breast cancer and anaesthesia: genetic influence. *Int. J. Mol. Sci.* 2021; 22(14):7653DOI: 10.3390/ijms22147653.
5. Anand S., Bajwa S. J. and KaurG. (2015). Anesthesia and cancer recurrences: The current knowledge and evidence. *Journal of Cancer Research & Therapeutics*, 11(3), 528–534. <https://doi-org.ric.idm.oclc.org/10.4103/0973-1482.157321>.
6. Шољакова М: Ефект на епидурално аплициран морфин врз метаболизмот на ногата при оперативни интервенции во општа и регионална анестезија, Докторска теза, УКИМ, Медицински факултет Скопје, 1987:1-10.

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7. Horowitz M, Neeman E, Sharon E, Ben-Eliyahu S. Exploiting the critical perioperative period to improve long-term cancer outcomes. *Nat Rev Clin Oncol*. 2015;12(4):213.
 8. Evans MT, Wigmore T, Kelliher LJS. The impact of anesthetic techniques upon outcome of oncological surgery. *BJA Education* 2019; 19(1): 14:20.
 9. Hiller JG, Perry NJ, Pouligiannis G, et al. Perioperative events influence cancer recurrence risk after surgery [Internet]. Vol. 15, *Nature Reviews Clinical Oncology*. Nature Publishing Group; 2018 [cited 2021 Mar 22]. p. 205–18. Available from: <https://pubmed.ncbi.nlm.nih.gov/29283170/>.
 10. Kim, S.H., Lee, J.Y., Lee, S.H., et al. (2018b). Effect of Equipotent Doses of Propofol versus Sevoflurane Anesthesia on Regulatory T Cells after Breast Cancer Surgery. *Anesthesiology*, 129(5), 921–931. <https://doi-org.ric.idm.oclc.org/10.1097/ALN.0000000000002382>.
 11. Melamed R, Bar-Yosef S, and Shakhar G, *et al* (2003) Suppression of natural killer cell activity and promotion of tumor metastasis by ketamine, thiopental, and halothane, but not by propofol: mediating mechanisms and prophylactic measures *Anesth Analg* 97 1331–1339 <https://doi.org/10.1213/01.ANE.0000082995.44040.07> PMID: [14570648](https://pubmed.ncbi.nlm.nih.gov/14570648/).
 12. Efremov SM, Kozireva VS, Moroz GB, et al. The immunosuppressive effects of volatile versus intravenous anesthesia combined with epidural analgesia on kidney cancer: a pilot randomized controlled trial. *Korean J Anesthesiol*. 2020 Dec;73(6):525-533. doi: 10.4097/kja.19461. Epub 2020 Feb 26. PMID: 32098012; PMCID: PMC7714631.
 13. Li Q, Zhang L, Han Y, et al. Propofol reduces MMPs expression by inhibiting NF- κ B activity in human MDA-MB-231 cells. *Biomed Pharmacother* [Internet]. 2012 Feb [cited 2021 Mar 21];66(1):52–6. Available from: <https://pubmed.ncbi.nlm.nih.gov/22264881/>
 14. Pirbudak Cocelli L, Ugur MG, Karadasli H. Comparison of effects of low-flow sevoflurane and desflurane anesthesia on neutrophil and T-cell populations. *Curr Ther Res Clin Exp*. 2012; 73:41–51.
 15. Cho JS, Lee MH, Kim SI, et al. The Effects of Perioperative Anesthesia and Analgesia on Immune Function in Patients Undergoing Breast Cancer Resection: A Prospective Randomized Study. *International Journal of Medical Sciences*. 2017 ;14(10):970-976. DOI: 10.7150/ijms.20064. PMID: 28924368; PMCID: PMC5599920.
 16. Lavon H, Matzner P, Benbenishty A, et al. Dexmedetomidine promotes metastasis in rodent models of breast, lung, and colon cancers. *Br J Anaesth* [Internet]. 2018 Jan 1 [cited 2021 Mar 21];120(1):188– 96. Available from: [/pmc/articles/PMC6246773/](https://pubmed.ncbi.nlm.nih.gov/pmc/articles/PMC6246773/).
 17. Kocak N, Ozen F, Yildirim IH, et al. Fentanyl inhibits tumorigenesis from human breast stem cells by inducing apoptosis. *Asian Pacific J Cancer Prev* [Internet]. 2017 Mar 1 [cited 2021 Mar 21];18(3):735–9. Available from: <https://pubmed.ncbi.nlm.nih.gov/27311111/>.

18. Colacchio TA, Yeager MP, Hildebrandt LW. Perioperative immunomodulation in cancer surgery. *Am J Surg.* 1994; 167:174–179.
19. Pérez-González O, Cuéllar-Guzmán LF, Soliz J, et al. Impact of Regional Anesthesia on Recurrence, Metastasis, and Immune Response in Breast Cancer Surgery: A Systematic Review of the Literature [Internet]. Vol. 42, *Regional Anesthesia and Pain Medicine*. Lippincott Williams and Wilkins; 2017 [cited 2021 Mar 21]. p. 751–6. Available from: <https://pubmed.ncbi.nlm.nih.gov/28953508/>.
20. Ramirez MF, Tran P, Cata JP. The effect of clinically therapeutic plasma concentrations of lidocaine on natural killer cell cytotoxicity. *Reg Anesth Pain Med.* 2015 Jan-Feb;40(1):43-8. doi: 10.1097/AAP.000000000000191. PMID: 25469757.

EFFECT OF *ESMOLOL* CARDIOPLEGIA ON POSTOPERATIVE COMPLICATIONS AND LENGTH OF IN-HOSPITAL STAY AFTER CORONARY ARTERY BYPASS SURGERY

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ABSTRACT

Introduction: Protection of the myocardium during coronary artery bypass surgery (CABG) refers to strategies and methods used to reduce or prevent perioperative infarction and/or post-ischemic ventricular dysfunction. *Esmolol* is a cardio-selective beta1-blocker which, due to its properties, is the drug of first choice for use as an adjunct to cardioplegia in patients with coronary artery disease (CAD).

Aim: The purpose of this study was to determine whether *esmolol* cardioplegia would reduce postoperative complications, reduce the length of stay in the intensive care unit (ICU) and the hospital stay of patients after CABG.

Material and Methods: 100 patients aged 40-80 years with CAD were included in this prospective, randomized, controlled study. Patients were grouped into two randomized groups according to whether they received *esmolol* according to a well-defined protocol or placebo.

Results: Comparison of postoperative complications between patients who received *esmolol* and those without it, showed the absence of statistically significant differences, except that atrial fibrillation (AF) occurred significantly more often in patients who received *esmolol* ($p=0.05$). The number of days spent in the ICU was statistically significantly shorter ($p=0.014$) in patients receiving *esmolol* compared to others. Also, the total in-hospital stay was statistically significantly shorter ($p=0.049$) in patients receiving *esmolol*.

Conclusion: Using *esmolol* as a pharmacological method for cardio-protection has been found to have a beneficial effect in reducing the duration of ICU and hospital stays for patients undergoing coronary artery bypass surgery. However, this treatment approach does not appear to have any significant impact on the occurrence of postoperative complications.

Key Words: cardiac surgery, cardio-anesthesia, coronary artery disease, *Esmolol*.

Introduction

Coronary artery bypass surgery (CABG) is an effective myocardial revascularization strategy that improves survival in high-risk patients (1). However, despite the use of the most effective myocardial protection, in patients with coronary artery disease (CAD), the heart is still subjected to significant acute global ischemia-reperfusion injury (IRI) during surgery, resulting in an increased risk of perioperative myocardial infarction and impaired left ventricular systolic function. Global IRI is potentiated in patients with Society of Thoracic Surgery (STS) score over 4, in patients with complex cardiac surgery procedure, longer duration of cardiopulmonary bypass, in older patients and those with more comorbidities (2,3). There are strategies and methods used to reduce or prevent postischemic ventricular dysfunction and perioperative myocardial infarction, referred as myocardial protection strategies (1,4,5,6).

The use of Beta-(β)-adrenergic blockers (BBs) is a pharmacological cardioprotective method for protecting the myocardium. They have the ability to reduce the degree of myocardial injury during ischemia and reperfusion if given before aortic clamping or together with cardioplegic solution (1,4,5,7,8,9). The most of BBs have a prolonged (hours) negative inotropic and chronotropic effect, thus possessing positive properties significant for the preoperative and postoperative period, but this limits their use during cardiac surgery (10,11,12). *Esmolol* is a cardio-selective BB, with an ultra-short action, which is usually applied as an addition to the cardioplegic solution in order to ensure adequate protection of the myocardium in the perioperative period (13,14,15).

The aim of this study was to determine whether the application of a fast-acting beta-1 selective adrenergic blocker – *esmolol*. immediately before CABG and as an adjunct to cardioplegia itself, would reduce postoperative complications, would reduce the length of stay in the intensive care unit (ICU) and the hospital stay of patients after CABG.

Material and Methods

Study Design, Specimens and Methods

Material

In this prospective, randomized, controlled study, 100 patients aged 40-80 years with coronary artery disease were included in the period 2021-2023. All patients met the criteria for inclusion in the study and had signed the informed written consent for their participation in the study which was previously explained to them in detail.

Patients were randomized into two groups according to whether they received *esmolol* or placebo. For appropriate randomization, a computer-generated list of random numbers was used. Randomization numbers were written and assigned to the participants on an opaque, sealed, numbered envelope, containing information about patient allocation (*esmolol* or placebo).

Methods

According to the intended protocol for the inclusion of *esmolol*:

The first dose of *esmolol* (1mg/kg in 10mg/ml solution) was administered immediately before clamping the aorta or after cannulation of the aorta, through a central venous catheter.

A second dose of *esmolol* along with antegrade cold blood cardioplegia (2mg/kg in a 10mg/ml solution) was given. The study group received a maximum dose of *esmolol* 100mg before aortic clamping, while the maximum dose of *esmolol* received with cardioplegia was 200mg.

A placebo (saline solution) in the same volume was given to the control group of subjects.

All patients included in the study were monitored for the following postoperative complications: (1) atrial fibrillation (AFF); (2) AFF repetitive; (3) AFF on discharge; (4) myocardial infarction (MI); (5) cerebrovascular insult (CVI); (6) revision; (7) acute renal failure (ARF); (9) hemodialysis; (10) reintubation. Also, all patients were monitored for: (11) length of stay in ICU and (12) length of total hospital stay.

Statistical Analysis

Percentages and continuous parameters (categorical parameters) were summarized as mean \pm standard deviation. Differences between groups were tested using Pearson's Chi-square test for categorical variables and Mann-Whitney non-parametric tests for continuous variables. Correlation was done using Pearson's or Spearman's analysis. All data analyzes were performed using SPSS version 25.0 (IBM SPSS, Inc., Chicago, Illinois, USA), and $p \leq 0.05$ was considered statistically significant.

Results

A total of 100 patients who met the study entry criteria were the subject of our investigation. Basal, clinical, preoperative characteristics of the study population are given in Table 1.

Table 1. Basic clinical characteristics of the study population.

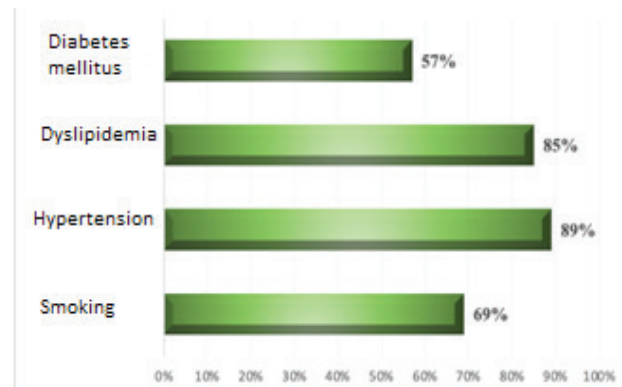
Parameters	n=100
Age (y)	65.57±8.57
Sex (%)	
Men	77
Women	23
BMI (kg/m ²)	27.76±4.45
Smoking (%)	69
Hypertension (%)	89
Dyslipidemia (%)	85
Diabetes mellitus (%)	57
COPD (%)	13
Previous PCI (%)	19
CHF (%)	1
PAD (%)	16
CVI (%)	8
Previous AFF (%)	3
CRF (%)	7
Carotid artery disease (%)	18
CCS classification	3.06±0.65
Class II (%)	18
Class III (%)	58
Class IV (%)	24
NYHA classification (%)	3.06±0.63
Class II (%)	17
Class III (%)	60
Class IV (%)	23
EuroSCORE	5.17±4.15
1-2 score (%)	65
3-5 score (%)	31
≥ 6 score (%)	4
STS score	2.10±2.18

BMI= body mass index; EuroSCORE = European system for cardiac operative risk evaluation; CABG=coronary artery bypass surgery; MI=myocardial infarction; NYHA=New York Heart Association; PCI=percutaneous coronary intervention; AFF=atrial fibrillation; CHF=heart failure; STS score=Score of Thoracic Surgery Society; COPD=chronic obstructive pulmonary disease; CRF=chronic renal failure; CVI=cerebrovascular insult; CCS=Canadian Cardiovascular Society.

The average age of the patients was 65, the youngest was 41 and the oldest was 80 at the time of surgery. In the studied group of patients, men were represented in percentage more than women, and the patients were dominated by increased body weight, that is, it ranged from the minimum of 18.0kg/m² to the maximum of 39.8kg/m².

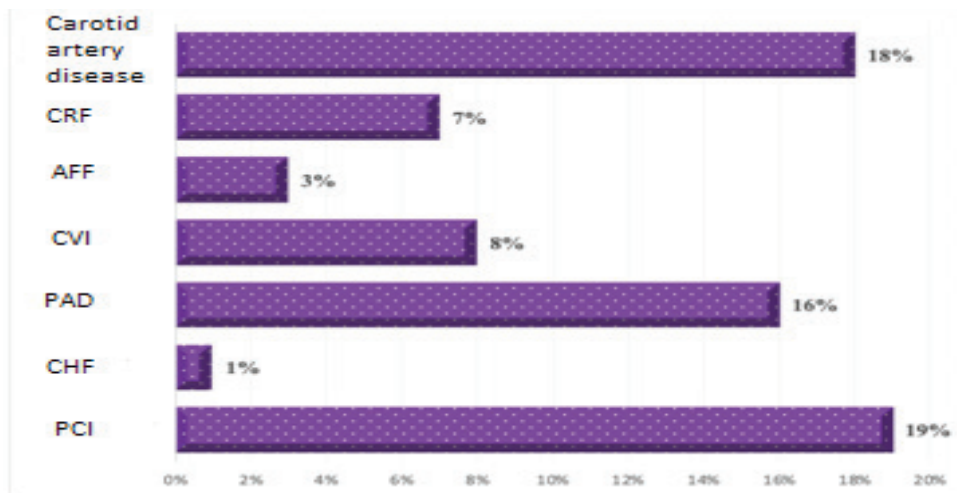
Of the risk factors for atherosclerosis (Table 1, Figure 1), arterial hypertension and dyslipidemia were represented the most often with 89% and 85%, respectively. Diabetes mellitus was present in slightly over half of the patients (57%), of which 32% were controlled by oral tablet therapy, 6% by a combination of oral therapy and insulin, and 18% by insulin alone. 69% of patients were active smokers before CABG.

Figure 1. Graphic representation of percentage representation of risk factors for atherosclerosis in the studied group.



Previous diseases were dominated by previous CAD for which percutaneous intervention was performed (19%) and carotid disease (18%) (Table 1, figure 2).

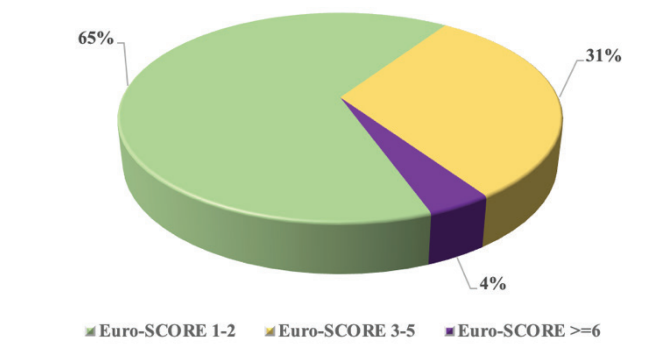
Figure2. Graphic display of percentage representation of associated diseases in the studied group.



The classification according to the Canadian Cardiovascular Society (CCS) showed mean values belonging to the third group (58%) which refers to those who have a more pronounced limitation of the usual activity, which also corresponded with the classification of the New York Heart Association (NYHA) where there was also the largest representation of the third classification group (60%) (Table 1).

As for the European system for cardiac operative risk evaluation (EuroSCORE), the patients on average belonged to the low-risk group (Euro-SCORE 1-2) i.e., 65% were at low risk, 31 % with medium risk (Euro-SCORE 3-5), and only 4% were with high risk (Euro-SCORE ≥ 6) (Table 1, Figure 3).

Figure 3. Graphic display of percentage representation of associated diseases in the studied group



The Score of Thoracic Surgery Society (STS) was generally lower, reflecting a lower risk of in-hospital mortality.

The comparison of the basal values of the patients divided into two groups of 50 patients each: those who received the fast-acting beta-1 selective adrenergic blocker-*esmolol* and those without it, are given in Tables 3 and 4.

Table 3. Comparison of anthropometric measurements and magnitude of clinical scores for pre-surgical performance of patients divided into those with and without *esmolol* given.

Parameters	With <i>esmolol</i> n=50	Without <i>esmolol</i> n=50	p
Age (years)	65.18±7.83	65.96±9.30	0.471
Sex Men (Women) (n/%)	70/30	84/16	0.077
BMI (kg/m ²)	27.45±4.58	28.06±4.34	0.398
NYHA classification	2.96±0.57	3.16±0.68	0.105
CCS classification	2.94±0.58	3.18±0.69	0.059
EuroSCORE	4.99±3.99	5.35±4.34	0.850
STS score	1.91±1.81	2.28±2.50	0.491

CCS=Canadian Cardiovascular Society; NYHA=New York Heart Association;
EuroSCORE=European system for cardiac operative risk evaluation;
STS score= Society of Thoracic Surgeons score.

Patients in both groups were almost identical in age (p=0.471) with a non-significantly higher representation of females in the group with *esmolol* (30%) compared to the group without *esmolol* (16%), (p=0.077). Patients from both groups had almost identical increased body weight (p=0.398).

Regarding the clinical classifications (NYHA and CCS class), the NYHA classification was statistically insignificantly higher in the placebo group, 3.16 ± 0.68 , compared to the *esmolol* group, 2.96 ± 0.57 , ($p=0.105$). The CCS classification was statistically marginally higher in the placebo group, 3.18 ± 0.69 compared to the *esmolol* group, 2.94 ± 0.58 , ($p=0.059$).

EuroSCORE in patients in the *esmolol* group was 4.99 ± 3.99 , while in patients in the placebo group it was 5.35 ± 4.34 , ($p=0.850$). The STS score was 1.91 ± 1.81 in the *esmolol* group while in the placebo group it was 2.28 ± 2.50 , ($p=0.491$). The values of both surgical scores were statistically insignificantly lower in the study group compared to the control group of patients, that is, they had more favorable clinical and pre-surgical performance (Table 1, Figure 4).

Figure 4. Graphical representation of the comparison of score size in patients with and without esmolol.

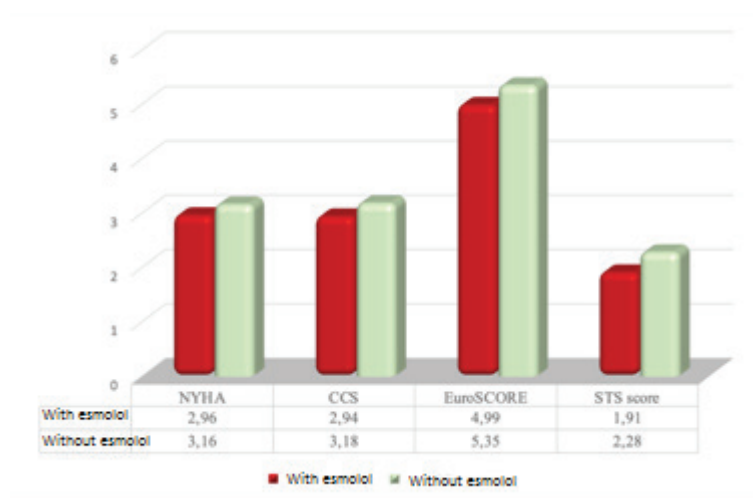


Table 4. Comparison of risk factors in patients divided into those with and without given esmolol.

Parameters	With esmolol n=50	Without esmolol n=50	p
Smoking (%)	70	68	0.500
Hypertension (%)	90	88	0.500
Dyslipidemia (%)	84	86	0.500
Diabetes mellitus (%)	56	58	0.500
COPD (%)	16	1 ⁰	0.277
Previous PCI (%)	22	16	0.306
CHF (%)	-	2.0	0.500
PAD (%)	12	20	0.207
CVI (%)	6	10	0.357

There were no statistically significant differences regarding the risk factors for atherosclerosis (Table 4), in participants with and without given *esmolol*.

Comparison of postoperative complications showed, in principle, the absence of significant differences between patients in the *esmolol* and placebo groups, except that AFF occurred statistically significantly more often in patients receiving *esmolol* (48%), compared to patients in the placebo group (30%), ($p=0.05$) (Table 5).

Table 5. Comparison of postoperative complications in patients divided into those with and without esmolol given.

Postoperative complications (%)	With esmolol n=50	Without esmolol n=50	p
AFF	48	30	0.050
Repetitive AFF	18	8	0.117
AFF on discharge	6	4	0.500
Postoperative MI	2	0	0.500
CVI	2	2	0.753
Revision	0	2	0.500
ARF	2	0	0.500
Hemodialysis	2	2	0.753
Reintubation	4	4	0.691

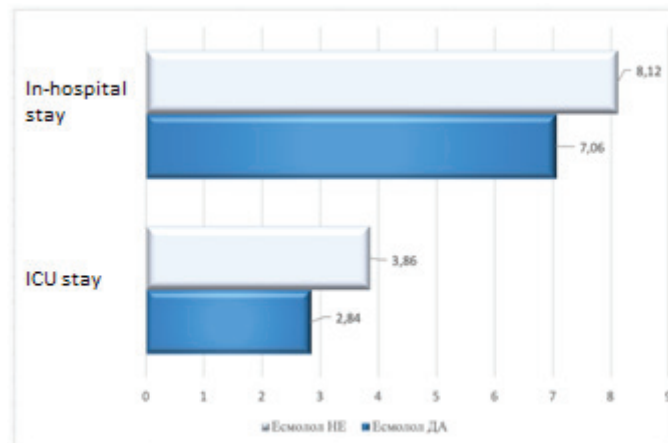
ARF=acute renal failure; ICU=intensive care unit; AFF=atrial fibrillation; CVI=cerebrovascular insult.

The number of days spent in ICU was statistically significantly lower in the *esmolol* group 2.84 ± 4.67 , compared to the placebo group 3.86 ± 6.40 , ($p=0.014$). Also, the total in-hospital stay was statistically significantly shorter in patients receiving *esmolol* 7.06 ± 5.18 compared to those without it 8.12 ± 5.68 , ($p=0.049$) (Table 6, Figure 5).

Table 6. Comparison of total number of days in ICU and length of in-hospital stay in patients divided into those with and without esmolol given.

Parameters	With esmolol n=50	Without esmolol n=50	p
ICU stay (days)	2.84±4.67	3.86±6.40	0.014
Length of in-hospital stay (days)	7.06±5.18	8.12±5.68	0.049

Figure 5. Graphic representation of the number of days spent in the ICU and total in-hospital stay in patients divided into those with and without esmolol given.



