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I.V. Paracetamol

БЕЗБЕДНА АНАЛГЕЗИЈА

менаџирање на болка кога сте загрижени за безбедноста

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

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

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

Резултат:

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

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

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

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

Табела3: *Споредба на ПОПГ помеѓу двете групи*

ПОГП	
I Група П	II Група НС
0	4

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

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

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- **Намалување на несаканите ефекти поврзани со монотерапија на NSAID и опоидни лекови**
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WHEN EARLY RECOVERY REALLY MATTERS

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CONTENT

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PATIENT'S SAFETY IN SURGERY: REACTIVE OR PROACTIVE?

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Safety as it is applied to healthcare today emerged in the late-90 s, with the publication of two seminal reports; *To err is human: Building a Safer Healthcare System*, by the US Institute of Medicine (IoM) (Institute of Medicine 1999) and *An organization with a Memory* by the UK Department of Health (Department of Health 2000) (1,2). The IoM report caught the public, professional and political attention when it reported that more people die from medical errors than from motor vehicle accidents (1).

In the UK following the publication of *An Organization with a Memory*, significant progress has certainly been made in some areas of patient's safety. For example, the field of human factors and ergonomics, together with quality improvement have gained awareness and traction in healthcare and become integrated into patients' care (3,4). There is a wider understanding of a system approach to safety as advocated by safety experts such as James Reason (5). This UK report resulted in the setting up of the National Patient Safety Agency and the National Reporting and Learning System. There have also been constant inquires, reviews and reports, such as that carried out by Don Berwick and his advisors which led to the publication *'A Promise to Learn, it was a Commitment to Act: Improving the Safety of Patients in England'* which led to a number of initiatives, including the Patient Safety Collaborative, the Q initiative and a five-years patient safety culture campaign called *Sign up to Safety* (Woodward 2017) (6,7).

However, in parallel with all this activity, safety experts from across the world were questioning whether the approach to safety was actually reducing harm and improving safety (Woodward 2019a, 2019b) (8,9).

The modern field of patients' safety emerged with ideas adopted from industries such as manufacturing and the airline industry.

Resilience engineers such as Erik Hollnagel (2014), safety experts such as Dekker (2014)[5] and Vincent and Amalberti (2016) as well as clinicians such as Robert Wears and Kathleen Sutcliffe, were asking 'why are we still not safe' (2019) (11,12,13).

Hollnagel coins safety as Safety I and Safety II (11). Dekker uses the term 'Safety Differently'(5,14). The mistake that people are making is in thinking that these are different constructs. They are all about safety – but they have a different lens through which they look at safety.

Safety I is mostly reactive and primarily focuses on failure and trying to prevent things from going wrong (11). It is assurance and rule based, using tools from other high-risk industries such as incident reporting and root cause analysis investigations, which are fit for linear systems of production. It is a bimodal model in which either work is considered as done correctly leading to an acceptable outcome, or work is considered done incorrectly leading to an unacceptable outcome. The language is about error and mistakes and harm which perpetuates the era of blame and the fear of speaking up (8). Erik Hollnagel recommends not using incident reports at all, but instead, focusing on studying normal work via interviews or 'exnovation'.

Safety-II acknowledges that systems are complex, and there are alterations in individual or collective behaviors in response to complex dynamic events. This is in contrast with simplicity, in which a standardized approach to a task or problem yields an expected outcome, and complicatedness, in which a larger complicated task can reasonably be broken down into a series of simple tasks. Healthcare in general is seen as a complex adaptive system (11). In complex systems, the relationships between cause and effect are not easily observed. The long-term effects of a causal event may be very different from the short-term effects. This makes traditional approaches to safety unhelpful, and a Safety-II approach is necessary. In order to achieve changes in a complex adaptive system, distributive, collaborative leadership must be encouraged and individuals must be trusted with a degree of autonomy.

Safety II centers around the fact that we can learn as much from how the system, organization and people are functioning just as much as how they fail (11). To study the failure in the light of the many times that work goes well (8,9). It is about measuring the functioning system rather than solely measuring when things go wrong in order to learn. Safety II is proactive and seeks to learn from our day-to-day work in order to increase the likelihood of things going well in the future or to prevent things failing in the first instance. Both safety I and II acknowledge the need to capture incidents related to harm, but in safety II the aim is to accept that cause and effect are not easily observed, that we may never find the causal event. Safety-II is a change in mind-set, to a more proactive approach (11).

At the heart of safety II is the understanding that healthcare is a complex adaptive system (13). A complex adaptive system is a *dynamic network of 'agents' acting in parallel, constantly reacting to what the other 'agents' are doing, which in turn influences behavior and the network as a whole*. In this kind of system, staff adapt and adjust their decisions and actions all of the time depending upon the circumstances that they face in order to maintain safety and to ensure things go okay. It is dynamic because conditions are always changing, and no two moments are identical. There is natural variability in performance which sometimes leads to success and sometimes leads to harm (10).

There is concern that Safety II is yet another new initiative, but in reality, it is a change in mindset. There is a level of investment in time and energy to understand Safety II and this is why it is being incorporated in the national patient safety strategy and new national patient

safety syllabus. Safety II's holistic approach to both safety and effectiveness is intuitive, and is backed up by well-established theories. It helps to provide a more motivational attitude and an appreciative approach to safety with staff thinking about days that have gone well, or indeed days that have just gone 'fine', to try to see which of their actions might have contributed to that (7-9).

It is hoped that this way of thinking will be supported at an organizational level and on those that regulate and commission, as well as those included in the future medical and nursing graduates. Safety science is as important as medical science and the potential for modern safety science, including the combination of safety I and safety II, to reduce patient harm is perhaps more potent in surgery than any other field.

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SEASONAL VARIATIONS OF *ACINETOBACTER SPP.* STRAINS IN SURGICAL INTENSIVE UNIT AND THEIR GENOTYPIC CONFIRMATION

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SUMMARY

Nosocomial infections in intensive care units are a major public health problem because they have the most severe course and outcome. The most often, intra-hospital infections in intensive care centers are associated to the use of medical devices. Colonization of medical devices with microorganisms is a prerequisite for nosocomial infection. Gram-negative bacteria: *Acinetobacter* spp., *Pseudomonas aeruginosa* and bacteria of the family *Enterobacteriaceae* are the most common colonizers. The incidence of *Acinetobacter* spp., isolated from intubated surgical patients from the Clinic for Anesthesiology, Resuscitation and Intensive Care, Skopje, has increased rapidly in the last two decades, highlighting this microorganism as the most important intra-hospital pathogen. *Acinetobacter* strains are bacteria with ability to become endemic and maintain in the hospital environment. Also, seasonal variations are the best observed in this genus. Hence, in this study we will investigate their existence in the hospital environment through colonization of endotracheal tubes and nasal cannulas and detect certain genotype. The research will determine their seasonality and the preventive measures that would result from it.

Key Words: Acinetobacter spp., intensive care unit, intra-hospital infection, seasonal variation.

Introduction

Nosocomial infections and antibiotics' resistance are major public health problems in developed and developing countries. To define an infection as intra-hospital infection, the patient should be admitted to a health facility for a health reason other than the infection being examined. Nosocomial infections become clinically evident during hospitalization (48 to 72 hours after admission) (1). Nosocomial infections are the most common in intensive care units and have the most severe course and outcome compared to all other infections. Mortality in intensive care units is four times higher than in other wards due to immunocompromised patients, invasive procedures and medical devices (2). At least half of all intra-hospital infections in intensive care units are related to the use of medical devices. Medical device colonization with microorganisms is a precondition for intra-hospital infection (3). Gram-negative bacteria: *Acinetobacter* spp., *Pseudomonas aeruginosa*, bacteria of the *Enterobacteriaceae* family, and Gram-positive: MRSA and *Enterococcus* strains are the most common colonizers (4). The incidence of *Acinetobacter* spp., isolated from intubated surgical patients from the Clinic of Anesthesiology, Resuscitation and Intensive Care (CARIC), has been 29-40% in the last two decades, with a tendency to increase its prevalence, highlighting this microorganism as the most important nosocomial pathogen. Seasonal variations are well described in the literature via *Acinetobacter* strains (5). The aim of the study was to specify bacterial colonization with *Acinetobacter* spp. strains of endotracheal tubes and nasal cannulas in CARIC patients, to detect their seasonal specificity and to determinate medical prevention. Also, the presence of a certain genotype of *Acinetobacter* spp. was observed.