Discussion

Coronary artery bypass surgery (CABG) is an effective myocardial revascularization strategy that improves survival in high-risk patients (1). However, despite the use of the most effective myocardial protection strategies, in patients with coronary artery disease (CAD), the heart is still subjected to significant acute global ischemia-reperfusion injury (IRI) during surgery, resulting in an increased risk of perioperative myocardial infarction and impaired left ventricular systolic function. Global IRI is potentiated in older patients and those with more comorbidities, STS score with a value above 4, and EuroSCORE with a value above 6, patients with complex cardiosurgical intervention, longer duration of cardiopulmonary bypass (3,8,16).

In our study, patients in the *esmolol* and placebo groups were almost identical in age ($p=0.471$) with a non-significantly higher representation of females in the *esmolol* group (30%) compared to the *non-esmolol* group (18%), ($p=0.077$). Also, patients from both groups had almost identical increased body weight ($p=0.398$).

Regarding the clinical classifications (NYHA and CCS class), the NYHA classification was statistically insignificantly higher in the placebo group compared to the *esmolol* group, ($p=0.105$). The CCS classification was borderline statistically significantly higher in the placebo group compared to the *esmolol* group ($p=0.059$).

The EuroSCORE value was statistically insignificantly lower in the study group compared to the control group of patients ($p=0.850$). Also, the STS score was statistically insignificantly lower in the *esmolol* group compared to the placebo group ($p=0.491$), that is, patients in the *esmolol* group had more favorable clinical and pre-surgical performance.

Regarding the risk factors for atherosclerosis in our study, there was no statistically significant difference in their representation in subjects with and without given *esmolol*.

Also, in our study, the comparison of postoperative complications between patients given *esmolol* and those in the control group showed, in principle, the absence of significant differences between

patients in the *esmolol* and placebo groups, except that AFF occurred statistically significantly more often in patients who received *esmolol* (48%), compared to patients in the placebo group (30%), (p=0.05).

The number of days spent in ICU was statistically significantly lower in the *esmolol* group compared to the placebo group (p=0.014). Also, the total in-hospital stay was statistically significantly shorter in patients receiving *esmolol* compared to those without it (p=0.049).

Worldwide, male gender is a well-known risk factor and, consequently, the prevalence of CAD is higher in men compared to women (1,786 vs. 1,522 cases per 100,000 population). All age groups represent this difference. In men, it occurs more often at a younger age (1). In the last 20 years, a great progress has been made in the strategy and methods for the protection of the myocardium during the cardiac surgery itself, with the aim of reducing or preventing the perioperative injury of the myocardium and thereby reducing the postoperative post-ischemic ventricular dysfunction and the occurrence of numerous postoperative complications (1,4,5,6).

Possibilities for administering Beta-(β)-adrenergic blockers (BBs) represent pharmacological cardioprotective methods of protection including administering the cardioprotective agent prior to aortic clamping, adding a pharmacological agent to the cardioplegic solution, or administering the cardioprotective agent at the time of aortic clamp removal, or a combination of these different approaches (1,4,5,7,8,9). The use of BBs in the perioperative period has been widely investigated in cardiac surgery and in non-cardiac surgery with relatively controversial findings (17). It comes from the fact that myocardial oxygen consumption can protect myocytes from necrosis, but on the other hand, the reduction of inotropism in the postoperative period can be harmful (18). THE POISE study confirms that the use of long-acting beta-adrenergic blocker metoprolol reduces myocardial ischemia in non-cardiac surgery, but on the other hand the mortality rate is much higher (19). It is also confirmed that negative inotropism in cardiac surgery in patients with reduced left ventricular ejection fraction (LVEF), could lead to difficulties in weaning from extracorporeal circulation (ECC) and increased need for inotropic support in the postoperative period (20,21,22).

Esmolol is a cardio-selective BB, with an ultra-short action, which is usually applied as an addition to the cardioplegic solution in order to ensure adequate protection of the myocardium in the perioperative period (13,14,15). *Esmolol* reduces myocardial metabolic demands before and during cardioplegic arrest, reducing ischemia-reperfusion injury (23). A meta-analysis of randomized trials showed a significant reduction in the rate of perioperative myocardial ischemia and arrhythmias after CABG when *esmolol* was administered during cardiac surgery, without an increased need for inotropic support (13).

In 2003, Scorsin et al., investigated the protective effect of *esmolol* during continuous retrograde cardioplegia (24). The result of the study is a reduced consumption and demand of the myocardium for oxygen, and thus a reduced IRI.

In two experimental studies, Fannelop et al. – 2008, Dahle et al. – 2015, the use of *esmolol* in cardioplegia improved left ventricular function in the postoperative period (25,26).

In 2011, Sun et al. (27), investigated the effect of *esmolol* as an adjuvant to cardioplegia on cardiac recovery after CABG.

In 2016, Liu et al., investigated *esmolol* as an adjuvant in cardioplegia and found a significant reduction of up to 61% in serum troponin T (28). In one group, 12 patients received a normal cardioplegic solution, and in the second group, 12 patients received a cardioplegic solution with *esmolol* before starting the cardiopulmonary bypass

Therefore, *esmolol* remains the drug of the first choice for use as an adjuvant to cardioplegia in patients undergoing coronary artery bypass surgery to avoid the possible side effects (hypotension, bradycardia, heart failure) of longer-acting BBs action that would be administered in the intraoperative period (13).

Conclusion

Using *esmolol* as a pharmacological method for cardio-protection has been found to have a beneficial effect in reducing the duration of ICU and hospital stays for patients undergoing coronary artery bypass surgery. However, this treatment approach does not appear to have any significant impact on the occurrence of postoperative complications.

REFERENCES

1. Cohn LH, Adams DH, editors. *Cardiac Surgery in the Adult*, 5e. McGraw Hill; 2017.
2. Hausenloy DJ, Boston-Griffiths E, Yellon DM. Cardioprotection during cardiac surgery. *Cardiovasc Res.* 2012;94(2):253-65.
3. Wagner R, Piler P, Gabbasov Z et al. Adjuvant cardioprotection in cardiac surgery: update. *Biomed Res Int.* 2014;808096.
4. Kouchoukos, Nicholas T, Kirklin JW, editors. *Kirklin/barratt-boyes Cardiac Surgery: Morphology, Diagnostic Criteria, Natural History, Techniques, Results, and Indications.* Philadelphia: Elsevier/Saunders; 2013.
5. Kunst G, Milojevic M, Boer C et al. 2019 EACTS/EACTA/EBCP guidelines on cardiopulmonary bypass in adult cardiac surgery. *Br J Anaesth.* 2019;123(6):713-757.
6. Sousa-Uva M, Head SJ, Milojevic M et al. 2017 EACTS Guidelines on perioperative medication in adult cardiac surgery. *Eur J Cardiothorac Surg.* 2018;53(1):5-33.
7. Bojar, Robert M, editors. *Manual of Perioperative Care in Adult Cardiac Surgery.* Chichester, UK: Wiley-Blackwell; 2011.
8. Hausenloy DJ, Boston-Griffiths E, Yellon DM. Cardioprotection during cardiac surgery. *Cardiovasc Res.* 2012;94(2):253-65.
9. Allen BS. Myocardial protection: a forgotten modality. *Eur J Cardiothorac Surg.* 2020;57:263–70.
10. Hans J. Geissler, Karen L. Davis, Glen A. Laine et al. Myocardial protection with high-dose b-blockade in acute myocardial ischemia. *European Journal of Cardio-Thoracic Surgery.* 2000;63–70.
11. Brinkman W, Herbert MA, O'Brien S et al. Preoperative β -blocker use in coronary artery bypass grafting surgery: national database analysis. *JAMA Intern Med.* 2014;174(8):1320-7.
12. Blessberger H, Lewis SR, Pritchard MW, et al. Perioperative beta-blockers for preventing surgery-related mortality and morbidity in adults undergoing non-cardiac surgery. *Cochrane Database Syst Rev.* 2019;9(9):CD013438.

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13. Zangrillo A, Bignami E, Noè B et al. Esmolol in Cardiac Surgery: A Randomized Controlled Trial. *J Cardiothorac Vasc Anesth.* 2021;35(4):1106-1114.
 14. Oliver E, Mayor F Jr, D'Ocon P. Beta-blockers: Historical Perspective and Mechanisms of Action. *Rev Esp Cardiol (Engl Ed).* 2019;72(10):853-862.
 15. Loscalzo J, editors. *Harrison's Cardiovascular Medicine*, 3e. McGraw Hill; 2016.
 16. Nashef SA, Roques F, Sharples LD et al. EuroSCORE II. *Eur J Cardiothorac Surg.* 2012;41:734–744.
 17. Zangrillo A, Turi S, Crescenzi G et al. Esmolol reduces perioperative ischemia in cardiac surgery: a meta-analysis of randomized controlled studies. *J Cardiothorac Vasc Anesth.* 2009;23: 625–632.
 18. Blessberger H, Kammler J, Steinwender C. Perioperative use of β -blockers in cardiac and noncardiac surgery. *JAMA.* 2015;313(20):2070-1.
 19. Devereaux PJ, Yang H, Yusuf S et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet.* 2008; 371: 1839–1847.
 20. Nishina D, Chambers DJ. Efficacy of esmolol cardioplegia during hypothermic ischaemia. *Eur J Cardiothorac Surg.* 2018;53:392–9.
 21. Kuhn-Régnier F, Natour E, Dhein S et al. Beta-blockade versus Buckberg blood-cardioplegia in coronary bypass operation. *Eur J Cardiothorac Surg.* 1999; 15: 67–74.
 22. Mehlhorn U, Sauer H, Kuhn-Régnier F. Myocardial beta-blockade as an alternative to cardioplegic arrest during coronary artery surgery. *Cardiovasc Surg.* 1999; 7: 549–557.
 23. Fujii M, Chambers DJ. Cardioprotection with esmolol cardioplegia: efficacy as a blood-based solution. *Eur J Cardiothorac Surg.* 2013;43(3):619-27.
 24. Scorsin M, Mebazaa A, Al Attar N et al. Efficacy of esmolol as a myocardial protective agent during continuous retrograde blood cardioplegia. *J Thorac Cardiovasc Surg.* 2003;125(5):1022-9.
 25. Fannelop T, Dahle GO, Matre K et al. Esmolol before 80 min of cardiac arrest with oxygenated cold blood cardioplegia alleviates systolic dysfunction. An experimental study in pigs. *Eur J Cardiothorac Surg.* 2008;33(1):9-17.
 26. Dahle GO, Salminen PR, Moen CA et al. Esmolol added in repeated, cold, oxygenated blood cardioplegia improves myocardial function after cardiopulmonary bypass. *J Cardiothorac Vasc Anesth.* 2015;29(3):684-93.
 27. Sun J, Ding Z, Qian Y. Effect of short-acting beta blocker on the cardiac recovery after cardiopulmonary bypass. *J Cardiothorac Surg.* 2011;6:99.
 28. Liu X, Shao F, Yang L, et al. A pilot study of perioperative esmolol for myocardial protection during on-pump cardiac surgery. *Exp Ther Med.* 2016;12(5):2990-2996.

MANAGEMENT OF DELIVERY IN PATIENTS WITH OPHTHALMIC DISEASES

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Abstract

Introduction: Cesarean section is used more and more often and represents a significant public health problem in medicine. Its frequency in some countries is 2-3 times higher than that recommended by the WHO, and ophthalmic diseases are still considered one of the most common non-obstetric indications for performing this procedure.

Purpose: With the intention of understanding the correlation between different ophthalmological entities during pregnancy and how much they are a true indication for avoiding spontaneous labor, we have made this literature review. Our goal is to indicate modern insights in the management of childbirth in patients with ophthalmic diseases.

Materials and Methods: When preparing this paper, we accessed several medically relevant databases such as: EMBASE, PubMed and GoogleScholar by entering words of interest: pregnancy, childbirth, ophthalmic diseases, myopia, obstetrics, retinal degenerations. We didactically processed the obtained data, in order to present useful conclusions that would find application in daily clinical practice both among ophthalmologists and among gynecologists and obstetricians.

Conclusion: The percentage of pregnant women with ophthalmological diseases who attend ophthalmological examinations during pregnancy is still very small.

Patients with certain ophthalmological diseases should be evaluated individually, and according to regular ophthalmological examinations (every trimester) during pregnancy, an individualized decision on the method of delivery should be made.

Key Words: *childbirth, myopia, obstetrics, ophthalmic diseases, pregnancy, retinal degenerations.*

Introduction

Pregnancy is a dynamic period accompanied by many changes in all organ systems. Starting from the endocrine and immune system, all the way to the hematological and cardiovascular system. Such drastic changes have impact on all body structures, including the eyes. The effect of pregnancy on the ocular adnexa, on the anterior and posterior segments of the eye has been observed. Some of the entities are physiological, while others are part of a pathological process of a coexisting disease or a new ophthalmic condition. They include change in the sensitivity and thickness of the cornea, increased sensitivity to contact lenses, reduction of intraocular pressure and refractive errors (1, 2). More serious conditions affecting the posterior segment of the eye, sometimes require special attention such as: worsening of diabetic retinopathy or central serous chorioretinopathy, increased risk in myopic patients for alterations in peripheral degeneration and retinal ablation, increased tendency to Valsalva maculopathy during spontaneous childbirth etc. (3).

Such findings have been known for many years and some of them cause real concern both for patients and for specialists in gynecology and obstetrics. For a long time, the question has been raised: how much such changes can harm the natural way of childbirth in patients who already have an accompanying ophthalmic or systemic condition. That is, does spontaneous childbirth represent a trigger factor for the worsening of an already existing disease or condition?

Regardless of the ophthalmological conditions, in recent decades, medicine has faced a rapid growth of caesarean section as a method of delivery. The data show that in some countries it is performed 2-3 times more often than the recommendations and expectations from the WHO (4). With these counts, it is safe to say that caesarean section represents a major public health problem in the modern health system, both in terms of increasing the risk of infections, bleeding, complications related to anesthesia, respiratory problems in the newborn, both in terms of economic costs which burden the health systems (5). According to the knowledge from several studies that ophthalmic diseases are still one of the main non-obstetrical indications for cesarean delivery today, it is important to ask: Can the natural way of childbirth cause or aggravate an ophthalmic disease?

Materials and Methods

When preparing this literature review, we accessed several medically relevant databases such as: EMBASE, PubMed and GoogleScholar by entering words of interest: pregnancy, childbirth, ophthalmic diseases, myopia, obstetrics, retinal degenerations. We received a significant number of studies that are from different decades, starting from the first decades of the 20th century, until today. In order to get a complete picture of the problem we are working on, we didactically processed and arranged the data. The final goal of this paper is to present useful conclusions that would find application in modern clinical practice both among ophthalmologists and among gynecologists and obstetricians.

Results and Discussion

Myopia and Rhegmatogenous Retinal Detachment

As we mentioned in the introduction, under the influence of various factors, among which the increased circulating blood volume and fluid retention during pregnancy, thickening of the cornea and changes in its curvature occur that can cause the appearance of temporary myopia up to -1DSph. This phenomenon improves sometime after delivery (6).

In contrast, patients with a high degree of myopia (diopter greater than -6DSph or axial length greater than 26mm) face an increased risk of retinal rhegmatogenous ablation and vision threat at a young age. Additional risk factors for occurrence of ablation in myopic eyes is, of course, the presence of peripheral retinal degenerations, especially Lattice like and retinal holes (7). The incidence of this ophthalmic condition has been constantly increasing in recent years, so it is estimated that it was 2.7% of the world population in 2000, and it is predicted to increase to 9.8% by 2050 (8). For decades, the question has been raised whether natural childbirth and the effort put forth by the mother increase the probability of retinal ablation in this ophthalmic condition. The concern goes so far, that the high degree of myopia even today in many countries is an absolute indication for a caesarean section or to support the second stage of labor with instruments. Kuba et al. explains that the increased intraocular pressure during childbirth is evenly distributed and pushes the vitreous body towards the retina, thus eliminating the risks of retinal rhegma with subsequent ablation (9). Intraocular pressure reaches its peak at the end of the second stage of labor, associated with the Valsalva maneuver. This very moment, on the other hand, is risky for myopic patients who have arcuate cracks on the fundus (mechanical

ruptures of the retinal pigment epithelium-Bruch's membrane-choriocapillaris complex) or a developed neovascular network, which during this maneuver can lead to subretinal bleeding. Fortunately, in the most cases, it is resorbed spontaneously. Neri et al and Prost analyzed the fundus in patients with high myopia before and after delivery, the conclusions were that no new degenerations or the appearance of new holes or tears were observed in patients after delivery (10, 11). The real concern for complications in myopic eyes today is focused on patients with a choroidal neovascular network which, as we mentioned, can bleed during spontaneous labor and is a possible indication for cesarean termination of pregnancy.

It is important to mention that the ophthalmological examination during pregnancy is of exceptional importance for evaluating the condition of patients with high myopia and making a good strategy for the way of delivery. Examination of the retinal periphery with a three-mirror lens or indirect ophthalmoscope during each of the three trimesters is a good clinical screening to monitor changes from possible high-risk peripheral degenerations. High myopia itself is not an indication for caesarean section, as it is still considered by a large part of ophthalmologists and gynecologists, if it is well evaluated with regular ophthalmological examinations during pregnancy.

Glaucoma

Glaucoma is typically a disease of the elderly population, a rule with many exceptions, but also a large proportion of women become pregnant even later in their reproductive period, which is one of the reasons why today we are faced with glaucoma not being so rare in pregnant women. Except for Brimonidine and Dipivefrine, which are class B, the rest of the antiglaucomatosos drugs belong to class C, according to their safety and side effects for the fetus, so the use of double or triple antiglaucomatosos therapy during pregnancy is a serious, real problem (12). Therefore, pregnancy planning in patients with triple antiglaucomatosos therapy, and the possible need for glaucomatous surgery to be performed before pregnancy, is a good strategy to control this neuropathy during pregnancy and immediately after delivery.

One of the ocular manifestations during pregnancy is the drop in intraocular pressure (IOP). Some of the authors explain this phenomenon through the effect of the increased level of hormones on the trabecular meshwork and a decrease in pressure in the episcleral veins, and some explain it as a false decrease in intraocular pressure through the reduced rigidity of the ocular sheaths (13). However, several studies have shown that during pregnancy, regardless of whether it is a patient with elevated blood pressure or not, IOP decreases in the range between 20-24%, which is a percentage very close to that performed by topical anti-glaucoma therapy 20- 30%. The decrease in IOP occurs in all trimesters of pregnancy, and regardless of the blood pressure that increases in the last trimester, IOP continues its downward trend. This phenomenon of IOP reduction is observed several weeks after delivery (14, 15).

Diabetic Retinopathy

There is more evidence from studies that claim that diabetic retinopathy worsens during pregnancy. Some of the studies associate this phenomenon with immune mechanisms that cause this condition, and they are reactivated during the gestation period. Others give importance to the overall changes in the body of the pregnant woman (16). That is, elevated blood pressure, preeclampsia, hyperglycemia during pregnancy, duration of diabetes, etc. In a certain percentage of patients during this period, the appearance or increase of macular edema occurs (probably due to proteinuria and hypertension), which in a large part of them recedes postpartum. Similarly, the overall condition of diabetic retinopathy after delivery improves moderately in some diabetic patients (17).

However, during pregnancy itself, studies have shown that there is a trend of progression of retinopathy and its appearance in patients with diabetes who did not have it before. Since diabetes and diabetic retinopathy are chronic diseases, their monitoring both before becoming pregnant and during the entire gestational period is of particular importance (18). In terms of therapeutic possibilities, the application of anti-VEGF (vascular endothelial growth factor) intravitreally remains a controversial area, although small studies have been published on their application in pregnant women, without complications and health problems for the newborn. However, animal studies associate ranibizumab with the occurrence of skeletal malformations, and bevacizumab with embryotoxicity and teratogenicity (19, 20). So, for now, the only safe option for the treatment of diabetic retinopathy (high degree of non-proliferative and proliferative form) during pregnancy remains laser photocoagulation therapy (21).

Other Ophthalmic and Neuro-ophthalmic Conditions

The condition of various ophthalmological diseases during pregnancy and immediately after it is different. It is important to note that ocular Herpes simplex is not a contraindication for natural childbirth since this form differs from genital herpes and is not associated with transmission to the fetus through the birth canal. The condition uveitis is quite specific. Namely, some infectious uveitis, such as toxoplasma retinochoroiditis, can reactivate during pregnancy and represent a risk for parasitemia in the mother and transmission to the fetus with possible numerous side effects (22). Non-infectious uveitis can mostly be reactivated in the first few months of pregnancy, and in the second and third trimesters they are often in remission, and they can relapse a few months after delivery (23). The situation with other autoimmune systemic diseases during pregnancy is similar. It is believed that during this period, women secrete large number of anti-inflammatory agents that keep such diseases under control. An example of this is multiple sclerosis, whose remission is characteristic during the gestation period itself, and is often accompanied by worsening of the disease several months after delivery. An exception to this “rule” is systemic lupus, which often reactivates during pregnancy (24).

Diseases of the endocrine glands can be exacerbated during pregnancy. An example of this is the worsening of Graves’ thyroiditis and pituitary adenomas. They can be presented with accompanying ophthalmological manifestations and changes in the field of vision in patients with an increase in pituitary adenomas (25, 26). Similar to pituitary adenomas and other tumors of the eye and CNS, they can be hormone-dependent and increase in diameter during pregnancy (e.g. choroidal melanoma) or give rise to the visual field (e.g. glioblastoma, meningioma) depending on the localization of the lesion (27).

Preeclampsia and Eclampsia

Preeclampsia is a clinical syndrome that affects 3-5% of the pregnant women and is one of the main causes of maternal mortality, especially in developing countries. By definition it represents new hypertension (>140/90mmHg) and proteinuria (>300mg/day) during the second half of pregnancy. If CNS symptoms also occur (tonic-clonic seizures), a life-threatening complication, the condition is known as eclampsia (28).

Ophthalmic complications are common, occurring in ¼ of patients with preeclampsia and half of patients with eclampsia. Since it is basically a hypertensive phenomenon, changes in the fundus in pregnant women resemble hypertensive retinopathy (narrowed arteries, impaired ratio between arteries and veins, soft exudates, hemorrhages, etc.). In a certain part of the patients, serous ablation of the neurosensory retina may occur, which fortunately resolves postpartum, with an improvement in the general state of health. Blurred vision, photopsia, and visual field outbursts are common. It has been shown that as result of hypertension and proteinuria, worsening of diabetic retinopathy and macular edema occurs. Rare cases of cortical blindness, proliferative

retinopathy, venous or arterial occlusion and optic neuropathy have also been described in the literature (29). Therefore, the timely recognition of this condition in gynecology is extremely important for the prevention of numerous systemic complications, including ophthalmic ones

Conclusion

The percentage of pregnant women with ophthalmological diseases who attend regular ophthalmological examinations during pregnancy is still very small. The most of the changes that happen to the eyes during pregnancy are temporary, and they normalize a few weeks after delivery. Modern protocols for patients with pre-existing conditions such as: diabetes, myopia, glaucoma, etc., say that it is necessary to attend three regular ophthalmological examinations (one in each trimester). Regarding high myopia, the views are still not completely clear. That is, majority of studies claim that it is not an indication for cesarean section if there is no accompanying neovascular network, but some do not agree with the same.

The conclusion would still be that patients should be evaluated individually, and according to regular ophthalmological examinations during pregnancy, an individualized decision on the method of delivery should be made.

REFERENCES

1. Naderan M, Jahanrad A. Topographic, tomographic and biomechanical corneal changes during pregnancy in patients with keratoconus: a cohort study. *Acta Ophthalmol.* 2017 Jun;95(4):e291-e296.
2. Dinn RB, Harris A, Marcus PS. Ocular changes in pregnancy. *Obstet Gynecol Surv.* 2003 Feb;58(2):137-44.
3. Gotovac M, Kastelan S, Lukenda A. Eye and pregnancy. *Coll Antropol.* 2013 Apr;37 Suppl 1:189-93.
4. Ahmad Nia S, Delavar B, Eini Zinab H. et al. (2009). Caesarean section in the Islamic Republic of Iran: prevalence and some sociodemographic correlates. *EMHJ-Eastern Mediterranean Health Journal*, 15 (6), 1389-1398, 2009.
5. Mohammadi SF, Letafat-Nejad M, Ashrafi E, et al. A survey of ophthalmologists and gynecologists regarding termination of pregnancy and choice of delivery mode in the presence of eye diseases. *J Curr Ophthalmol.* 2017 Jan 19;29(2):126-132.
6. Naderan M. Ocular changes during pregnancy. *J Curr Ophthalmol.* 2018 Jan 3;30(3):202-210.
7. Ohno-Matsui K, Kawasaki R, Jonas JB, et al.; META-analysis for Pathologic Myopia (META-PM) Study Group. International photographic classification and grading system for myopic maculopathy. *Am J Ophthalmol.* 2015 May;159(5):877-83.e7.
8. Holden BA, Fricke TR, Wilson DA, et al. Global Prevalence of Myopia and High Myopia and Temporal Trends from 2000 through 2050. *Ophthalmology.* 2016 May;123(5):1036-42.
9. Kuba GB, Kroll P. Geburtsleitung und Indikationen zur Interruptio und Sectio caesarea bei Augenerkrankungen--eine Übersicht [Labor monitoring and indications for

-
- abortion and cesarean section in eye diseases--an overview]. *Klin Monbl Augenheilkd*. 1997 Dec;211(6):349-53.
10. Neri A, Grausbord R, Kremer I, et al. The management of labor in high myopic patients. *Eur J Obstet Gynecol Reprod Biol*. 1985 May;19(5):277-9.
 11. Prost M. Wysoka krótkowzroczność a poród [Severe myopia and delivery]. *Klin Oczna*. 1996 Feb;98(2):129-30.
 12. Razeghinejad MR, Tania Tai TY, Fudemberg SJ, et al. Pregnancy and glaucoma. *Surv Ophthalmol*. 2011 Jul-Aug;56(4):324-35.
 13. Efe YK, Ugurbas SC, Alpay A, et al. The course of corneal and intraocular pressure changes during pregnancy. *Can J Ophthalmol*. 2012 Apr;47(2):150-4.
 14. Qureshi IA, Xi XR, Wu XD. Intraocular pressure trends in pregnancy and in the third trimester hypertensive patients. *Acta Obstet Gynecol Scand*. 1996 Oct;75(9):816-9.
 15. Qureshi IA. Intraocular pressure and pregnancy: a comparison between normal and ocular hypertensive subjects. *Arch Med Res*. 1997 Autumn;28(3):397-400.
 16. Kaštelan S, Tomić M, Pavan J, et al. Maternal immune system adaptation to pregnancy--a potential influence on the course of diabetic retinopathy. *Reprod Biol Endocrinol*. 2010 Oct 21;8:124.
 17. Liu G, Wang F. Macular vascular changes in pregnant women with gestational diabetes mellitus by optical coherence tomography angiography. *BMC Ophthalmol*. 2021 Apr 9;21(1):170.
 18. Chandrasekaran PR, Madanagopalan VG, Narayanan R. Diabetic retinopathy in pregnancy - A review. *Indian J Ophthalmol*. 2021 Nov;69(11):3015-3025.
 19. Polizzi S, Mahajan VB. Intravitreal Anti-VEGF Injections in Pregnancy: Case Series and Review of Literature. *J Ocul Pharmacol Ther*. 2015 Dec;31(10):605-10.
 20. Fossum P, Couret C, Briend B, et al. Safety of intravitreal injection of ranibizumab in early pregnancy: a series of three cases. *Eye (Lond)*. 2018 Apr;32(4):830-832.
 21. Rosenthal JM, Johnson MW. Management of Retinal Diseases in Pregnant Patients. *J Ophthalmic Vis Res*. 2018 Jan-Mar;13(1):62-65.
 22. Nath R, Guy E, Morrison A, Kelly SP. Toxoplasma retinochoroiditis in pregnancy: Using current evidence to inform management. *Clin Ophthalmol*. 2009;3:657-61.
 23. Chiam NP, Lim LL. Uveitis and gender: the course of uveitis in pregnancy. *J Ophthalmol*. 2014;2014:401915.
 24. Adams Waldorf KM, Nelson JL. Autoimmune disease during pregnancy and the microchimerism legacy of pregnancy. *Immunol Invest*. 2008;37(5):631-44.
 25. Nguyen CT, Sasso EB, Barton L, Mestman JH. Graves' hyperthyroidism in pregnancy: a clinical review. *Clin Diabetes Endocrinol*. 2018 Mar 1; 4:4.

26. Molitch ME. Pituitary tumors and pregnancy. *Growth Horm IGF Res.* 2003 Aug;13 Suppl A:S38-44.
27. Yust-Katz S, de Groot JF, Liu D, et al. Pregnancy and glial brain tumors. *Neuro Oncol.* 2014 Sep;16(9):1289-94.
28. Dieckman W.J. 2nd ed. CV Mosby; St Louis: 1952. The toxemias of pregnancy. p. 240–9.
29. Abu Samra K. The eye and visual system in the preeclampsia/eclampsia syndrome: What to expect? *Saudi J Ophthalmol.* 2013 Jan;27(1):51-3.

PANCREATICODUODENECTOMY: RETROSPECTIVE STUDY OF A SINGLE CENTER EXPERIENCE

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Abstract

Background: Whipple surgery (pancreaticoduodenectomy) is a complex surgery with high postoperative complication rate. We aimed to demonstrate the outcomes and rates of complications from patients who had undergone PD in our hospital.

Materials and Methods: Medical records of 22 patients, who underwent pancreaticoduodenectomy surgery between November 2018 and December 2022 at Department of Abdominal Surgery, City General Hospital "8th of September" in Skopje, North Macedonia, were examined retrospectively. Age, sex, localization of the lesion and pathohistological properties and postoperative morbidity and mortality were studied.

Results: A total of 22 patients (12 male, 10 female) with a mean age of 63,9 years who underwent pancreaticoduodenectomy were included in the study. Ten patients (45,45%) had pancreatic head malignancies, 7 patients (31,81%) had ampullary malignancies, 1 patient (4,54%) had duodenal and also 1 patient (4,54%) had common bile duct malignancies. Two of our cases (9,08%) underwent surgery for gastric antrum carcinoma and one patient (4,54%) for colon carcinoma. The most frequently encountered complications were pancreatic fistula (18,16%), biliary leakage (13,64%) and pulmonary complications (13,64%). The surgery related mortality rate was 9,09% (2 cases).

Conclusion: We represent outcomes of our surgical team compared to the published data of some other centers. Prospective randomized studies are needed to adequately assess postoperative complications. To improve the postoperative outcome, appropriate monitoring, multidisciplinary approach and further improvement of surgical techniques are needed.

Key Words: pancreaticoduodenectomy, postoperative complications, Whipple procedure.

1. Introduction

The pancreatoduodenectomy (PD), also known as the Whipple procedure, is the surgical procedure of choice for the resectable and the borderline resectable pancreatic ductal adenocarcinomas. It is commonly performed for malignant tumors of pancreatic head, ampulla, distal bile duct, but also may be performed for benign tumors, and trauma of pancreatic head and duodenum (1,2,3). Only 10-20% of the patients with diagnosed mass in pancreatic region, presented with a tumor that can be resected (4). Because of its complexity PD is associated to significant postoperative morbidity rates of which range from 30% to 60% (5-7). These complications include pancreatic leak or fistula, intra-abdominal abscess, bile leak, postoperative hemorrhage, delayed gastric emptying, surgical site infection, pulmonary or cardiac complications and sepsis (5,8). With the progress of surgical techniques and improvements in perioperative and critical cares, the mortality rate has recently been decreased from 25% to less than 5% (9).

In this study, we report our experience with PD with the aim to evaluate the spectrum of postoperative complications and clinical outcomes.

2. Materials and Methods

This retrospective study was conducted at the Department of Abdominal Surgery, General City Hospital, Skopje, North Macedonia. The study included data from patients that underwent pancreaticoduodenectomy in the period from November 2018 till December 2022 (including the period of Covid-19 Pandemic). It was performed on 22 patients with proven mass in the ampullary, periampullary or pancreatic head region who underwent a classic Whipple procedure, but also included patients with multivisceral resections due to multivisceral malignant tumor involvement.

2.1. Data collection

The patients' data were collected from the medical records including demographic characteristics (gender, age), preoperative findings and comorbidities (presence of DM, high bilirubin level, tumor location), intraoperative data (including type of operation, operation time) and postoperative complications and early outcome were also studied. From this study were excluded patients with missing information from their data registries, unresectable patients, and patients with distant metastasis.

2.2 Preoperative workup

All patients who were candidates for PD were admitted with symptoms of weight loss, obstructive jaundice, severe vomiting and anemia. Routine preoperative workup included ECG and chest x-ray and complete blood analysis including liver and renal functional tests, serum electrolytes and coagulation profile. Tumor location and staging were assessed by computed tomography scanning, MRI, abdominal US (ultrasonography). In order to achieve preoperative patient optimization, ERCP with biliary stent insertion was carried out for some cases as a therapeutic biliary drainage measure for jaundice, especially in those patients where the hyperbilirubinemia generate liver and brain function impairment.

2.3. Surgical technique

All patients received prophylactic antibiotic (Ceftriaxone) 30–60 minutes before the skin incision. For abdominal exploration the most frequently was used upper midline or transverse incision and in some cases was used Mercedes Benz modification of Kocher's incision. The peritoneum and liver were assessed for the presence of metastasis and the tumor for resectability. In the most of the patients standard Whipple procedure was performed, which consists of 20%–40% distal gastrectomy, cholecystectomy, PD and also the technique of "triangle resection" was included. Regarding the reconstructions, all the anastomoses were performed using the appropriate size of Maxon sutures. The first anastomosis is pancreatojejunostomy in the form of end-to-side anastomosis with interrupted sutures. According to the size of pancreatic duct in all patients with ductal diameter smaller than 3mm, pancreatojejunostomy was performed and duct-to-mucosa anastomosis, when ductal diameter was bigger than 3mm. The reconstruction was followed by end-to-side hepaticojejunostomy with interrupted single layer sutures. The third anastomosis is the gastrojejunostomy typically performed 40cm downstream from the hepaticojejunostomy. Braun jejunojunction, side-to-side, was added to other anastomoses at the end of the operation and it was performed using a standard, manual one-layer method. Some of the patients had another resection (right hemicolectomy, splenectomy, nephrectomy) because of the tumor spreading, beside PD. In all patients closed suction drains were placed in Morrison pouch and in the vicinity of the pancreatic and biliary anastomosis. None of the operated patients received any type of neoadjuvant therapy. The samples were sent for histopathological examination to confirm the type and pathological characteristics of the tumor.

2.4. Postoperative follow-up

Postoperative period management includes keeping the patient with nothing by mouth for day 1 and advancing with clear liquids and then gradually to a low-fat diet in frequent small feeds. Nasogastric tube for stomach decompression usually stays on operative and on the first postoperative day if there is no high output, and then is removed. The drains are removed gradually once the output is minimal and there is no evidence of pancreatic fistula or biliary leakage, usually between postoperative days 5 and 8. Mortality and morbidity were estimated within 30 days postoperatively. Postoperative complications were classified as procedure-related (pancreatic fistula, biliary leakage, delayed gastric emptying, acute pancreatitis, wound infection, wound disruption, postoperative bleeding) or general (pulmonary complications, cardiac complications, ketoacidosis, sepsis).

In this study pancreatic fistula was defined as amylase level of drainage fluid on postoperative day 3 exceeding three times of the serum concentration. Biliary leak was defined by the bilious aspect of the drainage fluid confirmed biologically. Both pancreatic and biliary leak were managed by drainage until resolution or reoperation.

Delayed gastric emptying was defined as intolerance to oral intake and need of gastric decompression after the seventh postoperative day. Other complications were defined as following: wound infection (purulent wound drainage); postoperative bleeding (requiring transfusion or endoscopic or operative intervention); acute pancreatitis (>3-fold increase in serum amylase or lipase from postoperative day four onward with a compatible clinical course or CT scan findings); pulmonary complications (pneumonia, effusion requiring drainage or re-intubation); postoperative mortality (death occurring in the first 30 postoperative days). Total hospital stay (number of days spent in hospital) was also evaluated.

2.5. Data analysis

SPSS (version 22) program was used for a statistical analysis. Data were analyzed using χ^2 test, student t-test and Fischer exact test as appropriate. A p-value of < 0.05 was considered as a statistically significant.

3. Results

In this study were included 22 patients, 12 male (54,54%) and 10 female patients (45,46%). The mean age was 63.9 ± 10.6 years with a range of 32 – 74 years. In preoperative period 16 patients (72,73%) had jaundice or higher level of serum bilirubin. The median of preoperative serum bilirubin was 118.03 ± 113.7 umol/L and preoperative ERCP with biliary stent insertion was carried out in 9 (40,91%) patients as a therapeutic biliary drainage measure for jaundice or cholangitis. Six patients had diagnosis of diabetes as comorbidity. Initial diagnosis of the patients was based upon baseline, clinical and radiological investigations. Further highlights regarding the tumor site, grade and other histopathological parameters are shown in **Table 1**.

Table 1. Histopathological details of the resected tumors.

Parameter		Frequency	Percentage
Tumor site	Pancreatic head	10	(45,45%)
	Ampullary	7	(31,81%)
	Duodenal	1	(4,54%)
	Choledochal	1	(4,54%)
	Gastric antrum	2	(9,08%)
	Colon	1	(4,54%)
	Tumor type	Well-differentiated adenocarcinoma	4
Moderately differentiated adenocarcinoma		13	(59,06%)
Poorly differentiated adenocarcinoma		3	(13,66%)
GIST (duodenum)		1	(4,54%)
Lymphoma malign anaplastic (large cell)		1	(4,54%)
Involvement of lymph nodes	Yes	10	(45,45%)
	No	12	(54,55%)
Surgical margins	Positive	2	(9,08%)
	Negative	20	(90,92%)

In this study, 19 patients (86,26%) underwent standard pancreaticoduodenectomy (PD, i.e., Whipple's procedure), 2 underwent PD with right hemicolectomy and one patient beside PD had splenectomy and nephrectomy of right kidney because of chronic pyelonephritis (End stage renal disease).

The average surgery time was 343.95 ± 98.5 minutes and the mean length of hospital stay of the patients was 15.41 ± 7.5 days. Postoperative complications data are presented in **Table 2**. Four of the 22 patients (18,16%) were identified as having pancreatic leakage after operation. Other procedure-related postoperative complications included biliary fistula (13,64%, 3); delayed gastric emptying (4,54%, 1); wound infection (9,08%, 2); wound dehiscence (4,54%, 1); pancreatitis (4,54%, 1); hemorrhage/anemia (4,54%, 1); lung complications (13,64%, 3); ketoacidosis (4,54%, 1). Two of the patients died in the early postoperative period, because of pulmonary complications, one diagnosed with lymphoma malign anaplastic (large cell) and other was simultaneously complicated with ketoacidosis.

Table 2. Postoperative complications after pancreatoduodenectomy

Postoperative complications	Cases (%)
Pancreatic fistula	4 (18.16%)
Biliary fistula	3 (13.64%)
Delayed gastric emptying	1 (4.54%)
Wound infection	2 (9.08%)
Wound dehiscence	1 (4.54%)
Pancreatitis	1 (4.54%)
Hemorrhage/anemia	1 (4.54%)
Lung complications	3 (13.64%)
Ketoacidosis	1 (4.54%)
Postoperative death (in 30 days)	2 (9.09%)

4. Discussion

Pancreaticoduodenectomy, modified and promoted in 1935 by Allen Whipple, has been burdened by a high morbidity and mortality rates and because of that resulted in initial reluctance to adopt this surgery for the management of pancreatic and periampullary tumors (10). Because of its complexity, some of the surgeons had a concept that this procedure is better not to be performed, because it is demanding and time-consuming procedure with poor long-term outcomes and necessitating the presence of an advanced critical care for its success. In our district, beside the fact that is not high-volume experienced center for pancreatic surgery, we decide to popularize PD and during the past 4 years of our experience in Whipple procedure, we developed a progressive improvement in the different aspects of the surgical technique including less intraoperative bleeding, less pancreatic anastomosis failure, shorter operative time and decrease in hospital staying days.

We carried out a single-center retrospective study of 22 patients undergoing PD to present early postoperative outcome and complications. Nearly half of the patients (10 patients) had pancreatic head tumor, 7 had ampullary tumor, 1 duodenal, 1 patient with tumor in distal choledochal and 3 patients had carcinomas that infiltrate in pancreas or duodenum (gastric and colon carcinoma).

The goal of PD is to achieve comprehensive oncological resection. Thus, it is considered as curative surgery for ampullary, periampullary and pancreatic head cancers which includes complete gross and microscopic resection of tumor elements (9, 11). We include the technique of "triangle operation", which is radical artery-sparing approach, allowing a sharp dissection (adventitial layer of arteries is opened longitudinally) with removal of all lymphatic and neural tissue structures to the basis of celiac axis and superior mesenteric artery (12). This results in an anatomic triangle bordered by superior mesenteric artery, celiac axis and portal vein, with complete lymphadenectomy and soft tissue removal in this area, in the light of a truly radical

surgical approach (13,14). In our study, pathohistological analysis of specimens showed positive surgical margins (retroperitoneal) in two patients (9,08%) with carcinoma of pancreatic head, and 20 patients (90,92%) were with all negative surgical margins. Ten patients (45,45%) had positive lymph nodes for metastatic deposits.

In our series, the postoperative complications we came across were pancreatic fistula (18,16%), bile leak (13,64%), lung complications (13,64%), wound infection (9,08%) Complications like acute pancreatitis, ketoacidosis, wound dehiscence, postoperative bleeding and gastric atony were presented in 4,54% (which corresponds for one patient respectively). Yeo et al. in a pancreaticoduodenectomy series of 650 patients showed that the most common three complications were delay in gastric emptying (19%), pancreatic fistula (14%), and wound infection (10%), respectively (15). Kargi E et al. in a study in Turkey, from a single-center, general hospital experience with small number of patients (71 patients) presented that the postoperative complications rate were pancreatic fistula (12%), lung infection (2.5%), wound infection (5.5%), postoperative bleeding (1%) and gastric atony (7%) (16). Among these complications, pancreatic fistula is the most important complication of PD because, directly or indirectly, it contributes to the other morbidity including delay in gastric emptying, post-pancreatectomy hemorrhage and death. In our patients the rate of pancreatic fistula was 18,16%. Although, the rate of pancreatic leak is considerably variable among the centers that ranging from 13 to 35% (17-19), our result is acceptable. To control potential pancreas leaks, in the most centers, during surgery, a drain is implemented around pancreatic anastomosis as we did in our cases. The most often, pancreatic leak comes to an end with conservative treatment, with control of drain fluid output and if the patient is relatively asymptomatic and if, despite of the normal diet, a fistula output below 200ml/day is observed, the patient can be discharged with the drain. In the most cases, the fistula closes in a few days.

Delay in gastric emptying is not life threatening and usually resolves spontaneously with parenteral nutrition support and nasogastric decompression until the complication is resolved. The higher percentage of lung complications in our series probably is due to previously suffered Covid-19 pneumonia and HOBB (all three patients had that in common in medical history). The overall perioperative mortality rate in this study was 9,09% (2 patients), which is higher than < 5% rate reported by other centers (17,19). The higher percentage is probably due to smaller series of patients in our study compared to high-volume centers. The importance of an adequate perioperative complication management in pancreatic surgery is essential and it is important to include multidisciplinary team approach to this - including interventional radiologists and endoscopists for non-surgical complication management and anesthesiologists for adequate postoperative care in ICU (20).

Even though our analysis highlights important findings, it has certain limitations. First, this work is a retrospective analysis, therefore, the possibility of bias cannot be eliminated and the associations of complications with the cause could not be developed. Second, the study was performed at a single-institution which is not referral center for pancreatic surgery, and it includes the limitations of performing this kind of operations during the period of Covid-19 pandemic in which our hospital functioned as Covid Hospital. Moreover, we used a convenience sampling technique for the selection of study participants. To overcome these limitations, a prospective multicenter study with more patients is necessary for better understanding of postoperative complications following pancreaticoduodenectomy.

5. Conclusion

We have decided for the first time to publish data of our experience and we believe that our study contributes to the development of pancreatic surgery in our country. Appropriate postoperative monitoring, multidisciplinary approach and further improvement of surgical team experience and surgical techniques can help in improving the postoperative outcomes.

REFERENCES

1. Scaife L. C, Hewitt C. K, Mone K. M, et al, Comparison of intraoperative versus delayed enteral feeding tube placement in patients undergoing a Whipple procedure, *HBP* 16 (2014) 62–69.
2. McGuigan A, Kelly P, Turkington RC, Jones C, et al: Pancreatic cancer: a review of clinical diagnosis, epidemiology, treatment and outcomes. *World j Gastroenterol.* (2018), 24:4846-61.
3. Leichtle W.S, Kaoutzanis C, Mouawad J.N, et al., Classic Whipple versus pylorus-preserving pancreaticoduodenectomy in the ACS NSQIP, *JSR* 183 (2013) 170–176.
4. Javed AA, Wright MJ, Siddique QH, Rahim FH: Outcome of patients with borderline resectable pancreatic cancer in the contemporary era of neoadjuvant chemotherapy. *J Gastrointest Surg* (2019) 23:112-21.
5. Eric C.H. Lai, George P.C. Yang, Chung Ngai Tang. Robot-assisted laparoscopic pancreaticoduodenectomy versus open pancreaticoduodenectomy – a comparative study, *Int. J. Surg.* 10 (2012) 475–479.
6. Clancy E. T, Ashley S. W. Pancreaticoduodenectomy (Whipple operation), *Surg. Oncol. Clin. N. Am.* 14 (2005) 533–552.
7. Sahara K, Morales-Oyarvide V, Thayer P. S, et al., The effect of antecolic versus retrocolic reconstruction on delayed gastric emptying after classic non-pylorus preserving pancreaticoduodenectomy, *Am. J. Surg.* 209 (2015) 1028–1035.
8. Martignoni M, Friess H, Sell F, et al. Enteral nutrition prolongs delayed gastric emptying in patients after Whipple resection, *Am. J. Surg.* 180 (2000) 18–23.
9. Perysinakis I, Avlonitis S, Georgiadou D, et al: Five year actual survival after pancreaticoduodenectomy for pancreatic head cancer. *ANZ J Surg.* (2015), 85:183-6.
10. O.A. Whipple, Pancreaticoduodenectomy for islet carcinoma: a five-years follow-up, *Ann. Surg.* 121 (1945) 847e852.
11. Sulzer JK, Sastry AV, Meyer LM, et al.: The impact of intraoperative goal-directed fluid therapy on complications after pancreaticoduodenectomy. *Ann ed Surg* (2018) 36:23-8.
12. Hackert T, Strobel O, Michalski CW, et al .The TRIANGLE operation – radical surgery after neoadjuvant treatment for advanced pancreatic cancer: a single arm observational study. *HPB* (2017) 19:1001–1007.
13. Rosso E, Zimmitto G, Ianelli A, et al. The “TRIANGLE Operation” by laparoscopy: radical pancreaticoduodenectomy with major vascular resection for borderline resectable pancreatic head cancer. *Ann Surg Oncol* (2020). 27(5):1613–1614.
14. Klotz R, Hackert T, Heger P, et al. The TRIANGLE operation for pancreatic head and body cancers: early postoperative outcomes. *HPB (Oxford)* (2021); S1365–182X(21)00614–6.
15. Yeo CJ, Cameron JL, Sohn TA, et al. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990's- Pathology, complications, and outcomes. *Ann Surg* (1997); 226:248-60.
16. Kargı E, Okay E, Gunes A, et al. Outcomes of pancreaticoduodenectomy surgeries: a single center experience with 71 cases. *J Turgut Ozal Med Cent* (2014);21:118-121.
17. John L. Cameron, One thousand consecutive pancreaticoduodenectomies and beyond: a personal series, *Am. J. Surg.* 194 (2007) S11–S15.
18. Castillo CF, Morales-Oyarvide V, McGrath D, et al., Evolution of the Whipple procedure at the Massachusetts General Hospital, *Surgery* 152 (2012) S56–S63.
19. Michael B. Ujiki, Mark S. Talamonti, Surgical management of pancreatic cancer, *Semin. Radiat. Oncol.* 15 (2005) 218–225.
20. Nießen A, Hackert T. State-of-the-art surgery for pancreatic cancer. *Langenbecks Arch Surg.* (2022) Mar;407(2):443-450.