Material and Methods

This research was a retrospective, analytical cross-sectional study, for a period of eight years (2010 – 2017). The study processed routinely obtained materials from endotracheal tubes and nasal cannulas of CARIC patients sent for microbiological analysis to the Institute of Microbiology and Parasitology at the Faculty of medicine, "Ss. Cyril and Methodius" University in Skopje. The laboratory data was obtained by a computer search method through the laboratory software for daily routine work at the Institute. The *Acinetobacter* isolation rate was compared by two climatic variables: average humidity and average air temperature. Official values for climate parameters were obtained from the Hydro-meteorological Service of Republic of North Macedonia. The presence of a certain genotype of *Acinetobacter* was determined by a molecular method of genotyping: rep-PCR (repetitive polymerase chain reaction), performed with the DiversiLab® system.

Results and Discussion

The seven most common bacterial pathogens in the whole sample of positive isolates for the eight-year period were: in the first place the non-fermentative multidrug-resistant bacteria: *Acinetobacter* spp. and *Pseudomonas aeruginosa*, followed by *Klebsiella* spp., MRSA; Coagulase negative *Staphylococcus* – Methicillin resistant; *Enterococcus* spp. and *Enterobacter* spp. The

literature data is consistent with the results obtained, as they highlight these pathogens as the most common colonizers and causative agents of infections (6). As expected, the most commonly isolated were *Acinetobacter* spp. strains-36.96% (7). In the whole sample of positive isolates, for the period of interest (from 2010 to 2017), the presence of *Acinetobacter* spp. was the largest in 2017 – 46.0%. The lowest prevalence of *Acinetobacter* spp. in the whole sample of positive isolates (tube and cannula) was recorded in 2010 – 32.2%. These results are very important because the line diagram of the variations as well as the development tendency (trend) of the presence of Acinetobacter in the whole sample of positive isolates from CARIC indicated a growing tendency of positive isolates of *Acinetobacter* spp. (8). For the period from 1997 to 2007 in CARIC, *Staphylococcus aureus*, especially MRSA strains, had an isolation rate of over 80%. In 2007 the isolation of MRSA was halved and replaced by the presence of Acinetobacter spp. (9). For the entire study period, *Acinetobacter* was recorded in all positive monthly isolates of the whole sample (10). The epidemiology of these bacteria allows them to become endemic in hospital systems and creating reservoirs in the environment (11). Distribution of *Acinetobacter* spp. strains on a monthly basis in the entire sample of positive isolates, showed the highest prevalence in 2013 (75% – January), followed by 2015 (66.67% – July) and 2011 (64% – December and 61.9% – June). It is interesting that in one of our previous research studies in CARIC (period from 2010 to 2012) the isolation rate of *Acinetobacter* spp. was the highest in 2012 in December – 65% (60% in May, June and July) (12). Highest values of the seasonal index, according to the values of the seasonal index above 100% (above the monthly average) for *Acinetobacter* spp. were seen in November – 171.67% and December – 118.33%, followed by February – 113.33%, March – 110% and June – 101.67%. The ability for long-term maintenance in conditions of high humidity, as well as in a dry environment gives it great importance as a nosocomial pathogen (13, 14). The correlation analysis (Spearman Rank Order Correlations) showed that the increase in humidity slightly increases the presence of *Acinetobacter* spp. (15-18). Molecular testing of Acinetobacter spp. with the automated molecular platform (DiversiLab® system) proved the existence of two different clones of Acinetobacter in CARIC. This result proved its endemicity in the hospital environment (19-22).

Conclusions

The findings of the research indicate that the detection of *Acinetobacter* spp. strains can be used to prevent, diagnose, predict empirical therapy and reduce nosocomial infections. Determining the seasonal variations in the hospital environment will provide stronger global and seasonally specific hospital precautions and preventive measures in the critical seasons, which will improve patients' and health workers' health, will reduce hospital days and will reduce treatment costs.

Declaration of Interest

None declared.

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SOME FEATURES OF THE PERSONS INCLUDED IN THE NATIONAL COLON CANCER SCREENING PROGRAM IN NORTH MACEDONIA

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ABSTRACT

Introduction: According the World Health Organization, colorectal cancer (CRC) is the third leading cause of death from malignant diseases in men and the fourth in women, responsible for 10% of deaths from malignant diseases in developed countries. EU members are taking joint action to implement national programs for colon cancer screening, with an organized population-based approach and adequate quality of service in all levels. In the Republic of North Macedonia, CRC is one of the most common malignancies (12% of all malignancies) occurring with an incidence of 15-30 new cases per 100,000 inhabitants annually.

Objective: The paper aimed to point out some demographic characteristics of the population covered by the national screening for colorectal cancer in North Macedonia in 2014 and to present the initial results of the screening in the period 2012-2018.

Material and Methods: The research was retrospective cross-sectional study that processed the screening for colorectal cancer at the national level, in the period from January 1 to December 31, 2014. The selection of 2014 as the year of choice for analysis, was made in accordance to the intensity of the CRC screening campaign that took place during this year.

Results: In the analyzed period of 2014, the national screening for CRC covered total of 2,160 respondents. In terms of gender 987 (45.7%) males vs. 1,166 (54.0%) females with a gender ratio of 0.85:1, which is a statistically significant difference. The mean age of the participants was 60.1±10.7 years with a minimum age of 24 and a maximum age of 87 years. 50% of respondents within the sample were older than 61 years. The percentage difference between the genders among the nationalities, for $p < 0.05$, was statistically significant between Macedonians and Albanians (Difference test: 6.6% [(3.4-9.9) CI 95%]; x^2=16.09; df=1 p<.001 vs. Difference test: 25.6% [(16.1-34.5) CI 95%]; x^2= 27.01; df=1 p<.001) having significantly more female participants than male ones.

The most of the respondents were from Skopje 614 (28.4%), followed by Ohrid 568 (26.3%), Struga 309 (14.3%) and Kochani 232 (10.7%). In the whole period of observation (2012-2018), a total of 25,499 FOB tests were performed in the country, out of which 10,003 (39%) were positive, and CRC was confirmed in 221 among them (2.2% out of positives).

Discussion: According to the world experience, the use of an occult blood test in the feces as an initial test in early detection of colon cancer leads to a reduction in the mortality rate between 18% and 33%. We also compared the participation rates in the developed countries and the reasons for participation or non-participation in the screening programs.

Conclusion: To achieve the potential benefit of CRC screening, there must be optimal quality at every step of the implementation process. Screening must include information, identification and personal invitation of the targeted population, proven performance of the screening test and, if necessary, treatment, supervision and follow-up care. The right to participate in screening for CRC remains inviolable to any individual regardless of gender, place of residence, access to health care, etc.

Key Words: *colon cancer, evaluation, FOB test, screening.*

Introduction

According to the data from the World Health Organization, colorectal cancer (CRC) is the third leading cause of death from malignant disease in men, and the fourth in women, responsible for 10% of deaths from malignant disease in developed countries (1). Considering the fact that in more than 90% of the patients, CRC develops as a result of pre-existing benign adenomatous polyps, the removal of which prevents the development of the cancer, as well as the fact that early detection of the disease leads to 5 years of survival in more than 90% of the patients, there is a need for establishing a preventive screening program as a prevention of this disease (2).

Colorectal cancer is particularly suitable for early detection. This type of cancer is not diagnosed and does not give symptoms in preclinical practice. It progresses from localized (stage I) to metastatic (stage IV) cancer, once it causes symptoms and is diagnosed. In the developed countries, approximately 40-50% of the population have one or more adenomas in their lifetime, the majority of which do not progress to colon cancer (3, 4). The average time for adenoma to develop into colorectal cancer is not observed, but it takes about 10 years to assess the condition (5). This long latent phase, offers an excellent window and opportunity for early detection of this disease. When detected in the adenomatous phase, removal of the adenoma can prevent transformation into colorectal cancer. When detected at an early stage, the prognosis is even better than at later stages. Several types of screening tests are available for CRC screening, including immunochemical FOB tests (Fecal Occult Blood Test).

Most of the knowledge about the implementation of cancer screening programs has been obtained through screening networks established by the European Union and the Program "Europe beating cancer plan" (6). EU networks show that the overall results and quality of the screening, depend on the effectiveness of each step of the screening process. In order to reach the potential benefits of cancer screening, quality must be optimal at every step of the process. At the same time, it must include information, identification and personal invitation of the target population, proven effectiveness of the screening test and, if necessary, treatment, observation and consecutive care. Screening is applied to mostly healthy people. Advanced quality assurance is also necessary to maintain a proper balance between the benefits and disadvantages, associated to the large number of people eligible to participate in the screening program. Achieving and maintaining high quality at every step of the screening process requires integration, basic access to the health services, and equal access to information. This approach is essential in terms of adapting the screening to its acceptance by those sections of the population that would benefit in terms of proper monitoring, evaluation and subsequent performance improvement (7).

At the end of 2007, five EU member-states (Finland, France, Italy, Poland and the United Kingdom), established a national population screening. Some of them (Austria, Bulgaria, Czech Republic, Germany, Greece, Latvia, Slovakia) have established a national CRC screening program. Another 5 countries have developed a pilot screening program for CRC (Hungary, Cyprus, Portugal, Romania and Slovenia). Out of these seventeen countries, only ten have accepted the FOB test, 6 of them use both, the FOB test and endoscopy, and one uses colonoscopy. Ten of them have developed or upgraded the screening program for CRC (Czech Republic, France, Ireland, Lithuania, Portugal, Slovakia, Slovenia, Spain, Sweden and United Kingdom). Denmark and the Netherlands are in the process of implementing the CRC screening program (8).

In the Republic of North Macedonia, CRC is one of the most common malignant diseases (12% of all malignancies), which occurs with an incidence of 15-30 new cases per 100,000 inhabitants per year (incidences worldwide are shown in Table 3).

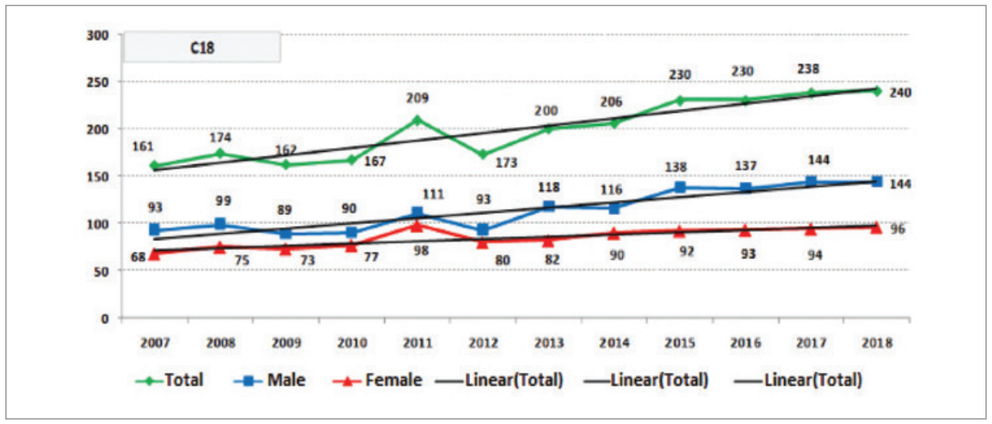
According to the data from the State Statistical Office, the number of deaths in which CRC was the cause, but also the mortality rate (per 100,000 inhabitants) is slightly increasing in the last 12 years (Table 1, Graph 1, Table 2, Graph 2)

Table 1. *Number of CRC deaths in R.N. Macedonia (2007-2018)*

ICD-10 code		Year											
		2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
C18	**Total**	161	174	162	167	209	173	200	206	230	230	238	240
	Male	93	99	89	90	111	93	118	116	138	137	144	144
	Female	68	75	73	77	98	80	82	90	92	93	94	96
C19-C21	**Total**	224	204	238	215	201	210	218	192	226	207	202	195
	Male	128	128	137	129	121	127	117	102	126	130	122	111
	Female	96	76	101	86	80	83	101	90	100	77	80	84

Source: State Statistical Office 2018

Graph 1. *CRC mortality (C18) in R.N. Macedonia by years (2007-2018)*



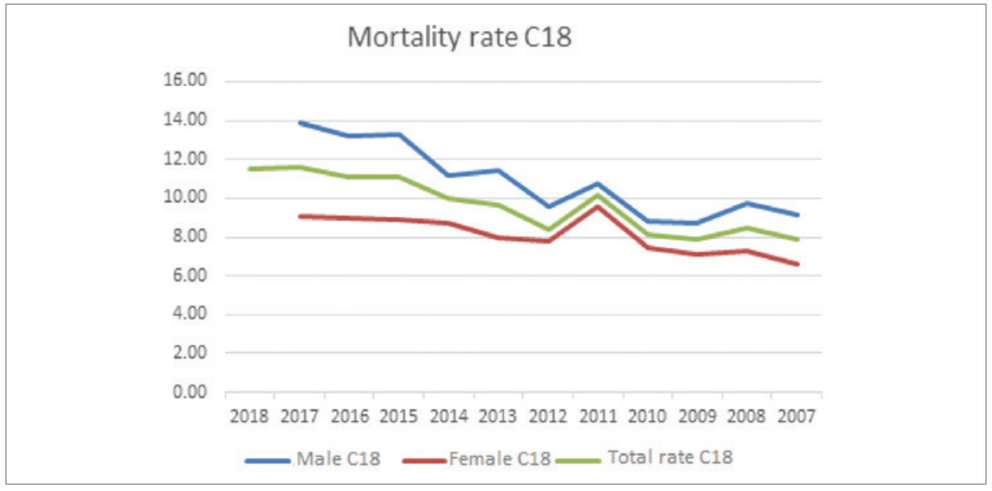
Source: State Statistical Office, 2018

Table 2. *CRC mortality rate in R.N. Macedonia for the period 2007-2018*

Year	2018	2017	2016	2015	2014	2013	2012	2011	2010	2009	2008	2007
Male		13.9	13.2	13.3	11.2	11.4	9.6	10.8	8.8	8.7	9.7	9.1
Female		9.1	9.0	8.9	8.7	8.0	7.8	9.5	7.5	7.1	7.3	6.6
Total rate	11.6	11.6	11.1	11.1	10.0	9.7	8.4	10.2	8.1	7.9	8.5	7.9

Source: State Statistical Office, 2018

Graph 2. *Trend of the CRC mortality rate (ICD-10 code C18) in R.N. Macedonia, by gender distribution*



Source: State Statistical Office, 2018

However, there are large differences in mortality between the regions. In the most countries

in Western and Northern Europe, the decreasing was generally noticed more in people under 65 years of age (9). But there was some heterogeneity between these countries, as the decreasing tends to be similar or more important in older people in Germany, Switzerland, Netherland, France and Finland. In Central and Eastern European countries, people aged 80 or older have a significant increase in mortality compared to their younger counterparts. In 27 member states of the European Union in the period between 2007 and 2011, 6.5% of all people who died of colorectal cancer were under the age of 55. In the United States in the period between 1989 and 2011, mortality fell by 39.8% for men and 38.8% for women, with the largest mortality decreasing for those aged 65 or older (10).

Among the EU member states, the rate of the total number of deaths attributed to colorectal cancer reached 4.2% in Croatia, while it is approximately half of this rate in Cyprus (2.1%), below 2.5% also registered in Lithuania, Bulgaria, Latvia, Finland and Greece; an even smaller rate is observed in Turkey (1.7% of all deaths). For almost all member states, the rate of deaths from colorectal cancer was higher in men than in women. In the Republic of North Macedonia, the specific mortality rate in 2016 was 13.2 for males, 9.0 for females, or a total of 11.1 (Table 2). These values indicate that we have higher mortality rate compared to the European. There is also a difference between men and women and their mortality rate, respectively in men is higher.

In 2016, the EU-28 standardized mortality rate for colorectal cancer was 30.4 per 100,000 inhabitants, which was just over half of the registered lung cancer rate. Gender analysis shows some gender benefits in standardized colorectal cancer mortality rates: the EU-28 rate for men was 74% higher than for women; however, but still this rate was significantly lower than the rate recorded for lung cancer.

As it is typical for cancer, the standardized mortality rate for colorectal cancer in people aged 65 and over was many times higher comparing to the younger people. In all EU member states, standardized colorectal cancer mortality rates were higher in men than in women. In terms of percentage, the closest rates were in Malta (where the rate for men was 4.2 points higher than the one for women), while in Sweden the rate for men was higher by 8.2 points. In opposite, in Slovakia, Croatia and Hungary the rates for men were at least 40.0 points higher than those for women (11).

In regard to the countries' profile, much lower rate is reported in the less developed countries compared to countries with a higher Human Development Index (HDI) (Table 3).

Table 3. CRC *Standardized rates worldwide, in countries with high and low Human Development Index*

Table 3. *Age-standardized rate of colon cancer among the countries in the world*

Age-standardized rate per 100,000			
Colon cancer	World (globally)	Very high HDI countries	Low HDI countries
Male	11.5	18.9	3.5
Female	13.1	22.1	3.7

Source: Bray F. et al. A. Global Cancer Statistics 2018: (12)

Since 2008, in the Republic of North Macedonia there is a national consensus for prevention, diagnosis, therapy and monitoring of the patients with colorectal cancer. In the period of six months in 2012 (July – December), the first pilot screening study for CRC in a population of 50-74 years was conducted. The results indicated that, by applying the FOB test, there is a possibility for early diagnosis of this type of cancer. The first organized implementation of CRC screening in the country started in 2012, but in 2014 it had extended the scope fulfilling the criteria for a real screening program.