SPONTANEOUS CORONARY ARTERY DISSECTION

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Abstract

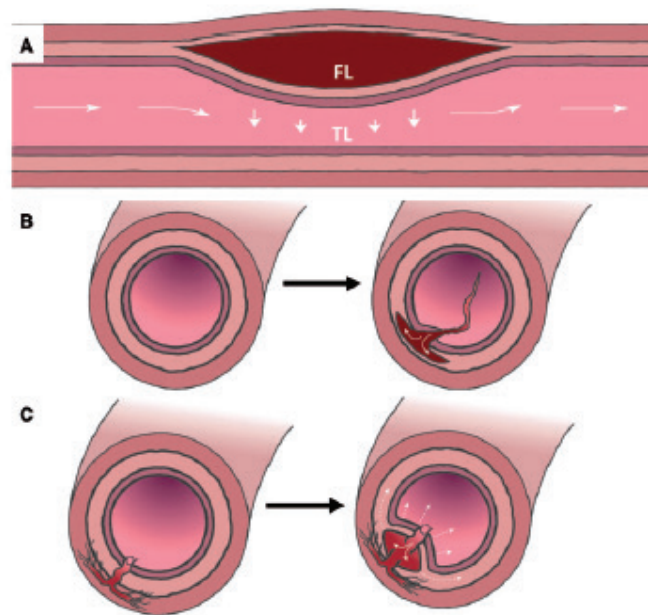
Spontaneous coronary artery dissection (SCAD) is non-iatrogenic, non-traumatic and non-atherosclerotic separation of the coronary artery wall caused by intramural hematoma development with or without simultaneous co-existence of coronary wall tear. The net effect is compression of the true coronary artery lumen with development of ischemia. SCAD typically occurs in relatively young population, dominantly females (around 90%), often in peripartum, in which there are absent or very rare classical risk-factors for coronary artery disease (CAD). The most frequent clinical manifestation of SCAD is acute coronary syndrome (ACS – STEMI or NSTEMI), rarely cardiogenic shock or life-threatening arrhythmias (VT or VF), and sometimes sudden cardiac death. Diagnosis (which sometimes can be challenging) is dominantly established by coronary angiography, and sometimes modalities of intravascular visualization may be useful (IVUS, OCT). The most of the patients with SCAD are treated conservatively and small proportion of them requires revascularization (PCI or CABG). In addition, we present several cases with SCAD.

Conclusion: Timely and accurate diagnosis and treatment is extremely important in SCAD, which is a potentially life-threatening condition.

Key Words: ACS, CABG, NSTEMI, PCI, spontaneous coronary artery dissection, , STEMI.

Definition and Pathogenesis

Spontaneous coronary artery dissection is defined as acute non-traumatic, non-iatrogenic and non-atherosclerotic separation of the coronary artery wall caused by intramural hematoma (IMH) development within the vessel wall with or without simultaneous coexistence of the coronary wall tear (rupture) (1-14). IMH may generate a false lumen which can further compromise normal blood flow through the true lumen and can cause ischemia. Pathogenesis of SCAD is not completely understood, although there are two basic pathogenetic mechanisms: 1) disruption of the integrity and continuity of the intima (endothelium) – tear or rupture – which during antegrade flow allows further separation of the coronary vessel wall layers and generation of false lumen with IMH (so-called “inside-out” hypothesis) and 2) rupture of vasa vasorum which leads to forming of IMH and false lumen (so-called “outside-in” hypothesis) (Figure 1). It is not very clear which of these two mechanisms is primary or dominant and whether it is possible simultaneous presence of them though. There are studies with optical coherence tomography (OCT) which confirm IMH without simultaneous presence of coronary vessel wall tear (2, 4, 6, 8-10, 14, 15).

Figure 1. Schematic illustration of spontaneous coronary artery dissection (SCAD).

Accumulation and axial propagation of blood forms false lumen which leads to external compression of the true lumen (A); blood can enter via endothelial/intimal disruption (tear) (B); or as a result of microvascular bleeding within arterial wall which leads to compression of the true lumen (C) (taken and adapted from Adlam D. et al.)

Epidemiology

The first case of SCAD was described by Pretty in 1931 (1, 3, 5). Awareness for this condition and improvement of the coronary diagnostics led to increased number of patients diagnosed with SCAD. The real incidence is not known, while the prevalence according to different authors is from 0,2% up to 4% in ACS (2,15). Females are dominantly involved in about 90% of the cases, and concerning age distribution – the medium age of occurrence is 44-55 years, though it can be seen in almost all ages (1, 2,4). It is thought that around 25% of myocardial infarctions during pregnancy and around 50% of postpartum coronary events are due to SCAD and because of that, this condition should not always be associated with peripartum period (2). It is very important to emphasize that peripartum forms of SCAD are generally associated to more severe clinical manifestation with involvement of the LM stem or multivessel involvement, left ventricular function impairment, more often with STEMI etc. (8).

Etiology and Risk Factors

The etiology of SCAD is not well established. It can be more or less discussed about certain risk-factors which might have impact on the development of this condition. Maybe the most important single risk-factor for occurrence of SCAD is fibromuscular dysplasia (FMD). It is a non-inflammatory, non-atherosclerotic vascular disease which is strongly associated with SCAD. It can be multifocal or unifocal, and that is why in situations of SCAD associated with FMD it is recommended screening for extracoronary localization. Pregnancy is also a condition that increases the risk for SCAD which is probably due to hormone alteration. Namely, it is known that increased progesterone value has an impact on collagen production while increased estrogen value has prothrombotic effect. Chronic inflammatory diseases like nodose polyarteritis (PAN), inflammatory bowel disease (IBD), sarcoidosis, Wegener granulomatosis, rheumatoid arthritis and different forms of vasculitis may lead to SCAD. It should not be forgotten that

connective tissue disorders like SLE, Marfan syndrome, Ehlers-Danlos syndrome and other also have role in occurrence of SCAD. Recently, stress has been described as more often trigger factor for SCAD, namely emotional stress in female and physical stress in male population (intensive physical loading, consuming significant portions of stimulants, energetic beverages, hormones, recreational drugs etc.). In those situations, the level of catecholamines suddenly increases and that may lead to increased coronary vessel wall shear-stress and risk for SCAD (1, 2, 6, 7). Some authors mention the role of genetic factors as well. One of the genetic loci which might be associated with SCAD is PHACTR-EDN1. Certain GWAS (genome-wide association studies) have detected genetic loci within the genes or near the genes LRP1, LINC00310, FBN1 and others which increase the susceptibility for SCAD (8).

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Diagnosis and Classification

The most important diagnostic method for SCAD is coronary angiography. In the most cases it is solely sufficient to establish diagnosis, but in some cases intravascular modalities like intravascular ultrasound (IVUS) and optical coherent tomography (OCT) are necessary (1, 2, 6-8, 10, 12, 13). Sometimes (if there is no hypotension), it is advised to administer intracoronary nitroglycerin in order to provide maximal coronary vasodilation and to exclude coronary vasospasm as possible cause.

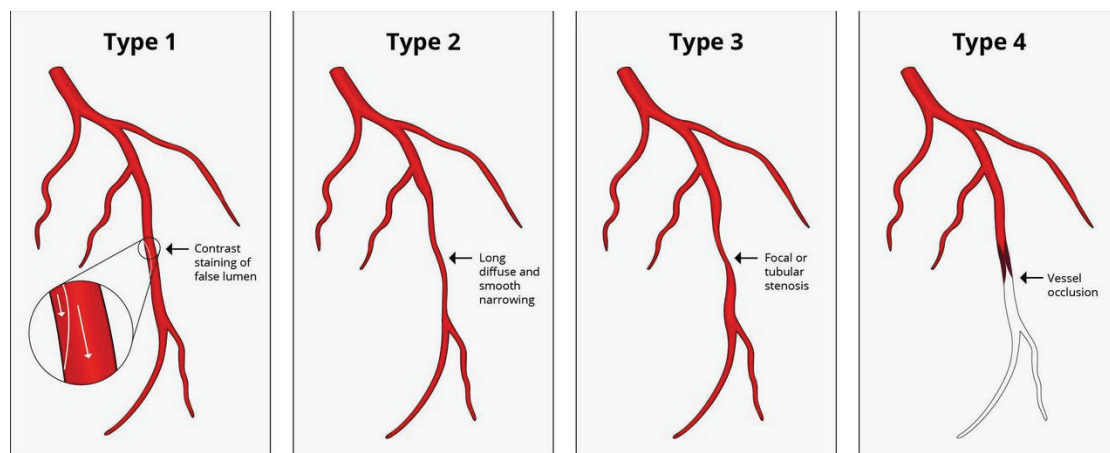
Involvement of the coronary stem with SCAD may be single vessel or multivessel. According to the literature, the most frequently involved coronary artery with SCAD is left anterior descending artery (LAD) (according to one group of authors 43-60%, according to other – over 70%) (1, 9, 10, 14). In about 5-15% of the cases there is a multivessel SCAD (2, 14). CT-coronary angiography is an additional diagnostic procedure which may be helpful in diagnosing SCAD, but it should not be used as a primary diagnostic procedure for diagnosis of SCAD because of its limitations (lower sensitivity and specificity) (1, 2, 7, 11). It is worth mentioning that a potential biomarker named fibrillin-1 has been recently identified and proposed for non-invasive diagnosis of SCAD, as well as for prediction of adverse events from this condition (10). In situations when diagnosis of SCAD remains uncertain or unclear by coronary angiography only, it is recommended to perform IVUS or OCT. When diagnosis is clear and established

by coronary angiography, then we should not insist on performing an additional intravascular procedure because it can sometimes impair normal coronary flow. These techniques can not only contribute towards confirming or excluding the diagnosis, but also towards planning revascularization procedure. IVUS allows tomographic pictures of the lumen and coronary wall by using ultrasound waves. Ultrasound waves have excellent in-depth penetration across the whole coronary wall up to lamina elastica externa including thrombus detection. The main disadvantage is relatively bad spatial resolution which makes IVUS not applicable for detection of more discrete structures associated with SCAD. OCT has much better spatial resolution, but weaker penetration than IVUS and can precisely detect thrombus, localization of the tear, length and orientation of the false lumen and IMH as well as its relation to side branches, presence of fenestrations, measurement of intima-media thickness etc. The disadvantage of OCT is necessary procedure for blood washout (clearance) from the coronary artery which is performed by intense contrast flush and quick pullback of the OCT catheter and this step might increase the risk of further false lumen extension (2, 6-9, 12).

Generally accepted classification of SCAD is the one according to Yip and Saw which is based on angiographic characteristics of the coronary dissection (Figure 2):

- Type 1 – multiple linear filling defects due to intimal tear along coronary wall, and sometimes they can be seen as double wall contours. Often there can be also present a phenomenon of “contrast staining”, “slow (coronary) flow” as well as impaired and “delayed (reduced) contrast washout” from the coronary arteries. This type of SCAD is angiographically visible, and IVUS/OCT is not necessary to establish diagnosis,
- Type 2 – manifests as diffusely narrowed longer segment of the artery (over 20mm) usually due to intimal or intramural hematoma. This type of dissections usually abruptly changes the diameter of the artery, they may continue towards the distal segment of the artery and return to the normal artery diameter. In type 2A there is normal diameter of the artery proximally and distally to the SCAD, while in type 2B the lesion is expanding diffusely up to the distal segments visible on angiography. OCT usually detects IMH with compressive effect,
- Type 3 – is similar to type 2, except it involves shorter segment, focal lesion, up to 20mm in length and it can simulate atherosclerotic lesion. Usually one of the intravascular modalities (OCT) is necessary to establish diagnosis, and
- Type 4 – it is manifested as coronary artery occlusion and looks like coronary thrombosis/ embolism. Angiographically it cannot be differentiated from atherothrombotic/ thromboembolic lesion (1, 2, 4, 6-9, 14).

Figure 2. Angiographic classification of SCAD according to Saw et al.



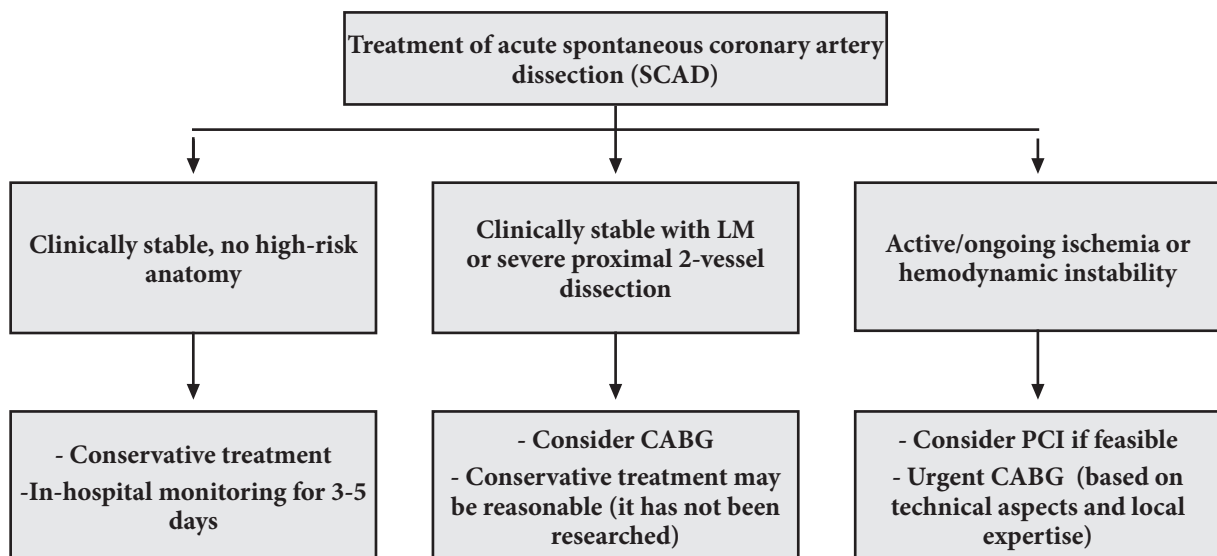
Clinical Manifestation

Clinical manifestation and its severity in patients with SCAD are heterogenous and they depend on multiple factors like the degree of reduction of the true lumen, length or extensity of coronary dissection, number of involved coronary arteries etc. SCAD may be completely asymptomatic (very rarely) or symptomatic, of which the most frequently as acute coronary syndrome (80-90%), rarely as cardiogenic shock (2-5%), cardiac arrest/ ventricular arrhythmias (around 10%), and sometimes as sudden cardiac death (1, 6-8, 10). It is thought that one small percentage from undiagnosed causes of sudden cardiac death is due to this condition. In addition, it is not uncommonly missed or delayed diagnosis of SCAD in those who require medical services (1, 2). Chest pain is the most present symptom in SCAD (up to 90% of the cases) which can irradiate to the left shoulder or neck, then backpain, shortness of breath, nausea, sweating etc (2, 8, 10). In almost all cases SCAD is followed by elevated levels of biomarkers (troponin), but in about 4% they may even be normal (10). So, it is reasonable to ask whether it is possible to exist SCAD with no myocardial infarction (7, 9, 15). Possible explanation for this situation is unstable angina or situation where biomarkers are determined too early after initial manifestation of SCAD (10).

Treatment

Up to date there are no randomized clinical trials that compare different treatment strategies for SCAD (1, 2, 4, 6, 7). Hence, one cannot be certain which is the optimal treatment for SCAD. But many observations and clinical experiences through the literature suggest that probably conservative approach (optimal pharmacological treatment) is the best choice in most of the cases. In a significantly smaller percentage of cases treatment of choice are revascularization procedures (PCI or CABG). Data from literature shows that only 1/5 of cases with SCAD are treated invasively. Such treatment approach is probably due to the fact that there are angiographic evidences for spontaneous healing of the coronary dissection in most cases (over 90%) (1, 7). In one of the largest prospective clinical trials for SCAD, CanSCAD, conducted on 750 patients in 22 centers in USA and Canada in 2014-2018, 84,3% were treated conservatively, 1,5% with fibrinolysis, while 14,7% were treated with revascularization (dominantly with PCI procedure – 14,1%) (16). Figure 3 shows algorithm for proper approach and selection of treatment for SCAD.

Figure 3. Algorithm for treatment of SCAD. LM – left main, CABG – coronary artery bypass grafting, PCI – percutaneous coronary intervention (taken and adapted from Hayes et al.)



Treatment approach for patients with SCAD mostly depends on clinical presentation and angiographic characteristics and these are the main determinants which should lead us towards proper decision if, when and how to revascularize patients (14). In general, patients diagnosed with SCAD who are clinically stable, without chest pain, should be treated pharmacologically. Those who are clinically or hemodynamically unstable (ex. with chest pain or active/ ongoing ischemia, completely occluded coronary artery, persistent ST-segment elevation, in cardiogenic shock or ventricular arrhythmia) should be treated with revascularization procedures (1, 3-7).

The aim of pharmacological treatment is to lessen symptoms, to improve outcome and to prevent recurrence of SCAD in future (7). Bearing on mind that SCAD is dominantly manifested as an ACS, primary pharmacological treatment is identical with the treatment of atherosclerotic ACS (anticoagulants, antiplatelets, antianginal drugs). After a SCAD diagnosis has been established, when treatment option is pharmacological, anticoagulation therapy should be stopped if there is no other indication. Antiplatelet therapy usually refers to acetylsalicylic acid (ASA). There is no clear evidence of justified use of DAPT with ASA and P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) in treatment of SCAD unless treated with PCI procedure. Hence, monotherapy only with ASA is usually sufficient. Nevertheless, there are authors who suggest use of DAPT for at least one year irrespective of choice of treatment in accordance to the guidelines for treatment of ACS. In patients treated with PCI, use of DAPT is also in accordance to the actual guidelines for treatment (12 months). Regarding GPIIb/IIIa inhibitors (eptifibatide, tirofiban) there is no evidence that supports their use. Beta blockers (if no contraindications) are used when there is left ventricular dysfunction or heart rhythm abnormalities as well as in treatment of hypertension. There is evidence that use of beta blockers is associated with reduced risk for recurrent SCAD and that is why they should be routinely used in all patients with SCAD (13). ACE-inhibitors and angiotensin-receptor blockers have a role after ACS with LV dysfunction and in treatment of hypertension. Statins should not be routinely prescribed in patients with SCAD, except in patients with established dyslipidemia, as a part of established atherosclerotic CAD and diabetes. Antianginal therapy encompasses use of nitrates, calcium channel blockers, and ranolazine taking into consideration some of their adverse effects (1,2,4,6-8,10,12,14,15).

PCI and stenting have a relatively limited role in the treatment of SCAD. Outcome from PCI in treatment of SCAD is less predictive and associated with increased rate of complications. Besides that, rate of procedural success from PCI in SCAD is relatively low (47-72%) (14). There are several reasons for that. Placement of the coronary wire carries risk of entering false lumen, potentially extend dissection and impair coronary flow. However, some authors prefer the use of non-hydrophilic wire first, and then switch with hydrophilic, which can lead to increased success from PCI. Use of balloon may also further extend dissection or IMH and can additionally jeopardize coronary flow. Selection of stent dimensions may be challenging. Longer stents or use of 2-3 stents with reasonable overlap are preferred in order to cover the whole dissected segment, but this strategy carries higher risk for "in-stent" thrombosis and restenosis. Sometimes choice of stent diameter can be an issue, which means wrong selection of stent with smaller diameter than required carries risk for stent malapposition after resorption of IMH and increased risk of subsequent thrombosis. It is recommended that the edges of the stent should cover at least 5-10mm out of the borders of dissection. If several stents are being used, then it is preferred to cover the borders of dissection first (first distal, then proximal), and at the end to implant third stent in the middle of previous two. Some experts prefer a more minimalistic approach and stenting of the entry tear only. Use of IVUS or OCT may be very important in establishing the diagnosis and determining the extensity of the dissection, but at the same time it is potentially dangerous step that carries risk of coronary flow impairment. Hence, it is not recommended their routine use, but only to use them in selected cases. Another possible cause of PCI failure is involvement of the distal segments and tortuous segments of the coronary arteries with SCAD, which makes approach for PCI and stenting very difficult and outcome - unpredictable. In some situations, cutting balloons may be helpful with intention to generate fenestration of intima-

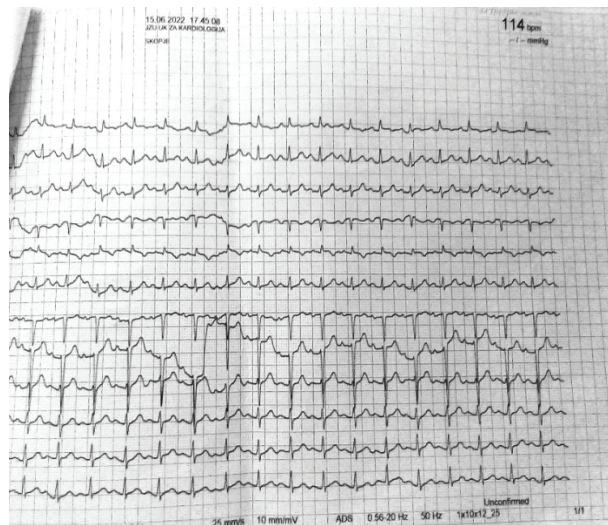
media and decompression of the false lumen as a solitary strategy or before stenting. In general, newer generations (second or third) of drug eluting stents (DES) are preferable. Some authors propose possible use of bioresorbable scaffolds (BRS), but it seems that their use currently is limited. According to this, PCI and stenting as a revascularization procedure is recommended in selected patients who are clinically or hemodynamically unstable, have chest pain, active/ongoing ischemia, coronary occlusion or cardiogenic shock and proximal segments of the coronary arteries have been involved (1,2,4,6,7,15).

Coronary artery by-pass grafting (CABG) is technically feasible revascularization procedure, but it is rarely used (<1% in patients with SCAD), usually in proximal multivessel involvement or LM involvement, after technical failure or unsuccessful PCI, complication of PCI, as well as in persistent ischemia beside optimal pharmacological treatment (14). Success from CABG in acute phase is high, but in mid-term and long-term very often graft occlusion can be seen which is probably a consequence of vascular healing and predominance of the flow in native coronary arteries (7,8,14,15).