Objective

The aim of the manuscript is to point out some characteristics of the population covered by the national screening for colorectal cancer in the Republic of North Macedonia and to present the initial results of the screening in the period 2012-2018.

Material and Methods

The research study was retrospective cross-sectional study that processed the screening for colorectal cancer (CRC) at the national level, in the period from January 1 to December 31, 2014. The selection of 2014, as the year of choice for analysis, was made in accordance to the intensity of the CRC screening campaign that took place during this year. The initial results of the screening in the period 2012-2018 are also presented.

Selection criteria

According to the inclusion criteria for screening, it was envisaged to cover respondents of both genders aged 50 to 74 years, with a normal risk of colon cancer. The screening recommendation referred to the population with moderate risk and without specific symptoms, as well as for younger members of this age group with a family history of CRC. The exclusions screening criteria refers to patients: a) examined for CRC; b) with chronic inflammatory intestinal diseases (Ulcerative colitis, Crohn's disease); c) with regular check-ups for polyps removed; and d) performed a colonoscopy with a normal diagnosis in the last 3 years.

Screening Implementation

The screening was done with the detection of occult bleeding – FOBT (Fecal Occult Blood Test). The tests were procured by the Ministry of Health and distributed through the regional Centers for Public Health to the GPs (General Practitioners). In accordance to the achievement of the preventive goals within the agreement with the Health Insurance Fund of Republic of North Macedonia, the GPs were obliged to inform their patients about the possibility of screening and to advise them to perform 3 consecutive FOB tests. For each patient who was given the opportunity to perform a FOB test, an appropriate questionnaire had to be completed by the responsible GP. For the purposes of this research, the electronic database which included the data in these questionnaires was analyzed.

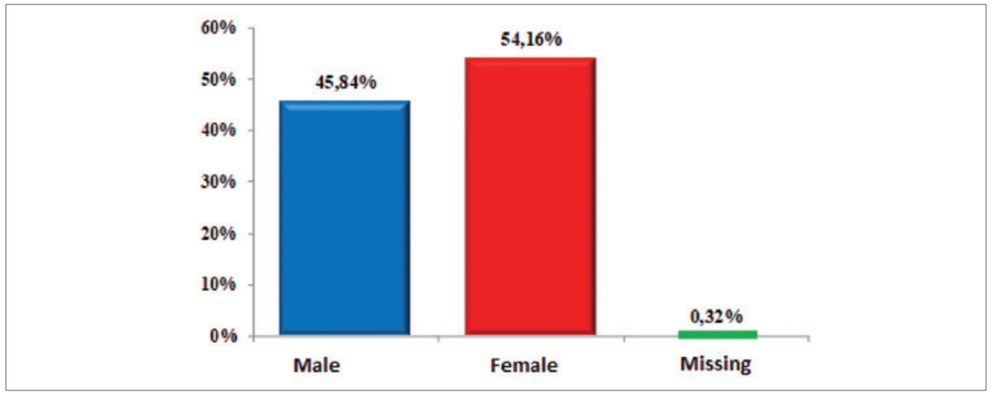
The screening process was preceded by education of GPs in Primary Health Care to advise patients on the use of FOB test kits, identification of the high-risk patients and refer them to Public Health Centers. The whole process was followed by the distribution of informative-educational material and a media campaign for colon cancer screening.

Results

Demographic characteristics of the respondents

In the period of research in 2014, the national screening for CRC covered a total of 2,160 respondents. The gender was registered for 2,153 respondents (99.7%).

Graph 3. *Gender distribution of respondents (%)*



Source: Author's calculations 2018

Male or female ratio was 0.85:1, with 987 (45.7%) males vs. 1166 (54.0%) females. The percentage difference between the genders in the sample, was statistically significant for $p < 0.05$, (Difference test: 8.3% [(5.3-11.3) CI 95%]; $x^2 = 29.7$; df = 1 p<.001) having significantly more females than males.

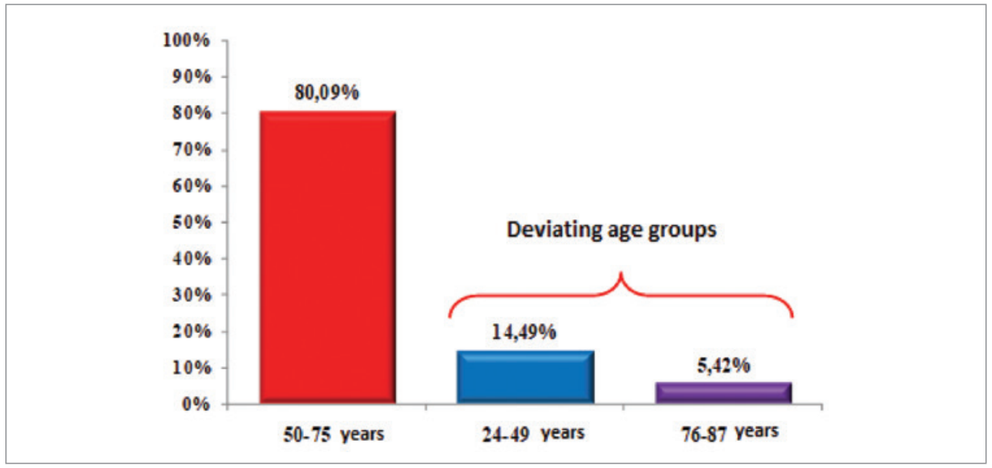
Table 4. *Gender and age distribution of the respondents*

Gender	Average (Mean) age	Number (N)	Std. Deviation	Min.	Max	Percentiles		
						25th	50th (Median)	75th
Male	61.6	987	10.3	30	87	55	63	68
Female	58.9	1166	10.9	24	85	53	60	66
Total	60.1	2153	10.7	24	87	54	61	67

Mann-Whitney U Test: Z=-6.0111; p=0.00001 * significant for p<0.05*

According to Table 4, the average age of the respondents in the sample was 60.1±10.7 years with a minimum age of 24 and a maximum age of 87 years. A total of 50% of respondents in the entire sample were older than 61 years for Median (IQR)=61(54-67). The average age of male and female respondents was 61.6±10.3 vs. 58.9±10.8 years with a minimum or maximum age of 30 vs. 87 for men for Median (IQR)=63(55-68) and in women aged 24 vs. 85 for Median (IQR)=60(53-66) years. For p<0.05, a significant difference was found between the respondents of both genders in terms of age (Mann-Whitney U Test: Z=-6.0111; p=0.00001) in addition to significantly older age in male respondents (U *(N_{male}*=987, *N_{female}*=1166), *z=6.011*, *p*<.001).

Graph 4. *Age distribution of the respondents*



Source: Author's calculations 2018

Additional analysis for perceiving the deviations from the predicted age of the respondents which was from 50-75 years indicated that 313 (14.5%) of them were aged 24-49 years while 117 (5.4%) were aged 76-87 years (Graph 4). A total of 430 (19.9%) of the respondents deviated from the specified age for screening.

The analysis of the sample according to the ethnicity, indicated that the most of the respondents 1,832 (84.8%) were Macedonians followed by 207 (9.61%) Albanians, 36 (1.7%) Serbs, 20 (0.9%) Roma, 17 (0.8%) Turks and 48 (2.3%) other nationalities (Table 5). The percentage difference between the genders among the nationalities, for p<0.05, was statistically significant between Macedonians and Albanians (Difference test: 6.6% [(3.4-9.9) CI 95%]; x^2=16.09; df=1 *p*<.001 vs. Difference test: 25.6% [(16.1-34.5) CI 95%]; x^2= 27.01; df=1 *p*<.001) having significantly more women compared to men have been tested (Table 4). For p> 0.05, no statistically significant gender difference was found between Serbs, Turks, Roma and other nationalities (Table 5).