Case Presentation No. 1

The first case is 60-years old female patient, non-smoker, with history for mild hypertension, epilepsy and osteoporosis. She has been treated with antihypertensive therapy on a regular basis (candesartan), antiepileptic, bisphosphonate, vitamin D3 and calcium. She has been hospitalized at the University Clinic of Cardiology in Skopje because of general weakness and malaise in the last few days accompanied with chest pain below sternum on the day of admission. The first ECG showed changes consistent with ACS with inverse T-waves in lateral leads (Figure 4)

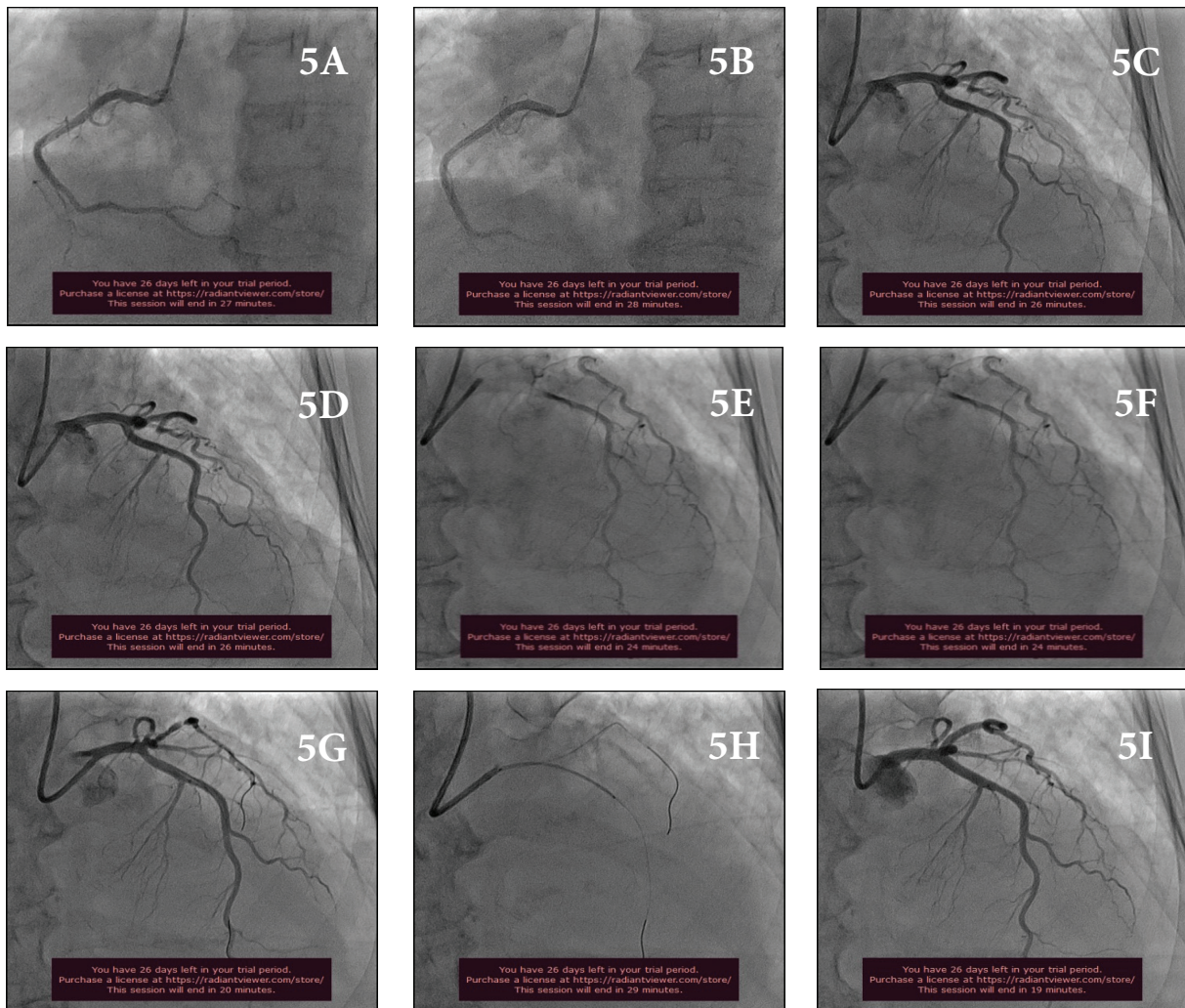
Figure 4. ECG on admission: changes consistent with ACS



The patient was admitted to the hospital in deteriorated clinical condition, tachycardic (114/min), dyspneic, tachypneic, hypotensive (98/71mmHg) – parameters which rise suspicion for development of heart failure. Laboratory findings showed high troponin levels hs Tn I 6326.2ng/L (ULN 15.6ng/L for women). The rest of the laboratory results were within the referent values. Lipid profile showed total cholesterol 5.8mmol/L (ULN 5.5mmol/L), LDL-c 2.6 mmol/l (ref. value 2.2-3.7mmol/l), HDL-c 2.7mmol/l (ref. value 0.9-2.0mmo/l) and TG 1.0mmol/l (ULN 2.0mmol/l). Regarding the clinical presentation, ECG changes and hs Tn I value, she was loaded with DAPT, anticoagulant (UFH) and underwent coronary angiography (CA). It showed no significant lesions of the coronary arteries, but there were angiographic phenomena typical for

SCAD – linear filling defects along the coronary arteries, contrast staining, slow flow and delayed contrast clearance from the coronary arteries (Figure 5A – 5G). Because of the unstable clinical condition patient underwent PCI and stenting of LM and LAD (“provisional stenting”) with DES 4.0/35mm x 12atm (Figure 5H) and subsequent postdilation with NC balloon 4.0/12mm x 16atm. We achieved optimal angiographic result with TIMI 3 flow (Figure 5I). Chest pain disappeared a few hours after intervention, while the rest of the symptoms during next days. Echocardiography revealed reduced global left ventricular systolic function (LVEF ~ 38%) with multiple hypokinetic segments: basal inferior wall, mid and distal third of the IVS and part of apex. The patient was clinically stabilized and additionally treated for heart failure as well.

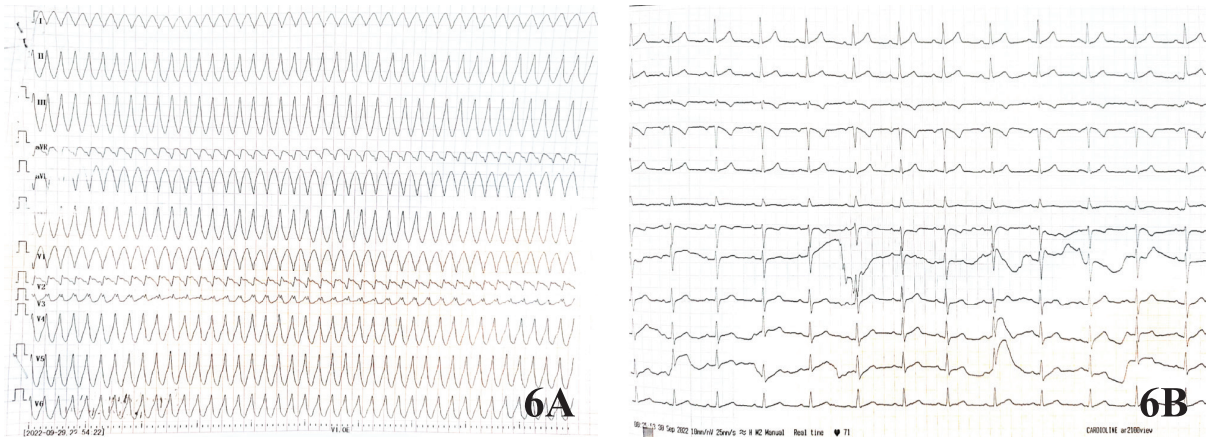
Figure 5A – 5I. Coronary angiography with multivessel SCAD (5A-5G).



Case Presentation No. 2

The second case refers to a 30-years old male who was hospitalized in a local hospital because of palpitations and ventricular tachycardia detected on ECG. He was treated with antiarrhythmics and converted in sinus rhythm. After that he was transported to the University Clinic of Cardiology in Skopje for further examination. The patient gave information that just before this event he had consumed large amounts of energetic beverages, creatin and proteins. He had no comorbidities. He was a nonsmoker, but positive family history for CAD (father died young). Figure 6A shows ECG from the local hospital (VT) and figure 6B - ECG in sinus rhythm on admission at our clinic.

Figure 6A. ECG with ventricular tachycardia (local hospital); Figure 6B. ECG in sinus rhythm on admission at the University Clinic of Cardiology in Skopje.



The laboratory blood analyses showed increased level of troponin (hs Tn I 605ng/L) and slightly elevated level of creatinine (133 μ mol/l) while the rest of them were within the referent values. Echocardiography showed normal LV dimensions with mildly reduced global systolic function and EF 50%, but with multiple hypokinetic segments – basal and mid-segment of the IVS and basal segment of inferior wall. The patient underwent coronary angiography with no significant atherosclerotic lesions, but with angiographic characteristics typical for SCAD: multiple linear filling defects, contrast staining and reduced contrast clearance from coronary arteries (Figure 7A-7E). Regarding the stable clinical and hemodynamic condition, the patient was treated conservatively. Five days after hospital admission, a coronary stress testing was performed, and it was interpreted as normal (negative). Patient was discharged home on beta blocker and ASA.

Figure 7A, 7B and 7C. Angiographic finding of the right coronary artery with linear filling defect (7A), left coronary stem with multiple linear filling defects (7B-7C).

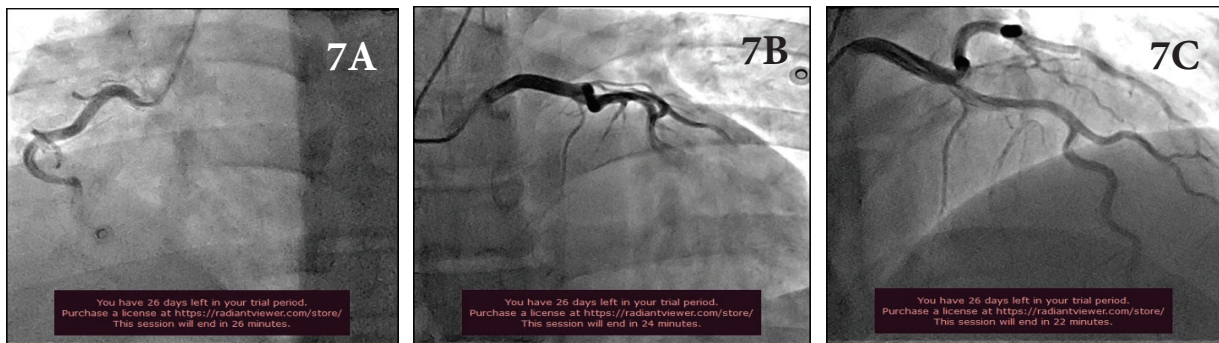
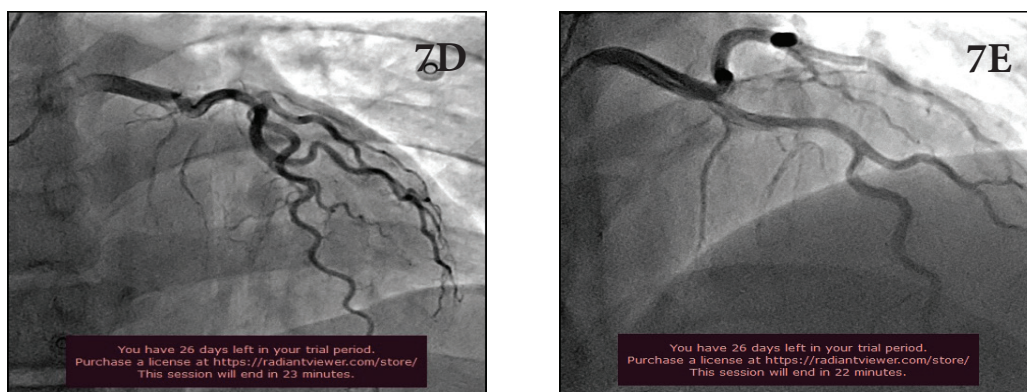


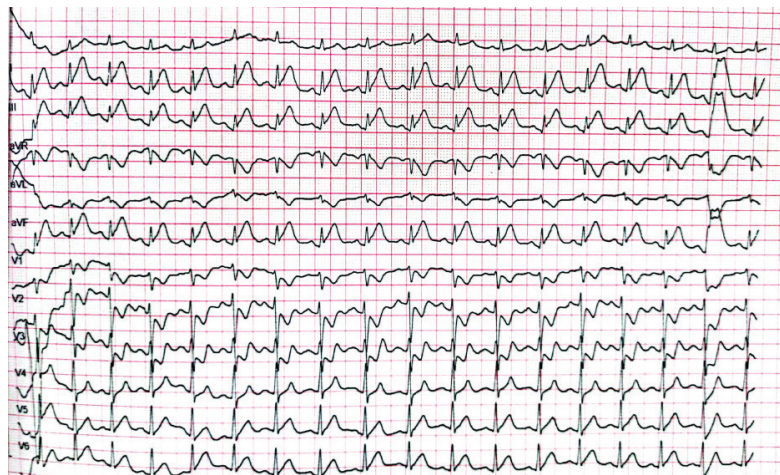
Figure 7D-7E. Angiographic finding of the left coronary stem with signs of contrast staining (7D) and linear filling defects of LM, LAD and Cx (7E).



Case Presentation No. 3

Thirty-one years old female patient with history for a recent backpain (less than 1 hour before admission) with propagation to the chest and arms during sleep has been admitted at the University Clinic of Cardiology in Skopje for further treatment. The patient had no comorbidities, only positive family history for CAD and she was former smoker. ECG on admission detected changes consistent with STEMI of inferoposterolateral wall (Figure 8).

Figure 8. ECG on admission with signs of inferoposterolateral STEMI.



She was initially treated with anticoagulant and DAPT and performed coronary angiography with highly suspected SCAD of the LAD causing contrast staining in the LM (Figure 9A) and linear filling defect along LAD (Figure 9B). The first angiography of the right coronary artery showed discrete and fine linear filling defect (Figure 9C) which in the next act of angiography made complete artery occlusion (Figure 9D). Consequently, PCI and stenting of the RCA was performed to close the tear entry (Figure 9E) and to restore normal coronary blood flow (Figure 9F). Preliminary laboratory analyses of blood showed normal levels of troponin which probably can be explained with short period from occurrence of symptoms to taking blood sample for analysis. But, next troponin levels taken after 24 hours were significantly higher (17 950ng/l). Echocardiographic assessment found normal global LV systolic function (EF 68%) without any hypokinetic segments.

Figure 9A, 9B and 9C. Angiography of LCA with highly suspected CAD (Figure 9A– contrast staining at LM, and linear filling defect along LAD – Figure 9B); angiography of RCA with discrete, fine linear filling defect (Figure 9C).

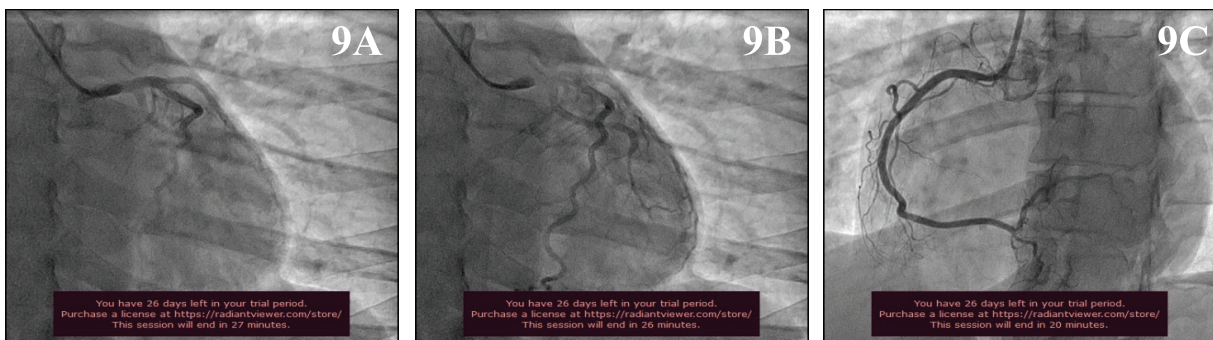
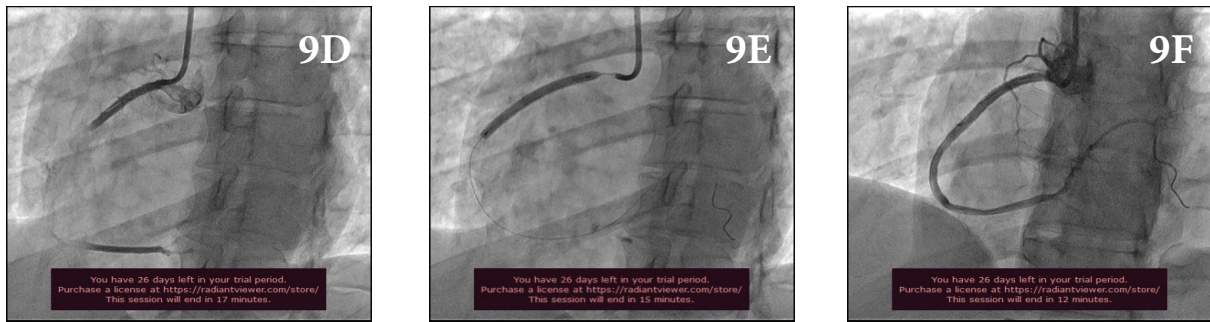


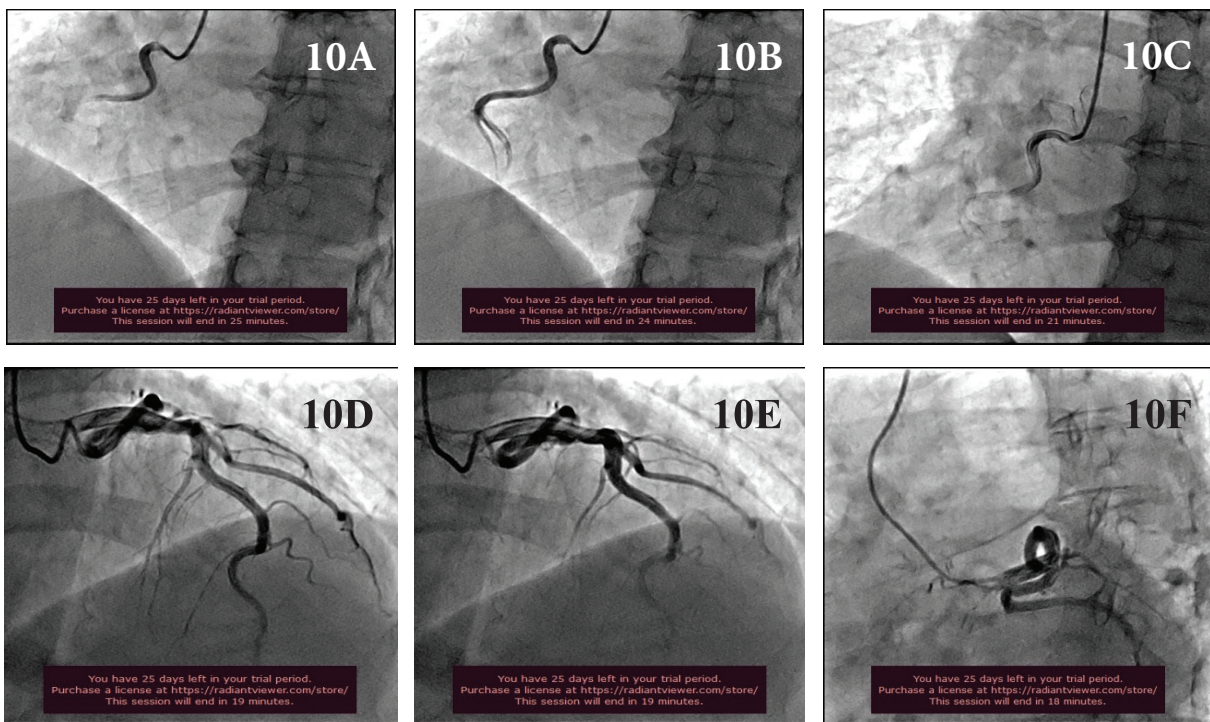
Figure 9D, 9E and 9F. SCAD which causes complete occlusion of RCA (Figure 9D); stenting of the RCA and closure of entry tear (Figure 9E); restoring of normal blood flow after stenting (Figure 9F).



Case Presentation No. 4

Female patient, 59-years-old was admitted at the University Clinic of Cardiology in Skopje because of chest pain which had occurred after exhausting night shift. She was a non-smoker, hypertonic on regular antihypertensive therapy. ECG on admission was without any morphologic changes and echocardiography detected normal LV dimensions with slightly reduced global LV systolic function (EF~51%), mild hypertrophy of the LV wall and no segmental hypokinesia. Preliminary troponin was normal, so the patient underwent coronary stress testing which was interpreted as positive (pathologic). The coronary angiography was indicated, and it detected tortuous coronary arteries with no significant atherosclerotic lesions, but with typical multiple linear filling defects, contrast staining and delayed contrast clearance from the arteries (Figure 10A-10F). The second troponin was higher with values 69.7ng/L (ULN 15.6 ng/L). Regarding the clinical condition, the patient was treated conservatively with beta blocker, ACE-inhibitor and ASA.

Figure 10A-10F. Coronary angiography of the RCA and LCA with multiple linear filling defects, contrast staining and delayed contrast washout from the coronary arteries typical for SCAD.



Conclusion

SCAD is a relatively rare, potentially life-threatening disease that dominantly occurs in female population at younger age. Usually, patients lack significant comorbidities and risk-factors for atherosclerotic CAD, though they may be present. The most frequent clinical manifestation is ACS, while angiographically there are no significant atherosclerotic lesions in the coronary arteries. Typical phenomena that describe SCAD (especially type 1) includes linear filling defects, contrast staining and reduced or delayed contrast washout from the coronary arteries. Sometimes it may be presented as a coronary artery occlusion or long narrowed segment of the artery mimicking thrombotic or atherosclerotic CAD. In some cases, angiography is not sufficient to establish diagnosis, so methods of intravascular visualization (IVUS, OCT) should be additionally used. The treatment is generally conservative, mainly in clinically and hemodynamically stable patients, while revascularization procedures with PCI or CABG are recommended for unstable patients. We should always think about and suspect this condition in relatively young persons presenting ACS without significant risk-factors in relatively good health shape in which angiography excludes significant atherosclerotic lesions of the coronary arteries.

REFERENCES

1. Pepe M. et al. How to Approach a Spontaneous Coronary Artery Dissection: An Up-To-Date. *IntervCardiol J* 2017, 3:1. DOI: 10.21767/2471-8157.100043.
2. Adlam D, Alfonso F, Maas A, et al. European Society of Cardiology, acute cardiovascular care association, SCAD study group: a position paper on spontaneous coronary artery dissection. *European Heart Journal* (2018) 39, 3353–3368. doi: 10.1093/eurheartj/ehy080.
3. Nishiguchi T. et al. Prevalence of spontaneous coronary artery dissection in patients with acute coronary syndrome. *European Heart Journal: Acute Cardiovascular Care*. 2016, Vol. 5(3) 263–270. DOI: 10.1177/2048872613504310.
4. Krittanawong C, Gulati R, Eitzman D, et al. Revascularization in patients with spontaneous coronary artery dissection: where are we now? *Am Heart Assoc*. 2021;10:e018551. DOI: 10.1161/JAHA.120.018551.
5. Ghani A. et al. Spontaneous coronary artery dissection: a case series of 9 patients with literature review. *Journal of Investigative Medicine High Impact Case Reports* (2018) Volume 6: 1–7.
6. Yip A, Saw J. Spontaneous coronary artery dissection – a review. *Cardiovasc Diagn Ther* 2015;5(1):37-48. doi: 10.3978/j.issn.2223-3652.2015.01.08.
7. Hayes NS et al. Spontaneous coronary artery dissection: current state of the science. *Circulation*. 2018;137:e523–e557. DOI: 10.1161/CIR.0000000000000564.
8. Kim SHE. Spontaneous coronary artery dissection. *N Engl J Med* 2020;383:2358-70. DOI: 10.1056/NEJMra2001524.
9. Adlam D. et al. Spontaneous coronary artery dissection. *J Am Coll CardiolIntv* 2021;14:1743–1756. <https://doi.org/10.1016/j.jcin.2021.06.027>.
10. Wuerdinger M, Camman V.L., Ghadri J.R., et al. Spontaneous coronary artery dissection: a rare event? *Heart Failure Clinics* (2022), 18(1):189-199. <https://doi.org/10.1016/j.hfc.2021.07.015>.
11. Kotecha D, Adlam D. Spontaneous coronary artery dissection: new insights on diagnosis and management. *REC IntervCardiol*. 2020;2(4):239-241. <https://doi.org/10.24875/RECICE.M20000096>.
12. Pristera N, Chaudhury P, Iterson Van HE, et al. Spontaneous coronary artery dissection: principles of management. *Cleveland Clinic Journal of Medicine* (2021) Vol. 88 No 11. doi:10.3949/ccjm.88a.20162.

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13. Parsa A, Saw J. Spontaneous coronary artery dissection: clinical considerations in diagnosis and treatment. <https://www.acc.org/latest-in-cardiology/articles/2019/12/20/11/41/spontaneous-coronary-artery-dissection>.
 14. Teruzzi G. et al. Spontaneous coronary artery dissection: a systematic review. *J. Clin. Med.* 2021, 10, 5925. <https://doi.org/10.3390/jcm10245925>.
 15. Hayes NS et al. Spontaneous coronary artery dissection. *J Am Coll Cardiol* (2020) Vol. 76 No 8. <https://doi.org/10.1016/j.jacc.2020.05.084>.
 16. Saw J. et al. Canadian spontaneous coronary artery dissection cohort study: in-hospital and 30-day outcomes. *European Heart Journal* (2019) 40, 1188–1197. doi:10.1093/eurheartj/ehz007.

SURGICAL MANAGEMENT OF DUODENAL GASTROINTESTINAL STROMAL TUMOR IN A YOUNG ADULT FEMALE PATIENT

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Abstract

Background: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms. They can arise anywhere in the digestive tract in adults and only in fewer than 5% of cases can be located in duodenum.

Case Presentation: We report on a rare case of duodenal GIST in 32-years-old female patient with several comorbidities (extreme obesity, HTA, glucose intolerance) and previous left adrenalectomy. The tumor mass was located in D2 portion of duodenum involving the papilla of Vater, with diameter of 5cm. It was diagnosed with upper GI endoscopy, abdominal US and CT scan, and confirmed histologically as GIST. The optimal surgical approach in this case was pancreaticoduodenectomy (En bloc resection) due to location and size of the tumor, and involving the adjacent anatomical structures. R0 resection (Whipple procedure) was confirmed with negative surgical margins. The postoperative course was prolonged due to respiratory complications and present pancreatic fistula. The patient was discharged from hospital in good health condition.

Conclusion: There is lack of consensus about appropriate surgical approach in these tumors, due to its rarity. Optimal surgical strategies for duodenal GISTs remain to be established.

Key Words: duodenum, gastrointestinal stromal tumor (GIST), surgical treatment, Whipple procedure.

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common non-epithelial neoplasms of the gastrointestinal tract. GISTs originate from the interstitial cells of Cajal and recently they have been defined as cellular spindle cell, epithelioid or occasionally pleomorphic mesenchymal tumors of the GI tract that express the c-kit protein (CD117-type of receptor for tyrosine kinase) and they are strongly and nearly uniformly CD117+ (1). Their localization is in the third and fourth layers (submucosal and muscular) with annual incidence rates reported worldwide as less than 10-20 per million, with no difference in gender or race which is less than three per 100,000 individuals and because of that are considered as rare tumors (2). GISTs in gastrointestinal tract can originate from any part, the most commonly from stomach (60%), small intestine (20-30%) and duodenum (5%). Clinical picture can be various and it can be presented with non-specific gastrointestinal pain, GIB (melena, hematemesis, hematochezia) and symptoms from compression of neighboring organs, in cases where tumor reaches a significant size (3,4,5). The pathophysiology or surgical treatment of duodenal GISTs poses particular challenges for either diagnosis or management. If the tumor is not presented with acute hemorrhage requiring emergency surgical treatment, the patient should be adequately prepared and surgical team could plan thoughtful elective treatment. To date, surgery with histologically negative margins is mainstream treatment for primary resectable GIST.

Case Presentation

A 32-years old female patient was admitted at the Department of Gastroenterohepatology in our hospital, with the complaints of abdominal pain, vomiting and obstructive jaundice for ten days before admission. Her medical history included glucose intolerance, hypertension, extreme obesity (BMI=46.1kg/m²), and previous suprarenal adrenalectomy on the left adrenal gland because of Adrenal Cortical Carcinoma (PH confirmed) one year ago.

Her laboratory findings showed elevated total bilirubin levels - 280umol/L (normal range 5-21umol/L), higher levels of AP (alkaline phosphatase), 730U/L (normal range 35-120U/L) and GGT (gamma glutamyl transferase), 408U/L (normal range 5-75U/L) and lower hemoglobin levels. Abdominal ultrasound was performed and showed a distended gallbladder with thickened walls with numerous calculi presented in the lumen. In the projection of the pancreatic head, a hypoechoic formation with dimensions of 40x48mm was present. Next, an upper GI endoscopy was performed, and it showed large exulcerative tumor mass in the D2 portion of duodenum, obstructing his lumen. Histological examination of the biopsy specimen revealed mesenchymal tumor tissue and the tumor mass was diagnosed as a GIST. Abdominal computed tomography (CT) scan confirmed the presence of a solid tumor mass in D2 portion of duodenum 5cm in diameter, which obstructs the papilla of Vater and consequently leads to retrograde dilatation of common bile duct. MRI was not performed due to patient's obesity and technical limitations of the scanner according to body weight. According to these radiological, endoscopic and histological findings, a primary GIST of the duodenum with consecutive obstructive jaundice was confirmed and surgical resection was planned as PD (pancreatoduodenectomy). Preoperatively, the patient was adequately prepared by endocrinologist with correction of hormone values, and she was substituted with blood derivatives due to anemic syndrome. Intraoperatively, the tumor was located in the upper part of the duodenum and because of its dimensions and location we decided to perform standard Whipple procedure (cephalic pancreaticoduodenectomy) - R0 resection and typical anastomoses were created, but with emphasis on the soft texture of pancreatic tissue on manual perception of pancreas (**Figure 1 a, b and c**).

Figure 1.

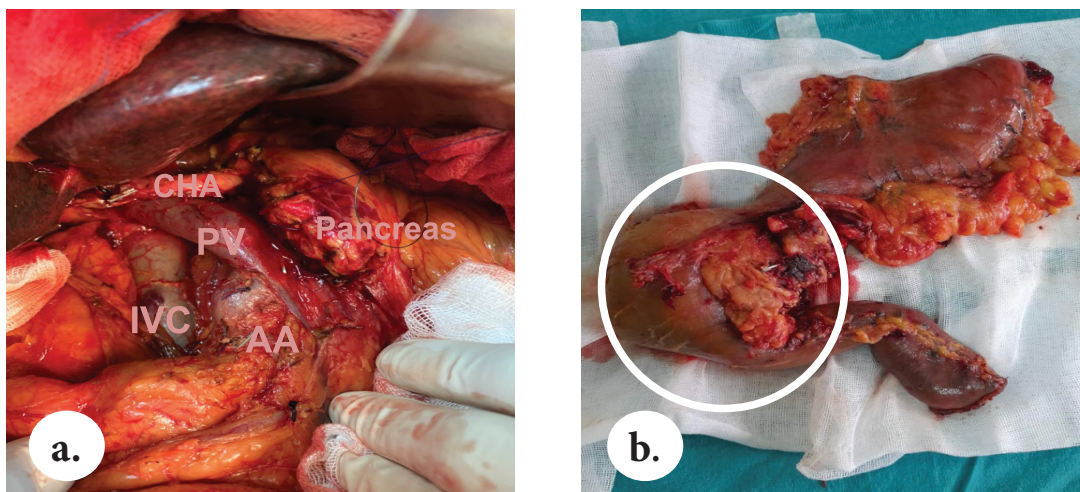




Figure 1- GIST of duodenum (a): Intraoperative photograph after pancreaticoduodenectomy was performed, CHA - common hepatic artery, PV - portal vein, IVC - inferior vena cava, AA - abdominal aorta and pancreas. (b): removed GIST of D2 portion of duodenum with adjacent anatomical structures in Whipple procedure (R0 resection); (c) GIST outlook in the duodenal lumen.

Histological examination of the specimen confirmed the same mesenchymal tumor tissue (positive for c-kit mutation and CD34 expression) within the duodenal wall without local invasion in the pancreatic, jejunal and gastric tissue. All surgical margins were negative for malignant cells and none of the lymph nodes showed malignant characteristics. The postoperative course was prolonged due to the pulmonary complications with pleural effusion which led to respiratory failure and the patient was on mechanical ventilation for 10 days. Also, a biliary and pancreatic content appeared in the abdominal drain tubes fluid which was confirmed with elevated levels of amylase (amylase level of drainage fluid after postoperative day 3 exceeding three times of the serum concentration) and bilirubin analyzed from the drain fluid. This led to prolonged stay at ICU. When the patient's respiratory function improved, oral nutrition was introduced, and the bowel function was normalized. The continuous pancreatic secretion on the left drain led to formation of pancreatic fistula (POPF- postoperative pancreatic fistula grade B). During the postoperative period, physical therapy was conducted. The patient was discharged from hospital on twenty-ninth postoperative day in good health condition with two abdominal drains for further monitoring of the amount of secretion. POPF was treated conservatively. Control of the fistula was maintained by drain fluid assessment and abdominal US and the drain was removed 5 weeks after surgery. A proper healthy diet and postoperative physical therapy and rehabilitation were recommended.

Discussion

GISTs present approximately 1% of the gastrointestinal tumors (6). The duodenum represents a very rare site of primary GIST. Duodenal GIST is typically observed in adults (50-70 years) with a slight preponderance in males. In young adults GISTs are sporadically present. All GISTs are potentially malignant even though they can have benign appearance (7). The median size of duodenal GIST lesions is about 4cm (7). In this report, a rare case of duodenal GIST was described in 32-years-old female patient, with tumor size on CT scan of 5cm which is slightly higher size than the average.

The leading symptoms were non-specific abdominal pain, vomiting and obstructive jaundice. In our case the tumor was detected at first with abdominal ultrasound and upper GI endoscopy with finding of exulcerative obstructing tumor mass in D2 portion of duodenum and then the final diagnosis of GIST was histologically confirmed. CT and MRI are standard diagnostic modalities for estimating the primary lesion and detecting the possible distant disease [7]. In our case only CT scan was performed which confirmed the presence of a solid tumor mass in D2 portion of duodenum, which obstructs the papilla of Vater and consequently leads to retrograde dilatation of common bile duct.

The treatment should be multidisciplinary, involving gastroenterologist, surgeon, pathologist, radiologist and oncologist. In the treatment of this patient, endocrinologist was also included because of the preoperative hormonal disbalance, due to previous adrenalectomy, insulin resistance and extreme obesity. Surgical treatment is a golden standard, although surgical approach varies depending on tumor size, location and invasion into adjacent organs (stage of disease) (3,8). Standard treatment of localized duodenal GIST is complete surgical excision (En bloc) with negative surgical margins (7,8). Treatment options range from pancreaticoduodenectomy (Whipple procedure) to local resection, mostly depending on tumor size and location (9, 10). In case of larger tumors or tumor localization in D2 portion of duodenum with involvement of head of the pancreas or the ampulla of Vater, should undergo pancreaticoduodenectomy (11). The anatomy of the duodenum, especially the second part and its proximity to important anatomical structures, such as duodenal papilla, pancreas and the pancreatic and biliary ducts, further complicate the surgical approach. In this case, with the characteristics mentioned, the best choice for surgical treatment was Whipple procedure, and in comparison to the literature, the treatment in our patient was adequate. Besides the extension of surgical procedure, in postoperative period present comorbidities worsened the patient's health condition and provoked respiratory complications which led to prolonged stay in ICU and postponed rehabilitation. About the POPF formation, there are many possible reasons and risk factors. Soft pancreatic tissue, based on intraoperative assessment, which was described in our case, is the most widely recognized risk factor for pancreatic fistula (12,13). Pathohistological findings confirmed duodenal GIST with c-kit mutation and CD34 expression, with heterogenous morphology, without tumor invasion in pancreatic, jejunal and gastric tissue, free surgical margins and none of the lymph node was positive for tumor cells, so R0 resection was achieved. It is important to mention that small intestinal GISTs (including the duodenal ones) are a histologically more homogenous than gastric GISTs. In contrast to gastric GISTs, all small intestinal GISTs >5cm have a significant tumor-related mortality, twice as high as gastric GISTs (around 40-50%) (14).

Conclusion

The primary treatment of duodenal GIST is the surgical approach, and its aim is to remove tumor En bloc, which means complete tumor resection and adequate margins, following the principles of oncologic surgery. Surgical approach depends upon tumor location and size. The recurrence rate depends upon tumor location and extend of removal. Because of its rarity, there is lack of consensus about role of lymphadenectomy and the most appropriate surgical approach is still unclear. Optimal surgical strategies for duodenal GISTs remain to be established.

Conflict of interest: None declared.

REFERENCES

1. Rubin BP, Heinrich MC, Corless Cl. Gastrointestinal stromal tumour. *Lancet*.2007;369(9574):1731-41.
2. Azcoitia MF. Tumores del estroma gastrointestinal, definicion, generalidades y epidemiologia. *Cir.Gen.* 2008;30: S5-S10.
3. C.Shen, H. Chen, Y.Yin, et al. Gastrointestinal stromal tumors: clinicopathological characteristics, surgery, and long-term outcome, *BMC Surg.* 2015; 15: 98.
4. S.J. Lee, K.B. Song, Y.J. Lee, et al. Clinicopathologic characteristics and optimal surgical treatment of duodenal gastrointestinal stromal tumor. *J. Gastrointest. Surg.* 2019; 23(2):270-279.
5. Yang F, Jin C, Du Z, et al. Duodenal gastrointestinal stromal tumor: Clinopathological characteristics, surgical outcomes, long term survival and predictors for adverse outcomes. *Am J Surg.* 2013; 206:360-367.
6. V.P.Valli, C. Valli, T. Pfammatter, et al. Life-threatening bleeding of a duodenal gastrointestinal stromal tumor in a teenager: a rare case report. *Endosc. Int. Open* 04; 2016: E1244-E1246.
7. M. Mokhtare, T. Taghvaei, H.T. Fakheri. Acute bleeding in duodenal gastrointestinal stromal tumor. *Middle East J. Dig. Dis.*5; 2013:47-51.
8. P.G. Casalli, N. Abecassis, S. Bauer, et al. Gastrointestinal stromal tuomours: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol* 4; 2018: iv68-iv78.
9. Cavallaro G, Polistena A., S'Ermo G, et al. Duodenal gastrointestinal stromal tumors: Review on clinical and surgical aspects. *Int J Surg.* 2012; 10(9): 463.
10. Chok AY, Koh YX, Ow MYL, et al. A systematic review and meta-analysis comparing pancreaticoduodenectomy versus limited resection for duodenal gastrointestinal stromal tumors. *Ann Surg. Oncol.* 2014; 21(11): 3429-38.
11. Beltrán MA, Valenzuela C, Diaz R, et al. Tumores del estroma gastrointestinal del duodeno: revisión de literatura científica actual con ébfasis en el tratamiento. *Rev Colomb Cir.* 2014; 29:140-154.
12. Lin JW, Cameron JL, Yeo CJ, et al. Risk factors and outcomes in postpancreaticoduodenectomy pancreaticocutaneous fistula. *J Gastrointest Surg.* 2004; 8:951-959.
13. Mathur A, Pitt HA, Marine M, et al. Fatty Pancreas: a factor in postoperative pancreatic fistula. *Ann Surg.* 2007; 246:1058-1064.
14. Miettinen M, Lasota J. Histopathology of Gastrointestinal Stromal Tumor. *J Surg Oncol.*2011;104(8):865-873.

INSULINOMA-ULTRASOUND, CT AND MRI FINDINGS

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Abstract

An insulinoma is a hormone-producing neuroendocrine neoplasm of the pancreas. Typically, these tumors are sporadic, solitary and less than 2cm in diameter. Insulinomas are insulin-secreting tumors and consequentially they cause hypoglycemia that results with multitude of characteristic symptoms. Imaging techniques like ultrasonography, multiphase CT scan and MRI with contrast are non-invasive techniques for localizing and confirming the diagnosis. We present a case of a patient with insulinoma to show the specific findings in an Ultrasound, CT and MRI examination. This leads to a fast confirmation of the diagnosis and fast treatment for the patient.

Key Words: computer tomography, diagnosis, insulinoma, ultrasonography, magnetic resonance imaging,

Introduction

Insulinomas are the most common hormone-producing neuroendocrine neoplasm of the pancreas (1,2). Their estimated incidence is 1–3 million cases per year, and overall, they represent 1%-2% of all pancreatic neoplasm (1,2). There are more common in the fifth decade of life, with a slight female predominance (1,2). 90% of insulinomas have been reported to be benign, 90% are solitary, 10% of insulinomas are multiple and less than 10% show malignant spread (1,2,3). The most of them are with intrapancreatic localization and equal distribution within the head, body and tail of the pancreas (1,2,3). The sensitivity of transabdominal ultrasonography in the diagnosis of insulinomas ranges from 9% to 64% (4,5). CT sensitivity has been reported to be 33%-85% and MRI sensitivity 40%-90% (1,4,5). Accordingly, the general consensus is that the sensitivity and specificity of MRI examination in patients with insulinomas is generally superior to that of CT (1,4,5). The aim of this case study is to show the specific findings in an Ultrasound, CT and MRI examination in a case of a patient with insulinoma.

Case Report

A 62-years old male patient was examined at the emergency department with the acute onset of lightheadedness, chills, shakiness and syncope. A glucose level detected with glucometer from the emergency team repeatedly was 1,6...1.7...2,5mmol/L. He was given high glycemic food, and his symptoms resolved. The patient reported that he had experienced similar symptoms, but of lesser severity for approximately 8 month duration before this episode. As per patient's information, the most of episodes were in the early morning between 4 to 9 am and were associated with prolonged fasting and over exertion. The serum cortisol level was normal suggesting intact pituitary adrenal axis. Thyroid function tests were within normal range. For further evaluation and management, the patient was advised to be hospitalized. He had no family history of diabetes, thyroid or pituitary disease. Physical examination showed a healthy man with a Body Mass Index (BMI) of 27.4kg/m². Blood laboratory tests demonstrated a low initial glucose level at 2.12mmol/L (3.8–6.3mmol/L), a high plasma insulin level at 35.24μIU/ml (2.6–24.9μIU/ml), and a high C-peptide level at 5.21ng/ml (0.8–4.2ng/ml). A prolonged supervised

fasting test was applied and produced symptomatic hypoglycemia with hyperinsulinemia. Urine for sulfonylurea screen was negative.

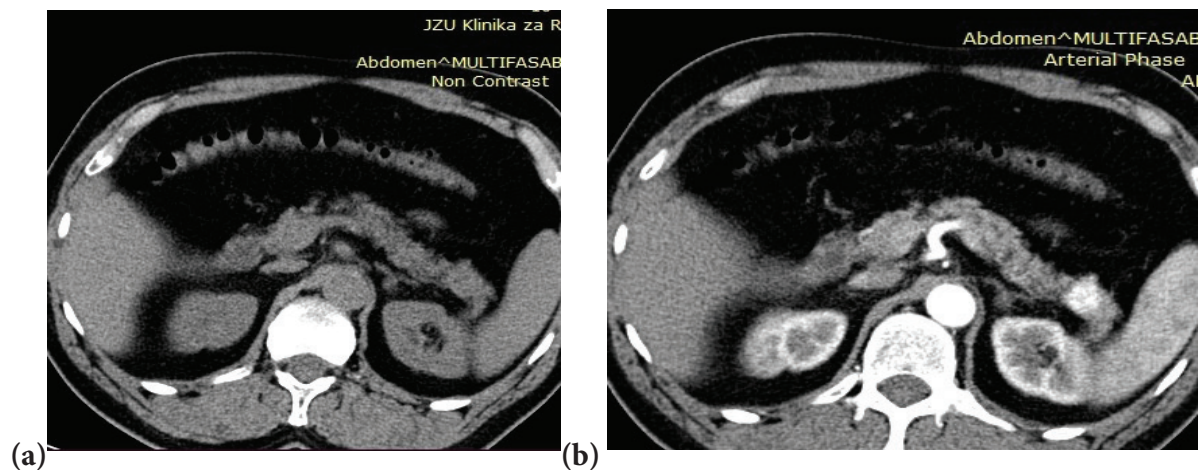
Abdominal ultrasonography was performed which revealed well-defined hypoechoic nodular lesion in the region of the tail of the pancreas measuring 16.3x14mm. The rest of the abdominal organs were with normal ultrasonographic findings.

Figure 1. Abdominal ultrasonography reveals well shaped, hypoechoic nodular lesion in the region of the tail of pancreas.



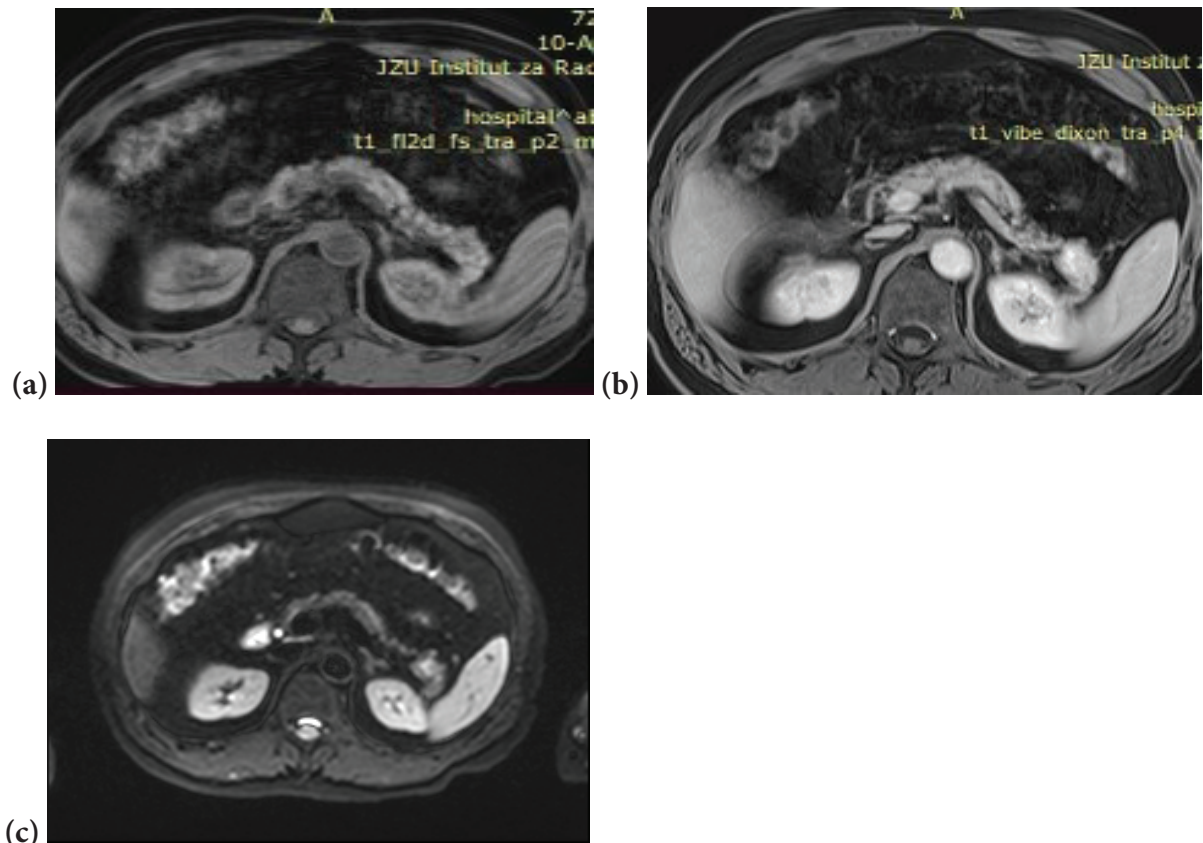
Abdominal multiphase CT scan was indicated and performed. A finding of a well-defined hyperattenuating lesion involving the tail of pancreas and measuring 20 × 17mm with homogeneous post-contrast enhancement during the arterial phase was noted. Enlargement of intra-abdominal lymph nodes or focal pathological changes on other abdominal organs weren't detected.