Table 5. *Respondents' distribution by nationality and gender*

Nationality		Gender		Total	Difference test
		male	female		
Macedonians	Number	852	973	1825	6.6% [(3.4-9.9) CI 95%]; x2=16.09; df=1 p<.001)*
	%	46.7%	53.3%	84.8%	
Albanians	Number	77	130	207	25.6% [(16.1-34.5) CI 95%]; x2=27.01; df=1 p<.001)*
	%	37.2%	62.8%	9.6%	
Serbs	Number	14	22	36	22.2% [(-0.8-42.2) CI 95%]; x2=3.51; df=1 p=0.06)
	%	38.9%	61.1%	1.7%	
Roma	Number	9	8	17	5.88% [(-25.2-35.4) CI 95%]; x2=0.11; df=1 p=0.74)
	%	52.9%	47.1%	0.8%	
Turks	Number	10	10	20	0% [(-28.4-28.4) CI 95%]; x2=0.00; df=1 p=1.00)
	%	50.0%	50.0%	0.9%	
Other	Number	25	23	48	4.2% [(-15.3-23.2) CI 95%]; x2=0.16; df=1 p=0.69)
	%	52.1%	47.9%	2.2%	

**significant for p<0.05; Source: Author's calculations, 2018*

The distribution of the respondents by cities indicated that the most of the respondents were from Skopje 614 (28.4%) followed by Ohrid 568 (26.3%), Struga 309 (14.3%) and Kocani 232 (10.7%) (Table 6). There was a significant absence of screening data for CRC in certain cities such as Gostivar, Gevgelija, Prilep, Kichevo, Strumica and other cities.

Table 6. *Distribution of respondents by place of residence*

City	Respondents	
	number (N)	%
Bitola	12	0.6
Kumanovo	95	4.4
Kriva Palanka	32	1.5
Kichevo	104	4.8
Delchevo	50	2.3
Kratovo	22	1.0
Resen	2	0.1
Tetovo	45	2.1
Struga	309	14.3

City	Respondents	
	number (N)	%
Kochani	232	10.7
Vinica	19	0.9
Berovo	22	1.0
Ohrid	568	26.3
Debar	32	1.5
Skopje	614	28.4
Shtip	1	0.0
Radovish	1	0.05

Source: Author's calculations, 2018

During the CRC screening in 2014, 108,000 FOB tests were provided, i.e. 3 consecutive tests for each patient, provided for 36,000 citizens aged 50-74 years. The tests were distributed in a timely manner by the 10 regional Centers of Public Health, to all GP doctors. Of the projected 36,000 citizens, 14,505 citizens, or just over 40%, took the FOB test. About 30% of them (4314) had a positive test, while 98 citizens got a confirmed diagnose of colon cancer presence.

Colon cancer screening results (2012-2018)

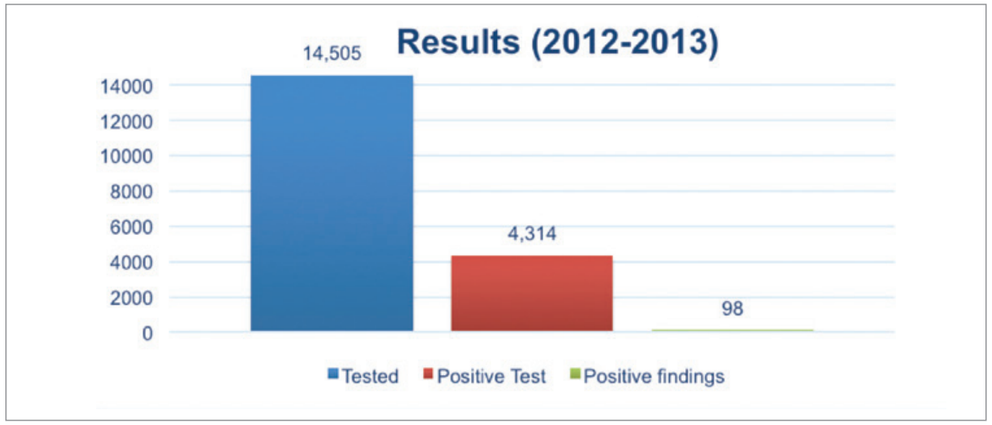
In the period from 2012 to 2018 out of the projected 85,000 citizens a total of 25,499 FOB tests were performed (30%), out of which 10,003 (39%) were positive, and CRC was confirmed by colonoscopy in 221 (2.32% out of the positives) (Table 7). The tests were timely distributed by the 10 regional CPHs to all GPs in 2014, while for the remaining years the tests were taken in the Public Health Centers according to the place of residence.

***Table** 7. Preliminary results of the CRC screening conducted in the period 2012-2018*

Year	FOB tests	Positive tests		CRC confirmed among positives	
	#	#	%	#	%
2012-2013	14505	4314	29.7	98	2.3
2014	3992	2012	50.4	80	4.0
2015	2761	1651	59.8	20	1.2
2016	1598	853	53.4	11	1.3
2017	733	358	48.8	4	1.1
2018	1910	815	42.7	8	1.0
Total	25,499	10003	39.2	221	2.2

Source: Author's calculations, 2018

Graph 5. *Overview of the CRC screening results in 2012-2013*

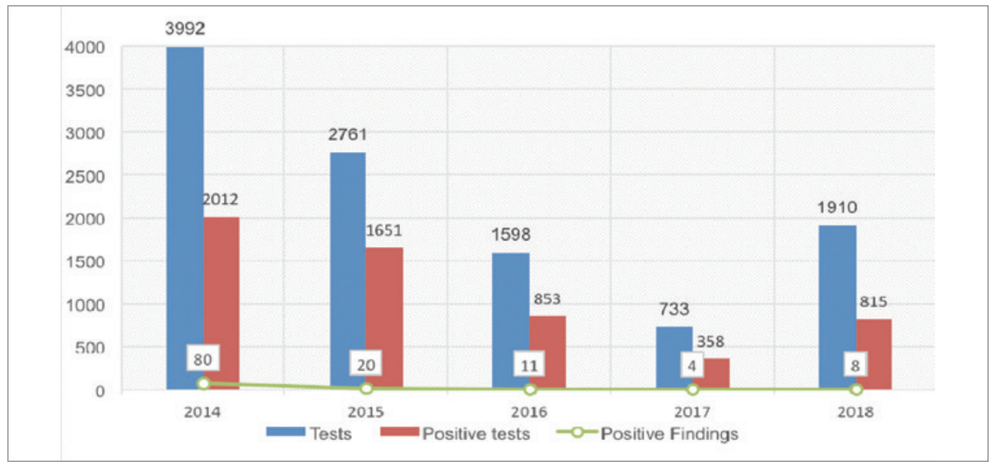


Source: Institute of Public Health of RNM 2018

During **2012-2013**, **14,505** citizens made the FOB test, **4,314** or about **30%** of them had a positive test, while **98** citizens were confirmed diagnose of colon cancer (Graph 5).

In **2014**, FOB test was performed by **3,992** people or only 11% of the procured and planned FOB tests for 36,000 citizens, for 2014. **2012** people had a positive test, or slightly more than 50%, while in **80** people diagnose of the presence of a polyp or colon cancer was confirmed.

Graph 6. *Overview of the results of the screening conducted in the period 2014 to 2018*



Source: Author's calculations, 2018

In 2015, in the Republic of North Macedonia **2,761** persons were tested, out of which **1,651** persons had a positive test (around 60%), and in **20** persons diagnose of CRC was confirmed.

In **2016**, a total of **1,598** people were tested, out of which **853** people or about 54% had a positive test, while **8** people had a positive diagnose, or 0.9%, and a benign neoplasm/ precancerous diagnose was confirmed in only 3 people from Skopje or 0.4%.

In **2017**, **733** people did a FOB test, out of which **358** people had a positive test or about 53%, with a positive diagnose were **2** persons and **2** persons from Skopje with a positive benign neoplasm / precancerous diagnose.

In **2018**, a total of **1,910** people were tested, out of which **815** people or 42.7% had a positive test, while 6 people had a confirmed CRC diagnosis (0.7%), and a benign neoplasm/precancerous diagnosis was confirmed in 2 persons from Skopje or 0.2% (Graph 6).

Discussion

In 2015, 24 countries from the European Union were preparing to organize CRC screening programs. Among them, Finland, France, Slovenia and the United Kingdom had fully implemented an organized screening programs. Screening programs have been launched in Belgium, Netherland, Denmark, Ireland, Italy, Malta, Poland and Spain. Norway, Portugal and Sweden were in the pilot phase. In opposite, other countries, including Slovakia, with the highest CRC rates in Europe, did not have a national screening program. Similarly, there were no screening programs in Bulgaria, Albania, Bosnia and Herzegovina, Kosovo, Macedonia, Montenegro, Romania, Serbia and Russia. The analysis of various programs in several European countries, showed that Croatia and the Czech Republic had the lowest participation rates (<25%). Other countries achieved better participation rates (over 45%); and the largest participation was

observed in the Netherlands, followed by Slovenia. The Netherlands had the highest positive test rate (positive test, 12.2%) (13).