Figure 2. (a) Axial non enhancing computed tomography of the abdomen revealing discreet, oval mass in the tail of pancreas. (b) Axial contrast enhancing computed tomography of the same level showing enhancing mass with significant contrast accumulation.



For further evaluation an abdominal MRI with contrast was performed. A finding of an oval clearly defined mass located at the tail of the pancreas without dilatation of the pancreatic ducts was noted. The mass was with low signal on the T1, with intensive enhancement on the T1 vibe post-contrast series, also there was restriction of diffusion present on the DWI series.

Figure 3. MRI of the abdomen with gadolinium contrast. (a) T1 FS revealed hyposignal mass in the tail of pancreas. (b) T1 post contrast showing enhancing mass in the tail. (c) DWI showing restriction of diffusion in the mass.



With the combined results of the performed imaging examination methods (ultrasound, CT and MRI) and clinical examinations, the working diagnosis of insulinoma was acquired. Accordingly, surgical treatment was recommended.

The laparoscopic distal pancreatectomy was performed, and the following histopathological report confirmed the diagnosis of insulinoma. Furthermore postoperatively, plasma glucose and insulin concentrations remained within the normal range and the symptoms of hypoglycemia were completely resolved.

Discussion

An insulinoma is a pancreatic neuroendocrine neoplasm originating from the Langerhans cells, and it is typically sporadic, solitary, and less than 2cm in diameter (3,6).

The most of insulinomas are located in the pancreatic parenchyma or they are directly attached to the pancreas (1). Extra-pancreatic insulinomas are extremely rare, and the most commonly can be found in the duodenal wall (1). Insulinomas are insulin-secreting tumors of pancreatic origin that cause hypoglycemia, and as a result of that there are a multitude of symptoms (1).

The most common symptoms of insulinoma are tremor, palpitations, dizziness, confusion, hunger behavioral changes, anxiety or irritability, double vision or blurred vision, seizure, and even coma (1,2,6). Symptoms often subside when consuming food (12).

Some of these symptoms like Whipple's triad that consists of fasting hypoglycemia (<50mg/dL), symptoms of hypoglycemia and immediate relief of symptoms after the administration of IV glucose are the first reason to start the glycemic tests and after that the standardized provocation test, i.e., a 72-h fasting test with monitoring of glucose, insulin and C-peptide levels (8). The imaging techniques like ultrasonography, multiphase CT scan and MRI with contrast are non-invasive techniques for localizing the source of pathological insulin secretion (10).

Histological evidence is the final in a range of morphologic and functional (nuclear or molecular) imaging methods (12). Ultrasonography as the cheapest, noninvasive free of radiation and fastest method is almost always the first choice in the initial assessment and definition of localization. However, the sensitivity for insulinomas is poor ranging from 9% to 64% (1,5).

CT is the main imaging modality used for localization, staging and monitoring of the response to treatment (12). Insulinomas are hypervascular lesions and they demonstrate a greater degree of enhancement in both the arterial and portal venous phases, whereas in modern CT scanners they are easily detected with a sensitivity of 30–85%, depending on tumor size (5).

MRI is an almost unavoidable method for detecting small insulinomas, as well as metastatic deposits in the abdominal cavity (the most commonly liver and bones). Using the conventional sequences, small insulinomas usually have a low signal on T1-weighted sequences and a high signal on T2-weighted sequences. Less frequently if they contain fibrosis, they show a weak signal on both the T1 and T2 sequences. Insulinomas typically show strong enhancement in the arterial phase (10). MRI sensitivity ranges from 40% to 90% (1,4,5). Previous empirical data suggest that a combination of all three methods still works the best (9). Surgical resection of insulinoma is the gold standard and the only option for a permanent solution. Medical therapy is applied in malignant disease progression which is present in less than 5% of the patients diagnosed with insulinoma and also in patients who are unable or unwilling for surgical treatment (5,7).

Conclusion

Insulinoma is usually presented with characteristic clinical symptoms. However, imaging noninvasive diagnostic techniques are of great importance for the detection of the mass and the confirmation of the diagnosis. For optimal diagnostic success, a combination of ultrasound, CT and MRI finding is recommended. This provides fast diagnosis, and accordingly fast treatment for the patients.

REFERENCES

1. Okabayashi T, Shima Y, Sumiyoshi T, et al. Diagnosis and management of insulinoma. *World J Gastroenterol.* 2013 Feb 14;19(6):829-37. doi: 10.3748/wjg.v19.i6.829.
2. Hofland J, Kaltsas G, de Herder WW. Advances in the Diagnosis and Management of Well-Differentiated Neuroendocrine Neoplasms. *Endocr Rev.* 2020;41(2):371-403. doi:10.1210/endrev/bnz004.
3. de Herder WW, Zandee WT, Hofland J. Insulinoma. [Updated 2020 Oct 25]. In: Feingold KR, Anawalt B, Boyce A, et al., editors. *Endotext* [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: <https://www.ncbi.nlm.nih.gov/sites/books/NBK278981/>.

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4. Future Oncology Vol. 6, No. 2 Review Free Access, Insulinoma: pathophysiology, localization and management Joyce J Shin, Phillip Gorden & Steven K Libutti. Published Online: 10 Feb 2010 <https://doi.org/10.2217/fon.09.165> .
 5. de Herder, Wouter and Niederle, et al. 2006, 02, 183-188, Well-Differentiated Pancreatic Tumor/Carcinoma: Insulinoma 84, Neuroendocrinology, doi = {10.1159/000098010}.
 6. Elizabeth A. Mittendorf, Yao-Chang Liu, Christopher R. McHenry, Giant Insulinoma: Case Report and Review of the Literature, The Journal of Clinical Endocrinology & Metabolism, Volume 90, Issue 1, 1 January 2005, Pages 575–580, <https://doi.org/10.1210/jc.2004-0825> .
 7. Taye A, Libutti S. Diagnosis and management of insulinoma: current best practice and ongoing developments. Research and Reports in Endocrine Disorders. 2015;5:125-133 <https://doi.org/10.2147/RRED.S86565> .
 8. Christ, E., Antwi, K., Fani, M., et al. (2020). Innovative imaging of insulinoma: the end of sampling? A review, Endocrine-Related Cancer, 27(4), R79-R92. Retrieved Dec 1, 2021, from <https://erc.bioscientifica.com/view/journals/erc/27/4/ERC-19-0476.xml> .
 9. Druce, M. R., Muthuppalaniappan, V. M., O’Leary, B., et al. (2010). Diagnosis and localisation of insulinoma: the value of modern magnetic resonance imaging in conjunction with calcium stimulation catheterisation, European Journal of Endocrinology, 162(5), 971-978. Retrieved Dec 1, 2021, from <https://ej.e.bioscientifica.com/view/journals/eje/162/5/971.xml> .
 10. Anaye, Anass & Mathieu, et al. (2009). Successful Preoperative Localization of a Small Pancreatic Insulinoma by Diffusion-Weighted MRI. JOP : Journal of the pancreas. 10. 528-31.
 11. Gorman B, Charboneau JW, James EM, et al. Benign pancreatic insulinoma: preoperative and intraoperative sonographic localization. AJR Am J Roentgenol. 1986 Nov;147(5):929-34. doi: 10.2214/ajr.147.5.929. PMID: 3020955.
 12. Hofland J, Kaltsas G, de Herder WW. Advances in the Diagnosis and Management of Well-Differentiated Neuroendocrine Neoplasms. Endocr Rev. 2020;41(2):371-403. doi:10.1210/endrev/bnz004

IDIOPATHIC CHOROIDAL NEOVASCULARIZATION TREATED WITH BEVACIZUMAB

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Abstract

Introduction: Choroidal neovascularization (CNV) is a common cause of legal blindness in developed countries. CNV can occur in younger people as a secondary manifestation of many inherited and acquired conditions such as angioid streaks, high myopia, trauma, choroidal tumors, familial macular dystrophies, and inflammatory retinchoroidopathy. However, in some young patients with CNV, no apparent cause can be detected, and the CNV is generally categorized as idiopathic CNV.

Purpose: To report a young woman with idiopathic choroidal neovascularization treated with an anti-VEGF (anti-vascular endothelial growth factor) agent (bevacizumab) observed during a period of 1 year.

Case Report: A young girl of 19 years age presented with worsening central vision in the left eye during several months. Funduscopy examination of the left eye revealed perifoveal change, choroidal neovascularization (CNV) with a surrounding zone of subretinal fluid accumulation. The patient was indicated for treatment with intravitreal application of Bevacizumab in three consecutive monthly applications. The finding after three monthly applications and the visit at fifth month after treatment (2 months after the last application) showed a complete resolution of the finding, inactive CNV. Observation was done every second month, and after 9 months from the last application (1 year after treatment) the condition was stable and visual acuity was 1.0.

Conclusion: CNV which often causes severe vision loss and eventually blindness, is a common pathologic change that may occur in more than 30 ocular diseases. ICNV is a disorder that primarily affects younger patients. Anti-VEGF therapy is the first line of treatment, and it is associated with better visual outcomes than other treatment modalities.

Key Words: *angiography, Bevacizumab, choroidal neovascularization, idiopathic choroidal neovascularization, optical coherence tomography.*

Introduction

Choroidal neovascularization (CNV) is a common cause of legal blindness in developed countries (1). The most common cause for CNV in old age is age-related macular degeneration (AMD), a condition manifesting with drusen (particularly soft drusen) and pigmentary alterations in the macular region (2).

CNV can occur in younger people (<50 years), who usually do not have conspicuous drusen or pigmentary abnormalities. In this age group CNV may occur as a secondary manifestation of many inherited and acquired conditions such as angioid streaks, high myopia, trauma, choroidal tumors, familial macular dystrophies, and inflammatory retinchoroidopathy. However, in some young patients with CNV, no apparent cause can be detected, and the CNV is generally categorized as idiopathic CNV (iCNV) (2).

Idiopathic CNV is a disorder that primarily affects younger patients and can cause severe loss of vision. Choroidal abnormalities, especially choroidal inflammation, have been thought to be involved in the pathophysiology of ICNV (3).

Although the natural progression and the final visual outcomes of iCNV are generally considered to be more favorable than CNV attributable to AMD, severe and irreversible visual loss can occur in some untreated eyes (4). Optical coherence tomography angiography (OCT-A) offers non-invasive detection of this clinical entity.

Nowadays, various iCNV treatments have been reported, such as intravitreal anti-vascular endothelial growth factor (VEGF) therapy or photodynamic therapy (PDT) with verteporfin. However, the optimal treatment for iCNV is not well established (5,6,7).

Purpose: To report a young woman with idiopathic choroidal neovascularization treated with an anti-VEGF (anti-vascular endothelial growth factor) agent (Bevacizumab) observed during a period of 1 year.

Case Report:

A young girl of 19 years age was presented with worsening central vision in the left eye during several months.

A complete ophthalmological examination was performed with additional investigations, namely fluorescein angiography (FA), fundus auto-fluorescence (FAF), optical coherence tomography (OCT) of the posterior segment and OCT with angiography (OCTA). Ophthalmological findings revealed a best-corrected visual acuity in the right eye of 1.0; and on the left 0.8; mild myopia, corrected by -1.0 Dsph; the anterior segment was normal, and the intraocular pressure was 15mmHg bilaterally. The posterior segment of the right eye was normal, bilaterally with no signs of myopic changes, but funduscopy examination of the left eye revealed perifoveal change, choroidal neovascularization (CNV) with a surrounding zone of subretinal fluid accumulation (Figure 1). Fluorescein angiography and OCTA of the right eye showed classic CNV (Figures 2,3). OCT showed subretinal reflection as well as subretinal and intraretinal fluid—consistent with classic choroidal change (Figure 4). Central macular thickness was 265µm. She denied systemic diseases, and all additional investigations were normal.

The patient was indicated for treatment with intravitreal application of Bevacizumab preparation (0.05cc-1.25mg/0.05mL), with three consecutive monthly applications with regular observation every month. Visual acuity improved to 1.0 one month after the first application.

The central macular thickness was reduced to 224µm, and the sub- and intraretinal fluid was largely resorbed, as detected by OCT.

The finding after three monthly applications, the visit at 5 months after treatment (2 months after the last application) showed a complete resolution of the finding, inactive CNV (Figure 5).

Observation was done every second month, and after 9 months from the last application (1 year after treatment) the condition was stable.

Visual acuity was 1.0 and control FFA showed late fluorescein staining of fibrotic CNV, with no signs of progression (Figure 6).

Figure 1.



Figure 2.



Figure 3.

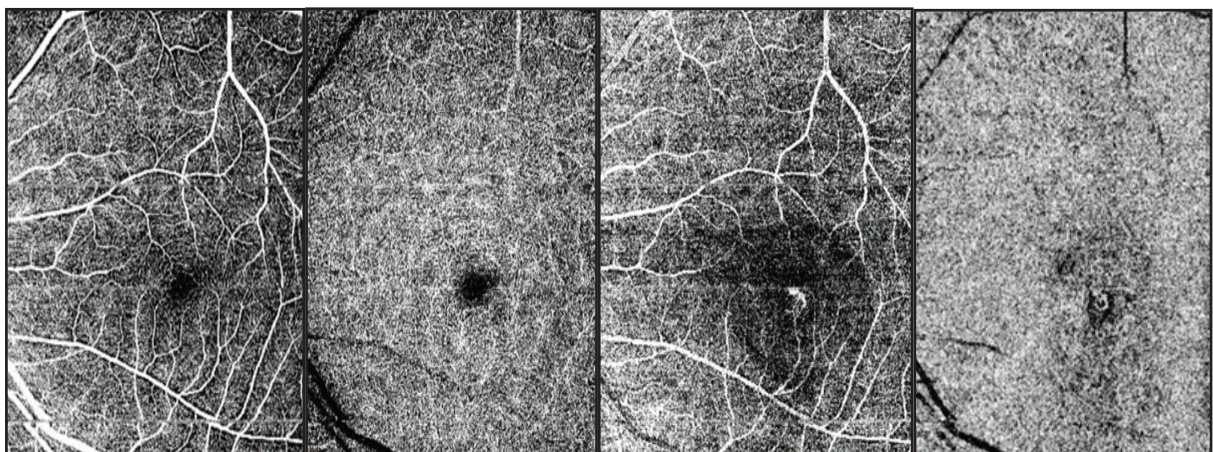


Figure 4.

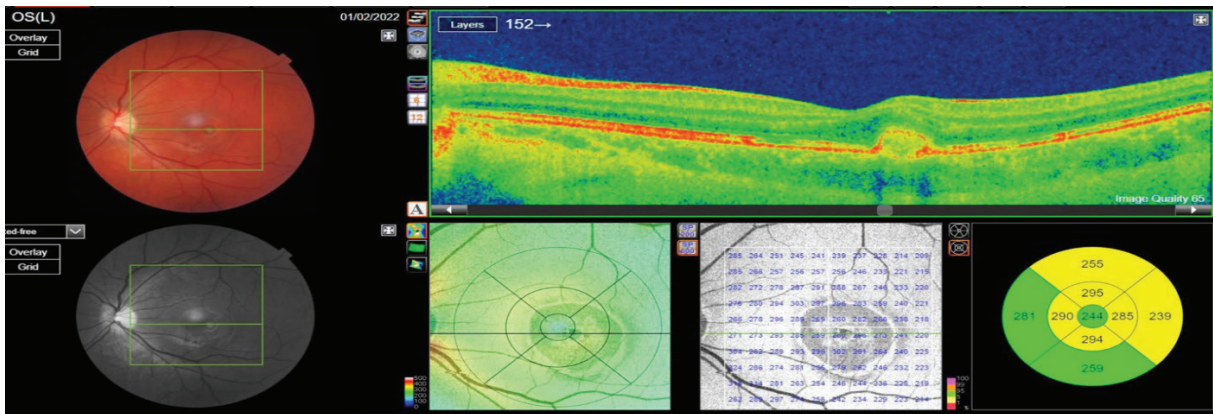
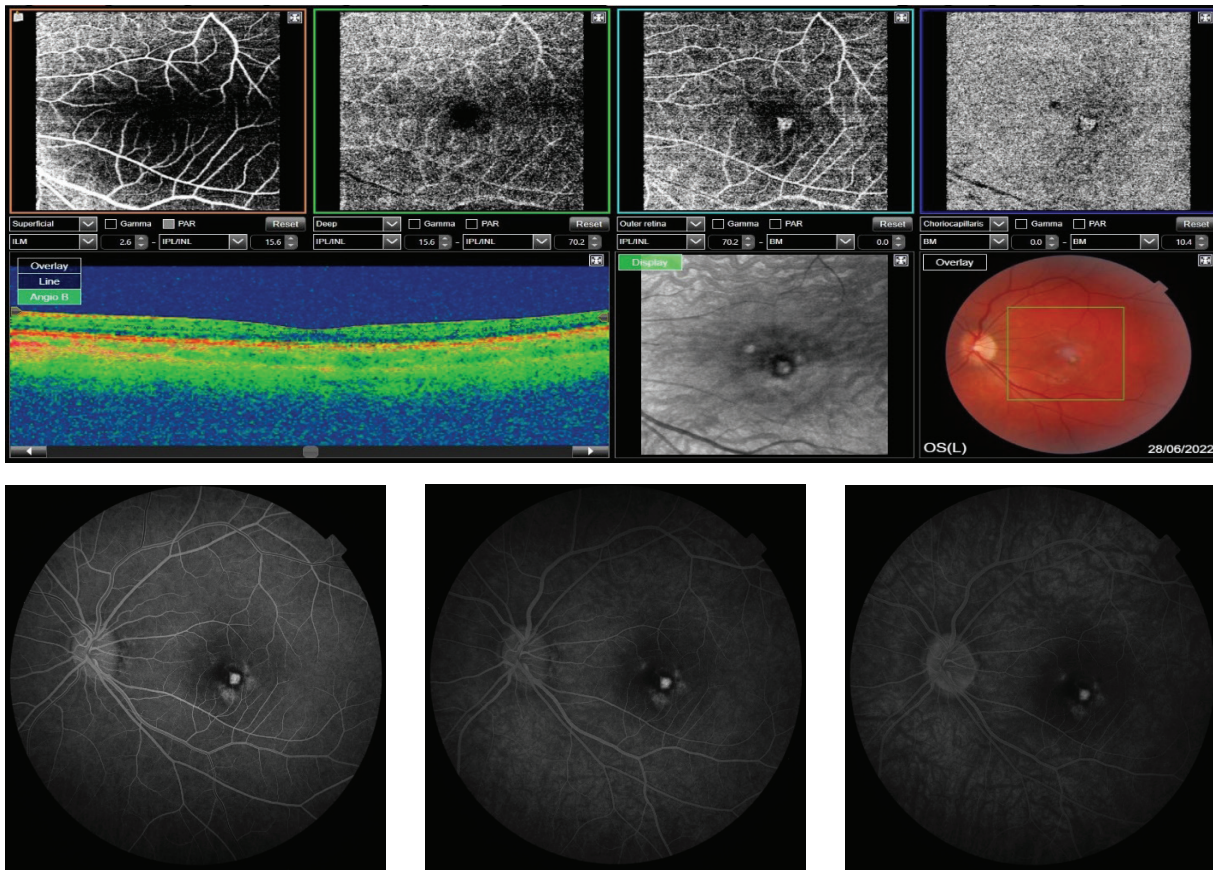


Figure 5.



Idiopathic choroidal neovascularization (iCNV) is a disorder that primarily affects younger patients. Choroidal abnormalities, such as focal choroiditis, compensation of choroidal vessels, choroidal ischemia, myopia, or impaired functional activities of circulating hematopoietic stem cells have been thought to be involved in the pathophysiology of iCNV. However, the exact pathogenesis remains unclear (3).

In their study, Yin H. et al. investigated the levels of 27 inflammatory cytokines in the aqueous humor of eyes with iCNV. Significantly higher levels of IL-2, IL-10, IL-15, IL-17, basic FGF, and GM-CSF were observed in patients with iCNV compared to controls. However, only IL-17 levels were significantly higher in patients with iCNV compared to controls, so they conclude that there may be an involvement of IL-17-related inflammatory processes in the etiology of iCNV (3).

In order to improve the iCNV treatment results, the complex molecular mechanisms involved in the pathogenesis of iCNV must be understood more completely. Although inflammatory cytokines, such as VEGF and immunoglobulin E, were found to be significantly elevated in the serum of patients with iCNV, studies of intraocular inflammatory cytokines in patients with iCNV are sparse (8).

The development and progression of CNV is associated with alterations in various pro- and anti-angiogenic factors. The collective evidence suggests that VEGF is a critical angiogenic factor for promoting ocular angiogenesis (9).

Ocular anti-VEGF therapy is highly effective for treating CNV, however, it is important to note that not all patients respond to such therapy, which suggests that VEGF-driven pathways are only part of the complex processes regulating angiogenesis, and that other molecules besides VEGF may play a crucial role in aberrant angiogenesis. Increasing evidence suggests that inflammation and the immune system may be involved in the development of CNV (9,10,11).

A lot of studies have reported promising results with anti-VEGF therapy in iCNV patients (5,6,7,12). Zhang et al. reported that the mean number of bevacizumab injections was 2 during the 12-months follow-up, and 40.0% and 70.0% of eyes had complete resolution of fluid after a single or an additional injection, respectively (6).

Lachowicz E. et al. had reported a twenty-nine-years old man with peripapillary idiopathic choroidal neovascularization treated with bevacizumab and observed during 9 months. The visual acuity improvement and rapid regression of posterior segment lesions after administration of three intravitreal injections of bevacizumab at monthly intervals (13).

Intravitreal anti-VEGF therapy on a pro re nata basis was effective for treating ICNV in the retrospective study of Wu Q et al. The study included 35 patients with iCNV from July 2012 to October 2017. The best corrected visual acuity (BCVA) and central retinal thickness (CRT) were recorded, and morphological improvement in optical coherence tomography (OCT) was assessed. Re-treatment with anti-VEGF could effectively lead to resolution of recurrent iCNV (14).

OCT is widely used to evaluate the prognosis and monitor the recurrence of iCNV because of its minimum side effects. Additionally, retinal morphological change from OCT, which represents retinal fluid, is convenient for clinicians to monitor the progression of disease (14).

While optical coherence tomography angiography is a useful imaging technique for the diagnosis and follow-up of iCNV, it is particularly useful in showing the extension of the neovascular network and response to treatment (15,16).

Conclusion

CNV which often causes severe vision loss and eventually blindness, is a common pathologic change that may occur in more than 30 ocular diseases. ICNV is a disorder that primarily affects younger patients. Anti-VEGF therapy is the first line of treatment and is associated with better visual outcomes than other treatment modalities. OCT-A was shown to be essential in diagnosing and follow-up of iCNV. Because of that, OCT-A must be part of diagnostic procedure for CNV detection.