The general conclusion is that very small number of citizens in our country took a FOB test, as well as further tests to confirm diagnose of colon cancer. Namely, out of a total of 108,000 distributed tests, from September 2014 to December 2015, only 20,259 FOB tests were used, or approximately 18% of the tests, i.e. if it is known that one person needs to take three consecutive tests then in the period from 2014 to the end of 2015, tests were performed for 6753 people or 18%. In comparison, the programs in Netherland and Slovenia had over 45% participation in 2015.

Compared to the results from Slovenia, where the rate was 57.8% (53.2% men, 62.3% women) we can say that our conclusions go in the direction that there is no big difference between male and female respondents (10). In other countries screening rates were higher for women than for men. This difference probably occurred because women were more aware of prevention programs; the most likely, the women had experience in breast screening and cervical screening. Special efforts should be made in all screening programs to increase the overall participation and participation rates of men.

In Europe, there are huge variations in the age-standardized incidence rates for CRC ASR is (age-standardized incidence rates); the lowest incidence was observed in men and women in Bosnia and Herzegovina (30 per 100,000 and 19 per 100,000, respectively) and in Albania (13 and 11 per 100,000, respectively). Distribution by age group showed the largest distribution between 50-70 years 80.1% which is actually the target group for the implementation of the screening program.

In general, participation rates in various CRC screening programs for populations around the world currently exceed the acceptable minimum of 45%, but they have not reached the desired target (>65%). Screening programs must use specific strategies to reach the target population and encourage participation in screening programs. A better understanding of barriers and facilitators for participation is needed in order to design strategies that promote an equitable approach. It is important to monitor, record and evaluate the minimum indicators and requirements of CRC population screening programs to ensure that they meet the standards of the European Quality Control Guide.

Having all these data and information, we can conclude that there are large variations in the incidence and mortality of CRC worldwide. Some regions with high CRC rates do not have screening programs, and other regions, such as Europe, have widespread organized screening programs. In addition, participation rates vary widely between programs around the world. The highest rates are found in the Netherlands and the lowest in Canada. The most common test used as a screening tool in organized screening programs was the fecal occult blood test. In countries with opportunistic screening programs, colonoscopy was the most commonly used for screening. Participation rates were higher among women, probably due to increased awareness of the importance of other screening programs, such as breast cancer screening. Positive test results and CRC detection rates were higher in men than in women; therefore, men's awareness should be increased to encourage participation in screening programs.

The high percentage of positive tests comes from the fact that many people used the right for a free test while not respecting the established formal criteria (of the Institute of Public Health of Republic of North Macedonia) to participate in the screening program.

The data above indicates the fact that the positive tests were either false positives or false negatives, i.e. the sample was not properly taken from an appropriate participant in the colon cancer screening program. As a conclusion, it is obvious that the criteria set in the program for early detection of malignant diseases in the area of colon cancer screening were not respected including the recommendations prepared by the Institute of Public Health (trough brochures, flyers and leaflets).

Many of the GPs who in 2014 in the preventive goals had the responsibility to advise their patients to do a FOB test, to achieve this goal and to be adequately paid by the Health Insurance Fund, have not done proper selection of the patients, and the percentage of false-positive and false-negative tests came as an evident consequence.

Conclusion

The general conclusion is that a very small number of citizens in our country have taken a FOB test, as well as further examinations to confirm or reject the diagnose of colon cancer.

Analyzing the period from 2012-2018, In our country, the participation rate is 39%, but we must say that there was a limited number of FOB tests, insufficient education of the GPs to select appropriate population in the screening program and lack of further monitoring of positive cases of FOB test. Participation rates were higher among women, most likely due to increased awareness of the importance of other screening programs such as breast cancer screening, cervical cancer screening.

Positive test results and CRC detection rates were higher in men than in women; therefore, it should be a motive for awareness-raising activities among men to encourage participation in screening programs.

There is also a lack of adequate monitoring (follow up) on the path from the GPs through the FOB test toward the colonoscopy and the diagnosis from the colonoscopy

General Recommendations

- In order to achieve the potential benefit of CRC screening, there must be optimal quality at every step of the implementation process.
- Screening must include information, identification and personal invitation of the target population, proven performance of the screening test and, if necessary, treatment, surveillance and consecutive care.
- For a program to be successful, it needs to be well designed and to have an appropriate algorithm for implementing the screening program.
- Better information of the population is needed for the benefit of the prevention programs, in order to increase the coverage of the population that has no symptoms.

- It is necessary to include the Health Insurance Fund of Republic of North Macedonia as a financier of the screening programs in order to guarantee the financial sustainability.
- More efficient activities are necessary to strengthen the awareness of the population about the need for colorectal examination, as well as education for proper use and interpretation of the FOB test.

Specific Recommendations

- It is also necessary to define indicators in accordance to the European CRC screening guidelines.
- A comprehensive approach should be applied in order the screening program to reach the entire population at risk.
- The positive tests, should be followed by a mandatory colonoscopy.
- A separate and continuous analysis is needed to compare the screening results and the endoscopic evaluations.

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CASE REPORT UDK: 616.831.9-006.311-089.853-06-005.1

A RARE CASE OF MENINGEAL HEMANGIOPERICYTOMA ACCOMPANIED WITH INTRAOPERATIVE BLOOD LOSS

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Introduction: Meningeal hemangiopericytomas are rare tumors of the meninges which are aggressive and pathohistologically belong to solitary fibrous tumors of the dura. The tumor might be found throughout the entire CNS, usually superficially and closely related to the meninges. Important characteristic is that they have a strong tendency for local recurrence and also are associated with extra cranial metastasis.

Case Report: In this study, we present a case of 71 years old man primarily asymptomatic, who presented with sudden symptoms of headache, dizziness, and loss of consciousness. He was immediately transferred to the department of urgent medicine where primary computer tomography (CT) scan was done. For a certain diagnosis to be established magnetic resonance imaging (MRI) was secondly done.

MRI showed extra axial, solitary, supratentorial masses, lobulated in contour, highly vascular with a tendency to erode the nearby parietal bone. In T1 and T2 waited images it was isointense to grey matter. In Diffusion waited images (DWI) this tumor showed intermediate restricted diffusion (less than meningioma). After intravenous application of contrast medium – gadolinium, it shows vivid enhancement, heterogeneous, and a dural tail sign was seen.

Total surgical excision was done with the complication of intraoperative bleeding, and the diagnosis of meningeal hemangiopericytoma obtained on MRI was pathohistological confirmed.

Conclusion: Meningeal hemangiopericytoma (HPC) are aggressive lesions with a tendency for extracranial metastasis, also this tumor has a tendency for high rates of recurrence, and is characterized with local aggressive behavior.

On both CT and MRI modality distinguishing a hemangiopericytoma from a meningioma, sometimes can be difficult because of their similar appearance, but is important the interpretation to be adequate especially with MRI because of the need for pre-operative catheter embolization in order to prevent the intraoperative blood loss, and also adjuvant radiotherapy might be required to reduce the risk of local recurrence and distant metastasis

Key Words: *blood loss,* ***meningeal hemangiopericytoma, MRI, surgery treatment****.*

Introduction

Intracranial hemangiopericytomas (HPC) are rare vascular tumors as this tumors account for less than 1% of all intracranial tumors and pathohistologically belong to solitary fibrous tumors of the dura. HPC is more commonly located supratentorial and the younger age group has predilection for this tumor. The tumor might be found throughout the entire CNS, usually superficially and closely related to the meninges. Important characteristic is that they have a strong tendency for local recurrence and also are associated to extracranial metastasis (1,2).

Case Report

We present a case of 71 years old man primarily asymptomatic, who was presented with sudden symptoms of headache, dizziness, and loss of consciousness. He was immediately transferred to the department of urgent medicine where primary computer tomography (CT) scan was done.

The report from the CT was hyperdense mass localized in the left parietal region next to the parietal bone with lisis of the bone; there was no calcification in that mass, and its dimension was 5 cm in diameter. For more precision diagnosis magnetic resonance imaging (MRI) was secondly done.

MRI shows extra axial, solitary, supratentorial masses, lobulated in contour, highly vascular with a tendency to erode the nearby parietal bone. In T1 and T2 waited images it was isointense to grey matter. In Diffusion waited images (DWI) this tumor shows intermediate restricted diffusion (less than meningioma). After intravenous application of contrast medium – gadolinium, it showed vivid enhancement, heterogeneous, and a dural tail sign was seen.

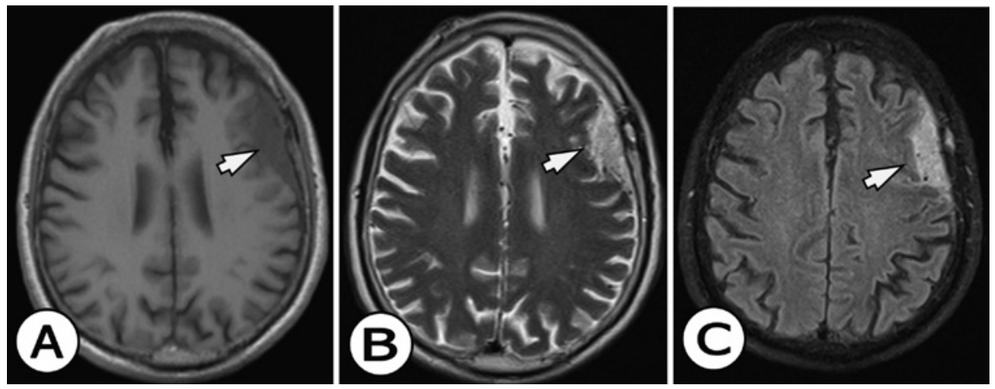
MRI as a method of establishing the diagnosis was superior to the CT scan due to the multiplanar projection, great resolution and the possibility of analyzing tumor presentation after intravenous contrast administration.

Although the size of the tumor, its lobulated contour, MRI signs of high vascularized lesion was enough to establish the suspicion of non-clear meningeal lesion, therefore in differential diagnosis option of meningeal hemangiopericytoma was taken in matter.

Total surgical excision was done with the complication of intraoperative bleeding, and the diagnosis of meningeal hemangiopericytoma obtained on MRI was pathohistologically confirmed.

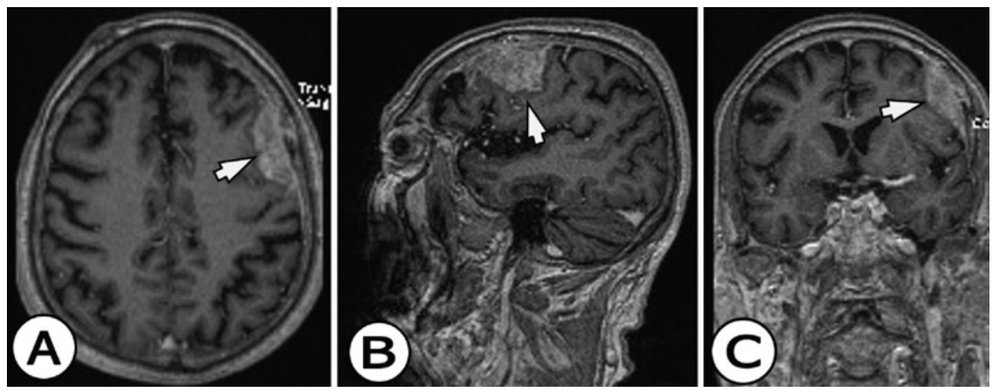
Unfortunately the option for preoperative embolization of small vessels in order to prevent intraoperative blood loss was not considered as necessary, but this case is surely giving a direction for the neurosurgeon to have that fact in mind in the cases when MRI has certainty in establishing the diagnosis.

Figures 1 A, 1 B, and **1 C**.



MRI images of 71 years old man who was presented with sudden symptoms of headache, dizziness, and loss of consciousness. A) An unenhanced MRI T1 WI shows TU slightly hypointense to gray matter (white arrows). B) An unenhanced MRI T2 WI shows TU was slightly hyperintense to gray matter (white arrows). C) An unenhanced MRI T2 WI-FLAIR shows TU hyperintense to gray matter (white arrows).

Figures 2 A, 2 B, and **3 C**



MRI images of 71 years old man who was presented with sudden symptoms of headache, dizziness, and loss of consciousness. A) An enhanced MRI T1 WI in the axial plane show homogenous and intensive enhancement of TU located on meninges, without the “dural tail” sign (white arrows). B) An enhanced MRI T1 WI in the sagittal plane shows homogenous and intensive enhancement of TU located on meninges, without the “dural tail” sign (white arrows). C) An enhanced MRI T1 WI in the coronal plane shows homogenous and intensive enhancement of TU located on meninges, without the “dural tail” sign (white arrows).

Discussion

Hemangiopericytomas were first described in 1942 by Stout and Murray as tumors arising from the pericytes of Zimmerman, which are modified smooth muscle contractile cells surrounding capillaries (1). Angioblastic meningioma as a term was used by Bailey et al in 1928 to describe a meningeal tumor observed in three of their cases (3).

In 1954, Begg and Garret, in their single case of a hemangiopericytoma of the meninges and six cases of angioblastic meningioma described by Cushing and Eisenhardt, proposed that all of these tumors should be designated as hemangiopericytomas (4).

In the 1993 classification of the World Health Organization (WHO) established the term hemangiopericytoma instead of angioblastic meningioma. Those tumors are aggressive, have high rate of local recurrence and also are associated to distant metastasis. Those are important reasons which highlight the need of adequate preoperative diagnosis.

By the Guthrie et al total surgical excision of intracranial hemangiopericytomas is recommended, and postoperative irradiation to minimize the risk of local recurrence is also required.

Histologically intracranial hemangiopericytomas are neoplasms of pericytes that originate in the meninges, but are actually different form without a meningioma component (5-8).

Hemangiopericytomas are well-demarcated masses attached to the dura and are associated to profuse bleeding while resection. These are aggressive lesions and give extracranial metastasis; the most common sites are the bones, lung, liver, kidney, pancreas, and adrenals. Postoperative radiation therapy and/or chemotherapy is recommended to increase the survival time (9-12).

The most frequent symptom is headache alone or accompanied with sudden loss of consensus.

Intracranial hemangiopericytomas are multilobulated tumors more than 3 cm in diameter with presentation of hydrocephalus, edema, and mass effect (13).

The location of hemangiopericytomas is similar to that of meningiomas. Hemangiopericytomas are extra axial lesions and also dural-based, might show change in the shape of the white matter. Their localization can be presented as sphenoid/ parasellar, lateral convexity, and superior parasagittal as middle fossa, anterior fossa, and posterior fossa, with a basal predominance, also parasagittal/ falx, convexity, posterior fossa, and tentorial; none occurred as purely intraparenchymal masses. The most of them are supratentorial in distribution parasagittal area is the commonest location (14, 15).

Almost all hemangiopericytomas have lobulated margins and are dense on CT with contrast enhancement on CT and MRI. The main differential diagnosis of HPC includes angiomatous/ anaplastic meningiomas and Solitary Fibrous Tumor (16).

MRI features are **T1 waited images:** isointense to grey matter, **T1 C+ (Gd)** vivid enhancement heterogeneous may have a narrow base of dural attachment, and dural tail sign.

T2 waited images: isointense to grey matter, multiple flow voids on MRI.

Diffusion waited images: intermediate restricted diffusion (less than meningioma).

HPC's clinical behavior is more aggressive than that of benign meningiomas and have a strong tendency for local recurrence and extracranial metastasis (17 – 19).

Sometimes the histopathologic features of an HPC and meningioma can overlap so immunohistochemistry staining is used in this situation for adequate histopathology diagnosis. Immunohistochemistry staining for MHPC shows an intense reactivity to vimentin, but not to epithelial membrane antigen (EMA), unlike meningioma that is positive for vimentin and EMA (20,21).

Conclusion

Meningeal hemangiopericytoma (HPC) are aggressive lesions with a tendency for extracranial metastasis, also this tumor has tendency for high rates of recurrence, and is characterized with local aggressive behavior.

On both CT and MRI modality distinguishing a hemangiopericytoma from a meningioma sometimes can be difficult because of their similar appearance, but it is important interpretation to be adequate especially with MRI because of the need for pre-operative catheter embolization in order to prevent the intraoperative blood loss, and also adjuvant radiotherapy might be required to reduce the risk of local recurrence and distant metastasis

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ORIGINAL RESEARCH UDK: 616.599-002.4-085.382

USE OF PLATELET RICH PLASMA AND SPLIT THICKNESS SKIN GRAFT IN POST-INFECTION SOFT TISSUE DEFECTS, OUR INITIAL EXPERIENCE

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ABSTRACT

Introduction. Necrotizing soft tissue infections (NSTI) are severe, potentially life-threatening medical emergencies that are accompanied with devastating and rapidly spreading destruction of soft tissue as a result of bacterial infection and systemic toxicity. Patients with NSTI who undergo split thickness skin graft (STSG) experience high rates of complications. Platelet-rich plasma (PRP) has shown to have positive effect on the healing of acute, chronic and diabetic wounds. The aim of this study was to analyze the outcome of skin grafting with PRP in post-infectious soft tissue defects.