REFERENCES

1. Cohen SY, Laroche A, Leguen Y, et al. Etiology of choroidal neovascularization in young patients. *Ophthalmology*. 1996;103(8):1241–1244.
2. Spaide, Richard F. MD. Choroidal neovascularization in younger patients. *Current Opinion in Ophthalmology* 10(3): p 177-181, June 1999.
3. Yin H, Fang X, Ma J, et al. Idiopathic Choroidal Neovascularization: Intraocular Inflammatory Cytokines and the Effect of Intravitreal Ranibizumab Treatment. *Sci Rep*. 2016 Aug 25; 6:31880.
4. Ho A. C., Yannuzzi L. A., Pisicano K. et al. The natural history of idiopathic subfoveal choroidal neovascularization. *Ophthalmology* 102, 782–789 (1995).
5. Sudhalkar A., Yogi R. & Chhablani J. Anti-Vascular Endothelial Growth Factor Therapy for Naive Idiopathic Choroidal Neovascularization: A Comparative Study. *Retina* 35, 1368–1374 (2015).
6. Zhang H., Liu Z. L., Sun P. et al. Intravitreal bevacizumab for treatment of subfoveal idiopathic choroidal neovascularization: results of a 1-year prospective trial. *Am J Ophthalmol* 153, 300–306, e301 (2012).
7. Kang H. M. & Koh H. J. Intravitreal anti-vascular endothelial growth factor therapy versus photodynamic therapy for idiopathic choroidal neovascularization. *Am J Ophthalmol* 155, 713–719, 719 e711 (2013).
8. Yang F. et al. Serum inflammatory factors in patients with idiopathic choroidal neovascularization. *Ocul Immunol Inflamm* 18, 390–394 (2010).
9. Sene A., Chin-Yee D. & Apte R. S. Seeing through VEGF: innate and adaptive immunity in pathological angiogenesis in the eye. *Trends Mol Med* 21, 43–51 (2015).
10. Coughlin B. et al. Connecting the innate and adaptive immune responses in mouse choroidal neovascularization via the anaphylatoxin C5a and gammadeltaT-cells. *Sci Rep* 6, 23794 (2016).
11. Tan X. et al. Choroidal neovascularization is inhibited via an intraocular decrease of inflammatory cells in mice lacking complement component C3. *Sci Rep* 5, 15702 (2015).
12. Carreno E. et al. Phase IIb clinical trial of ranibizumab for the treatment of uveitic and idiopathic choroidal neovascular membranes. *Br J Ophthalmol* (2015).
13. Lachowicz E, Kubasik-Kładna K, Mozolewska-Piotrowska K, et al. Idiopatyczna neowaskularyzacja podsiatkówkowa--opis przypadku [Idiopathic choroidal neovascularization--case report]. *Klin Oczna*. 2014;116(1):35-8. Polish.
14. Wu Q, Chen X, Feng K, et al. Evaluation of efficacy and recurrence for anti-vascular endothelial growth factor therapy in idiopathic choroidal neovascularization. *BMC Ophthalmol*. 2020 Mar 19;20(1):115. doi: 10.1186/s12886-020-01390-4. PMID: 32192468; PMCID: PMC7082985.
15. Preziosa C, Staurenghi G, Pellegrini M. optical coherence tomography angiography findings in a case of choroidal neovascularization secondary to unilateral retinal pigment epithelium dysgenesis treated with intravitreal bevacizumab therapy *RETIN CASES BRIEF REP*. 2021 SEP 1;15(5):598-601.
16. Pajtler Rosar A, Bochicchio S, Giani A, et al. acute idiopathic maculopathy complicated by choroidal neovas. *Retin Cases Brief Rep*. 2021 Sep 1;15(5):593-597.

CT FINDINGS IN PROGRESSIVE XANTHOGRANULOMATOUS PYELONEPHRITIS

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Abstract

Resulting from recurrent subacute or chronic urinary infections, a chronic pyelonephritis develops, which can be represented as several entities. Xanthogranulomatous (XGP) pyelonephritis is one of those entities which has characteristic radiographic features. The inflammatory process following the recurrent infections causes destructions to the parenchymal wall of the kidneys and over time it is replaced with a mass of reactive granulomatous tissue, containing lipid-laden macrophages, which surrounds the typical form of calculi – staghorn calculi. These are the pathognomonic radiological signs. CT is the modality of choice in diagnostic imaging for xanthogranulomatous pyelonephritis for two reasons – in the most of cases it demonstrates a highly specific tirade of findings that allow a confident diagnosis and offers accurate follow-up of the disease which is of great importance for the further surgical treatment.

We present the CT findings of a clinical case throughout 6 years long follow up of chronic pyelonephritis which advanced to development of XGP and a complication with purulent collection in the left kidney, which resulted in left sided nephrectomy. This article describes the role of diagnostic imaging and correlates the radiologic findings to the underlying disease process. Additionally, we emphasize the diagnostic importance of CT in treatment, follow-up and preoperative planning.

Key Words: CT, nephrectomy, pyelonephritis, xanthogranulomatous.

Introduction

Recurrent subacute or chronic urinary infections result in chronic pyelonephritis, which can be represented as several entities. One of the rare and aggressive variants is the xanthogranulomatous pyelonephritis, which has characteristic radiographic features. On pathological sections, the characteristic presence of the lipid-laden macrophages appears bright yellow in color, giving the name of this type of granulomatous pyelonephritis, which comes from the Greek word "xantho" meaning yellow. It has 2:1 female predilection and the most frequently is presented in middle-aged to elderly patients, most probably resulting from increased incidence of nephrolithiasis leading to chronic obstruction and urinary infections. In literature there has been described an increased incidence in patients with diabetes mellitus.

One of the first clinical signs is malaise, flank pain, fever and hematuria, also in the most cases pyuria and positive urinary cultures are present. The signs and symptoms are often vague and nonspecific.

The CT appearance is somewhat more specific, reflecting the variability of the pathologic changes seen in different stages of XGP. Nevertheless, it is a diagnostic modality of choice because it provides accurate follow up of the disease, which is of great importance for further management and treatment.

Clinical Case Report

We present a case of a 43-years-old woman, whose first visit to the emergency department (ER) is in the year of 2015, who complained about fever and lower back pain.

From that moment on, the patient was frequently treated in the ER and several ultrasounds were performed, and other conventional diagnostic imaging with the findings of urolithiasis, but her symptoms have been progressing.

CT urography was indicated. The findings showed the presence of bilateral pleural effusion, with greater extent on the right and consecutive atelectatic lung parenchyma, both kidneys were increased in volume, with bilaterally reduced renal parenchyma, bilateral nephrolithiasis and hydronephrosis grade III with consecutively dilated ureters.

Over the course of the next 3 years the patient underwent three ultrasonic lithotripsies on both kidneys, with placement of double JJ stents, but the nephrolithiasis and hydronephrosis progressed. On the control CT which was indicated in the year 2018, bilateral hydronephrosis grade II of the right kidney and grade III of the left kidney, with bilateral nephrolithiasis, were confirmed.

Figure 1.



Figure 2.

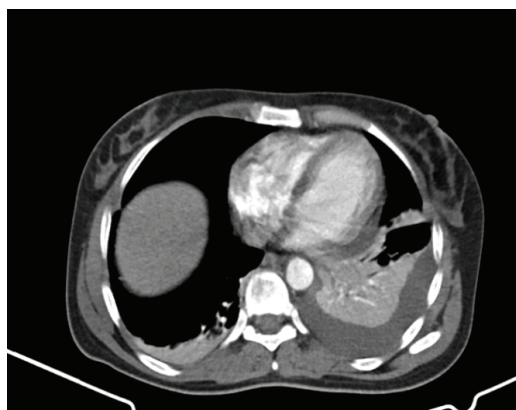


Figure 3.

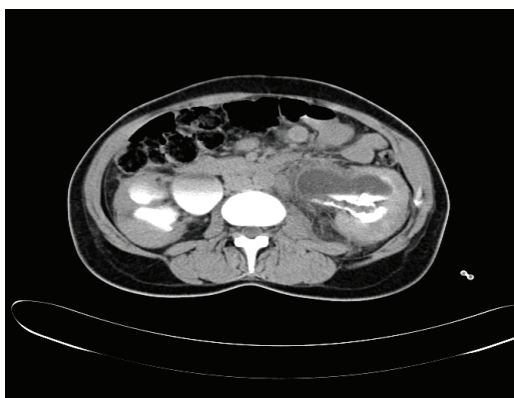


Figure 4.



- Figure 1. Contrast enhanced axial CT scan - presence of bilateral pleural effusion, with a greater extent on the left, and consecutive atelectatic lung parenchyma.*
- Figure 2. Non contrast CT axial scan - findings of voluminous enlargement of the left kidney, with nephrolithiasis, on this scan only seen in the left kidney.*
- Figure 3. contrast enhanced axial CT scan – showing bilaterally dilated calyces and dilated pelvic-urethral segment.*

Figure 4. Delayed phase axial CT scan showing hydronephrosis grade II-III in the left kidney, with delayed contrast elimination, and hydronephrosis grade II of the right kidney, as well as perirenal and perihilar fat stranding.

Because of the worsening symptomatology in 2020, a control CT was performed, and the patient was diagnosed with xanthogranulomatous pyelonephritis of the left kidney, with the distinctive findings of voluminous enlargement of both kidneys, particularly in the left kidney, dilated pyelocalyx system and ureter, flattening of the calyces and inclusions of trapped air in them, with nephrolithiasis and ureterolithiasis, with persistent hydronephrosis grade II of the right kidney and grade III- IV of the left kidney.

Figure 5



Figure 6



Figure 7

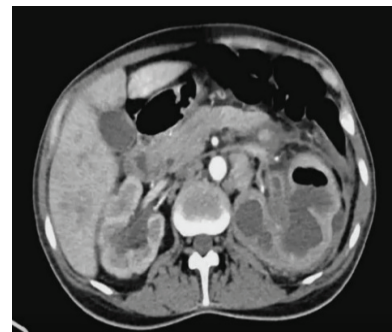


Figure 5. Non contrast CT - showing bilateral nephrolithiasis in the inferior calyces.

Figure 6. Contrast enhanced CT - axial scan showing bilateral nephrolithiasis, as well as left sided ureterolithiasis, persistence of the hydronephrosis grade II of the right kidney and grade III of the left kidney. Double JJ sonde placed on the right side can be seen on figure 6.

Collections of trapped air in the upper calyces of the left kidney.

Figure 7. Axial contrast enhanced CT (arterial phase) shows multiple low attenuation areas - dilated calyces filled with air - with the characteristic cross-sectional appearance as the bear paw sign, the changes are present in both kidneys, predominantly in the left kidney.

Figure 8

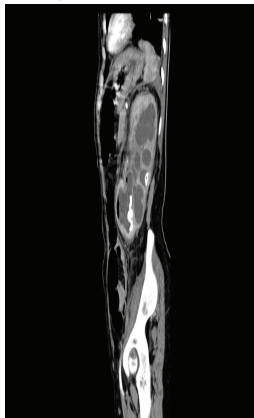


Figure 9



Figure 8. Coronal, delayed CT phase - shows edematous, voluminous, dysfunctional left kidney left kidney with slowed elimination of the contrast medium in the right kidney, as well as a dilated right ureter.

Figure 9. Sagittal plane shows, dilated pyelocalyx system, hydronephrosis grade III- IV of the left kidney, with flattening of the calyces, as well as inclusions of trapped air in them with nephrolithiasis.

After six months, in 2021, our patient on the follow-up CT was diagnosed with pyonephrosis with the involvement of the renal fascia and perirenal fat, with persisting of the fluid/gas collections in the collecting system, which suggests stage III XGP, therefore the patient was elected for nephrectomy of the left kidney. After one year our patient underwent bilateral nephrectomy.

Figure 10



Figure 11



Figure 12



Figure 10 and 11. Axial contrast enhanced CT shows double JJ sondage placed bilaterally, bilateral nephrolithiasis, as well as perirenal fat stranding, with a perirenal and perihilar inflammatory reaction suggesting hydronephrosis grade III-IV. The higher density in the renal pelvis suggests pyonephrosis, which is indication for nephrectomy.

Figure 12. Axial contrast enhanced CT scan - showing bilaterally enlarged paraaortic and pericaval lymph nodes, predominantly left sided.

Discussion

CT is the modality of choice for evaluating chronic pyelonephritis because it provides comprehensive anatomic and physiologic information that accurately characterizes both intra- and extrarenal pathologic conditions. Computed tomography is the mainstay of diagnostic imaging for xanthogranulomatous pyelonephritis. Imaging studies may demonstrate diffuse or focal form (8).

The combination of a nonfunctioning enlarged kidney, a central calculus within a contracted renal pelvis, expansion of the calices, and inflammatory changes in the perinephric fat is strongly suggestive of xanthogranulomatous pyelonephritis. Xanthogranulomatous pyelonephritis is a rare chronic destructive inflammatory process of the renal parenchyma, associated with long-term urinary tract obstruction and infection.

Almost all patients are symptomatic, and the most common symptoms are flank or abdominal pain, lower urinary tract symptoms, fever, palpable mass, gross hematuria, with laboratory findings of leukocytosis and positive urine cultures. (The most commonly isolated *E. coli*).

A clinical-radiologic-pathologic correlation study was performed in 18 (17 female) patients with xanthogranulomatous pyelonephritis (XGP) with CT scans available for analysis. Presenting signs and symptoms included pain (66%), urinary frequency (66%), dysuria (66%), nocturia (66%), palpable mass (56%), leukocytosis (50%) and fever (50%) (1).

The inflammatory process following the recurrent infections causes destructions to the parenchymal wall of the kidneys and over time it is replaced with a mass of reactive granulomatous tissue containing lipid-laden macrophages, which surrounds the typical form of calculi – staghorn calculi. These are the pathognomonic radiological signs associated with greater or lesser degree of hydronephrosis. Alongside with the above-mentioned histopathological findings, as has been mentioned in our case, the presence of the “bear paw sign” (the characteristic cross-sectional appearance of multiple low attenuation areas - dilated calyces) should be the leading signs for a radiologist to consider the diagnosis of XGP.

Xanthogranulomatous pyelonephritis can be classified as: diffuse (diffuse involvement of the kidney), segmental involvement of the kidneys, focal (involvements within the cortex of the kidney).

Another classification is through staging, based on the level of extension to the perirenal tissues and adjacent tissues:

Stage I - the disease is localized only in renal parenchyma.

Stage II – the disease extends to the perirenal fat.

Stage III – extension of the disease to the perirenal and pararenal spaces as well as the retroperitoneum.

The most common complication is pyonephrosis, as described in our case which is an indication for nephrectomy. The described case also describes the importance and value of CT in the follow up of this progressive condition.

CT is preferred over conventional radiography and ultrasonography (US) as it provides highly specific findings and accurate assessment of the extrarenal extent of disease, which is essential for surgical planning (2).

This type of chronic granulomatous infection over time eventually results in kidney failure, leading to the loss of one or both kidneys.

There are two reasons why CT is the modality of choice in diagnostic imaging for xanthogranulomatous pyelonephritis:

1. *The* most of the cases demonstrate a highly specific tirade of findings that allow a confident diagnosis.
2. It offers accurate follow up of the disease which is of great importance for further surgical treatment.

Conclusion

The distinctive CT findings which are equivalent to the pathological findings, had made a step ahead for CT to become the leading diagnostic method of choice for making the preoperative diagnosis of XGP, because of its ability to provide extensive anatomic and functional assessment, and in the most cases it allows proper management and further surgical planning.

REFERENCES

1. Goldman SM, Hartman DS, Fishman EK, et al. SS. CT of xanthogranulomatous pyelonephritis: radiologic-pathologic correlation. *AJR Am J Roentgenol.* 1984;142(5):963-969. doi:10.2214/ajr.142.5.963.
2. Rajesh A, Jakanani G, Mayer N, et al. Computed tomography findings in xanthogranulomatous pyelonephritis. *J Clin Imaging Sci.* 2011;1:45. doi:10.4103/2156-7514.84323.
3. Loffroy R, Guiu B, Watfa J, et al. Xanthogranulomatous pyelonephritis in adults: clinical and radiological findings in diffuse and focal forms. *Clin Radiol.* 2007;62(9):884-890. doi:10.1016/j.crad.2007.04.008.
4. Zorzos I, Moutzouris V, Korakianitis G, et al. Analysis of 39 cases of xanthogranulomatous pyelonephritis with emphasis on CT findings. *Scand J Urol Nephrol.* 2003;37(4):342-347. doi:10.1080/00365590310004752.
5. Tonolini M, Bonzini M. Xanthogranulomatous pyelonephritis: when CT findings suggest the diagnosis. *ISSN1563-4086.doi:10.1594/EURORAD/CASE.14129.*
6. Li L, Parwani AV. Xanthogranulomatous pyelonephritis. *Arch Pathol Lab Med.* 2011 May;135(5):671-4. doi: 10.5858/2009-0769-RSR.1. PMID: 21526966.
7. Lee JH, Kim SS, Kim DS. Xanthogranulomatous Pyelonephritis: “Bear’s Paw Sign”. *J Belg Soc Radiol.* 2019 May 13;103(1):31. doi: 10.5334/jbsr.1807. PMID: 31139769; PMCID: PMC6524550.

7TH SCHOOL OF REGIONAL ANESTHESIA

Respected Editor,

On March 11, 2023, in Leskovac, Republic of Serbia, the 7th School of Regional Anesthesia took part. The school was organized by the Serbian Medical Association Society (SMAS) in cooperation with the Anesthesia and Reanimation Department at the Leskovac General City Hospital. This experts' meeting was supported by the Anesthesiology, Intensive Therapy and Pain Therapy Section of SMAS, the Serbian Active for Regional Anesthesia, the Obstetric Anesthesia Active and the Kybele Foundation for Safe Childbirth Everywhere in the World.

The opening speech was given by Dr. Radomir Mitic, anesthesiologist, president of the Serbian Active for Regional Anesthesia of SMAS and Dr. Ivan Velichkovic, an anesthesiologist who works in New York, United States of America. In the educational part participated numerous lecturers from the Republic of Serbia, Montenegro, Bosnia and Herzegovina, as well as from our country. Our lecturers Prof. Dr. Atanas Sivevski and Ass. Prof. Dr. Dafina Karadzova, from the University Clinic for Gynecology and Obstetrics in Skopje, successfully presented themselves with their lectures in front of the auditorium.

The workshop was divided into two parts. The first part included lectures on basic knowledge of Point of Care Ultrasound (POCUS). Hereby the Focused Assessment Transthoracic Echocardiography – FATE, Focus Assessment with Sonography in Trauma –FAST and Lung Ultrasound –LUS protocols were presented. In this part Prof. Dr. Atanas Sivevski gave his speech lecture “Parasternal transverse and longitudinal view of the heart”, while Ass. Prof. Dr Dafina Karadjova presented a lecture on “Apical view of the heart”.

In the second part of the workshop, peripheral nerve blocks were presented. There was a special review of the most important peripheral nerve blocks of the hand, foot, as well as the most important interfacial blocks.

The practical part of this professional meeting must also be noted. Namely, after acquiring basic knowledge of the above topics, the participants had the opportunity to practically apply their knowledge of POCUS.

We hope that this positive trend of application of appropriate and fast diagnostic methods in Intensive Care Units will continue. This simplification of protocols for rapid diagnosis of critically ill patients will greatly affect the course of treatment and therapy of these patients. It will affect the survival but also the improvement of the further quality of life for the patients in Intensive Care Units.

We look forward to the next professional meetings. The exchange of acquired knowledge, as well as mastering the new techniques and work protocols, will have an impact on even greater development of the anesthesiology, resuscitation and intensive care treatment in the Republic of North Macedonia.

Author:

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INDICATIONS FOR 18F-FDG PET/CT AS A PART OF THE FIRST MACEDONIAN GUIDELINES FOR B AND T LYMPHOPROLIFERATIVE DISORDERS

Dear Editor,

With this letter I would like to inform you and your readers that on the 28th of December 2022 in the hotel “DoubleTree by Hilton” in Skopje, organized by the Macedonian Hematology Association, the first Macedonian Guidelines for diagnosis and treatment of B and T lymphoproliferative disorders were officially promoted. Our Institute for Positron-Emission Tomography in Skopje took part in its implementation, in particular with indications for 18F-FDG PET/CT scan in patients with different types of lymphoproliferative disorders. These indications were added in a special chapter of these Guidelines. They were written according to the Guidelines from European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN). These are the first Macedonian Guidelines, in which indications for 18F-FDG PET/CT are clearly described. We hope that in the future, other Guidelines in Macedonian language will be published about indications for 18-FDG PET/CT, especially in other hemato-oncological diseases, so they can help the current and future doctors in taking clinical decisions and in proper management of the patients with malignancies.

Thank you very much.

Yours sincerely,

Slavko Tasevski, MD – Nuclear Medicine Physician

PHI University Institute for Positron-Emission Tomography – Skopje.

PERSONALITY DISORDERS IN THE NEW ICD 11

Dear Editor,

I want to inform you about a research that is being carried out in our hospital and which is related to the new International Classification of Diseases 11th (ICD 11). ICD 11, which has been in use in some countries since January 2022, brings innovations in both the diseases coding system and the categorization of diseases. The biggest changes are in the chapter of mental disorders. These changes include re-categorization of some diseases, exclusion of certain and inclusion of other disorders. The diagnostic approach to certain types of mental disorders is also changing from categorical to dimensional. Such changes are in the Schizophrenia section, where subtypes of schizophrenia are excluded, and dimensioning by categories of symptoms is included, in the Pervasive Developmental Disorders section, which are merged into one category - Autism Spectrum Disorders, as well as in the Personality Disorders section. In the section of personality disorders, one category is introduced that is graded according to the severity of the dysfunctionality, which can be specified according to the main characteristics. Also, a new category of Personality Difficulties is introduced, which can be understood as part of the continuum between healthy and pathological personality organization and functioning.

In the light of these changes and the gradual transition to the new Classification, new diagnostic questionnaires and scales are being constructed, new research is being done on the usability and validity of the new classification, as well as on deepening of knowledge according to the diagnostic changes.

This kind of research on the prevalence and degree of severity of personality disorder was carried out among users of methadone substitution therapy at the Addiction Center at General Hospital in Kumanovo. The entire research with the results has been submitted for presentation at the upcoming 23rd World Psychiatric Congress in Vienna from September 28th to October 1st this year.

Adriana Bogdanovska Toskic, MD, Specialist in Psychiatry

General Hospital Kumanovo

GUIDELINES FOR AUTHORS

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

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

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

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

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

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5. Electronic reference

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

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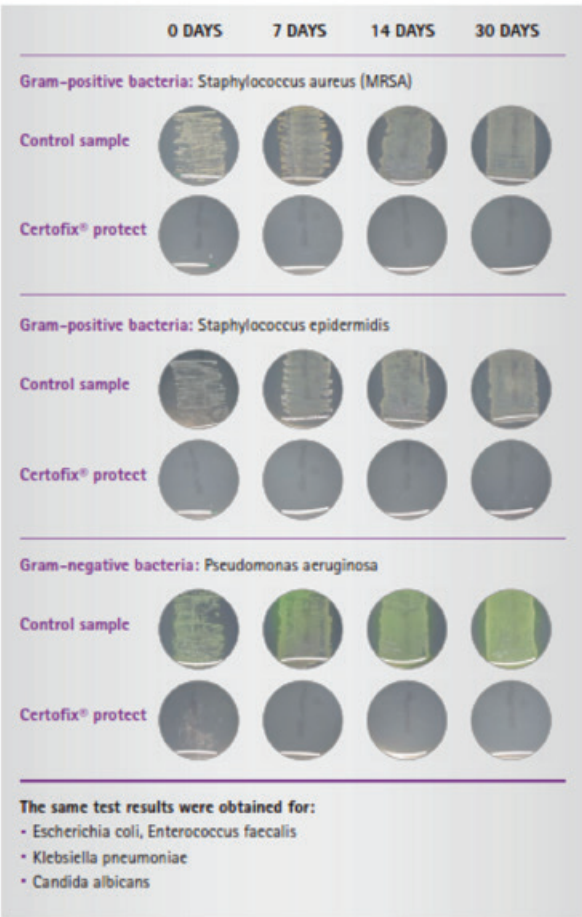
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