Materials and Methods. Fourteen patients were randomized in two groups: an experimental group – wound coverage with STSG and PRP, and control group – with STSG alone. PRP was applied to the donor site in the experimental group. Patients' follow up was until complete healing of wounds. In both groups we analyzed the healing time, the need for regrafting, secondary infections, pain and adverse effects.

Results. Patients in the PRP group have had significantly reduced healing time (32.5 days) versus control group (72.5 days). In the experimental group, the rate of skin graft success was 90.2% vs. 77.2% in the control group. The need for regrafting occurred in one patient in the control group. Pain at the donor site in experimental group was statistically significantly lower. No adverse effects were reported.

Conclusion. The combination of STSG and PRP reduces healing time and lowers the complication rates. It is safe to use with no adverse effect. Further studies are needed with larger number of patients to further validate its efficacy.

Key Words: *Fournier gangrene, necrotizing fasciitis, necrotizing soft tissue infections, platelet-rich plasma, split thickness skin graft.*

Introduction

Necrotizing soft tissue infections (NSTI) are severe, potentially life-threatening medical emergencies that are accompanied with devastating and rapidly spreading destruction of soft tissue as a result of bacterial infection and systemic toxicity (1). Different names are used to describe the various forms of necrotizing infections. Naming is based on clinical features rather than surgical or pathologic findings. The most common names in literature are necrotizing fasciitis (NF), Fournier gangrene, necrotizing myositis, gas gangrene etc. The necrotizing infection can involve many soft tissues: the process starts primarily in the deep subcutaneous fascia and spreads to deep fascia, and muscle and to the skin and superficial fascia. Necrotizing infections may be categorized based on microbiology and presence or absence of gas in the tissues (1,2). The localization of the infectious process may be presented anywhere in the body, from some pre-existing focus, trauma or without apparent cause and it is characterized with rapid horizontal spread of the infection site and progressive systemic deterioration of the patient. The risk of mortality can be up to 20% if a limb amputation is warranted as a result of the infection (3-7).

There are considerable challenges in management of NSTI. The first challenge is prompt diagnose of the NSTI, when the disease process is in the early stage (7). In this stage, the patient may appear healthy, skin features of the disease may not be present or may be misdiagnosed as cellulitis or other superficial skin infections. This may lead to delay in treatment in a patient (3,4). When a NSTI is suspected or furthermore confirmed the algorithm for treatment is administration of empirical antibiotics, fluid replacement, other supportive therapy and emergent surgery as soon as possible. After the initial assessment and treatment, daily changes of the wound dressings are required, adjustment of antibiotics based on the results of the tissue cultures and treatment of the comorbidities as needed. Surgery is the only definitive treatment for NSTI and should be as early and as aggressive as possible. The delayed surgical intervention increases the risks of morbidity and mortality, so, one of the most important factors in patient's survival is the time from the diagnosis to surgical debridement (8,9).

The second challenge is need for excisional debridement of all infected non-viable tissue. The debridement should be aggressive and should commence with incision of skin and subcutaneous tissue deeply and widely entering into healthy tissues and excision of all necrotic fascia and non-viable skin and subcutaneous tissue. Since the process can still progress after the initial surgery, daily inspection of the wounds and repeated debridement is often required (9). These procedures are mutilating, sometimes a limb amputation might be necessary, especially in diabetic patients or in patients with peripheral vascular disease. Usually, the wounds are left open, to heal by secondary intention and wound dressings are changed once or twice a day depending on the degree of exudation.

Prompt and successful coverage of the skin and soft tissue defects is the third challenge in the management of NSTIs. After the successful treatment of the NSTI large skin defects are present, which often have bacterial of fungal super-infection that contributes to fluid loss, pain, immobilization and overall prolonged hospitalization. Therefore, wound closure is at outmost importance

as soon as local and systemic factors permit it. The preferred method of closure of large soft tissue defects is skin grafting although local and regional flaps are used for smaller defects or when split thickness skin graft STSG is not applicable (bone, tendon, nerve exposure) (8-10).

Patients with NSTI who undergo STSG, experience high rates of complication; skin grafting success depends on patient comorbidities, wound size and location. The most common complications are graft necrosis due to infection or hematoma, migration of the graft, donor site infection, delayed wound healing. Since the most of the patients have comorbidities and advanced age, wound healing is impaired, and thus prolonged hospitalization and multiple surgeries are required for wound closure and wound healing (10).

Wound healing is a complex biological process and is divided in three phases that overlap: inflammatory, proliferative and remodeling. The process starts as soon as the tissue is injured with hemostasis. The main cells that play central role in this process are the thrombocytes and their released cytokines and growth factors. The inflammatory phase overlaps, a process in which the cellular debris and the bacteria is cleaned from the wound as a preparative for the next phase, the proliferative phase in which collagen synthesis and deposition is obtained. In the inflammatory phase main cells that play role are the macrophages which are transformed from the monocytes that circulate in the blood stream activated by the cytokines from the thrombocytes. All infected wounds are stuck in the inflammatory phase. That's why a surgical intervention is an imperative and its goals are to restore tissue regeneration and wound healing (11).

Platelet-rich plasma (PRP) is a product of autologous whole blood. PRP contains large number of platelets in a small plasma volume, with complete set of coagulation factors in physiological concentrations (12). The production of PRP is done by taking whole blood with or without anticoagulant and centrifugation, after which platelets are separated from erythrocytes within a small amount of plasma. There are many methods for obtaining PRP and therefore different final products. Therefore, PRP differs in number of thrombocytes, leucocytes and fibrin (12-14).

Platelets produce and store more than 1100 active substances: cytokines, growth factors, messengers of the immune system, enzymes, enzyme inhibitors and other bioactive substances that are encompassed in various mechanisms of the wound healing process (15-17). Anitua and al. recently gave a detailed overview: platelet derived growth factor acts chemotactically on macrophages, TGFβ, PDGF and IGF help in mitogenesis and chemotaxis of stem cells, osteoblasts, capillary growth angiogenesis, bone matrix formation, collagen synthesis (18). TGFβ and PDGF help in bone mineralization. Additionally, adhesive proteins such as fibrinogen, fibronectin, vitronectin, TSP1 participate in thrombus formation and have mitogenic properties. In chronic wounds, some of the proteins secreted by thrombocytes are absent, further proving their role in wound healing (18).

Platelets also secrete various molecules that have antimicrobial properties. These molecules include some chemokines and cytokines that induce the recruitment and activation of immune cells, as well as microbicide proteins including kinocidins [PF4 (CXCL4), CXCL7 and CCL5];

defensins [human β-defensin 2 (BD2)], thymosin β4 (Tβ4); and antimicrobial peptides (fibrinopeptide A or fibrinopeptide B and thrombocidins) (19).

Numerous studies have described the role of PRP in wound healing. PRP is used in many surgical specialties and in wound treatment (19). In surgery PRP despite its regenerative properties, is also used as hemostatic and adhesive substance which lowers intraoperative and postoperative bleeding, promotes tissue apposition and adherence of grafts and flaps and promotes bone and fat cells regeneration when used with other bioactive materials. There are several studies where has been shown that PRP has a positive effect on the healing of acute, chronic and diabetic wounds. In meta-analysis, in studies where PRP has been evaluated, the rate of infection and pain were reduced in all types of wounds. A review of the literature on the usage of PRP in diabetic wounds has shown positive results in speeding healing and reducing complications (20, 21).

Taking into consideration the regenerative, adhesive, hemostatic and antimicrobial properties of PRP, its addition in skin grafting may improve the outcome of patients after NSTI. The aim of this study was to analyze the outcome of skin grafting with PRP in post-infectious soft tissue defects.

Materials and Methods

The data for this study were obtained from a study that was conducted from June 2017 till September 2020. Patients were recruited from the University Clinic of Plastic and Reconstructive Surgery in Skopje, North Macedonia. The patients who signed informed consent were included in a prospective study. Fourteen patients with NSTI were randomized in two groups: an experimental group – wound coverage with split thickness skin graft (STSG) and PRP, PRP was also applied to the donor site and a control group – split thickness skin graft (STSG) with mechanical fixation and standard wound dressing to the donor site wound. Inclusion criteria were patients 18 years or older and loss of substance >1% of TBSA (total body surface area) with successful debridement of NSTI and the wound met the criteria for STSG (no active infection, no necrotic tissue, granulation tissue). The exclusion criteria were age under 18 years, patients with hematologic disease, patients with thrombocytes disorders, patients with history of cancer and patients with HIV, hepatitis B and hepatitis C. Patients' follow up was until complete healing of the wounds. In both groups we analyzed the healing time, the incidence of complications, need for regrafting, secondary infections, pain and adverse effects.

Preparation of PRP

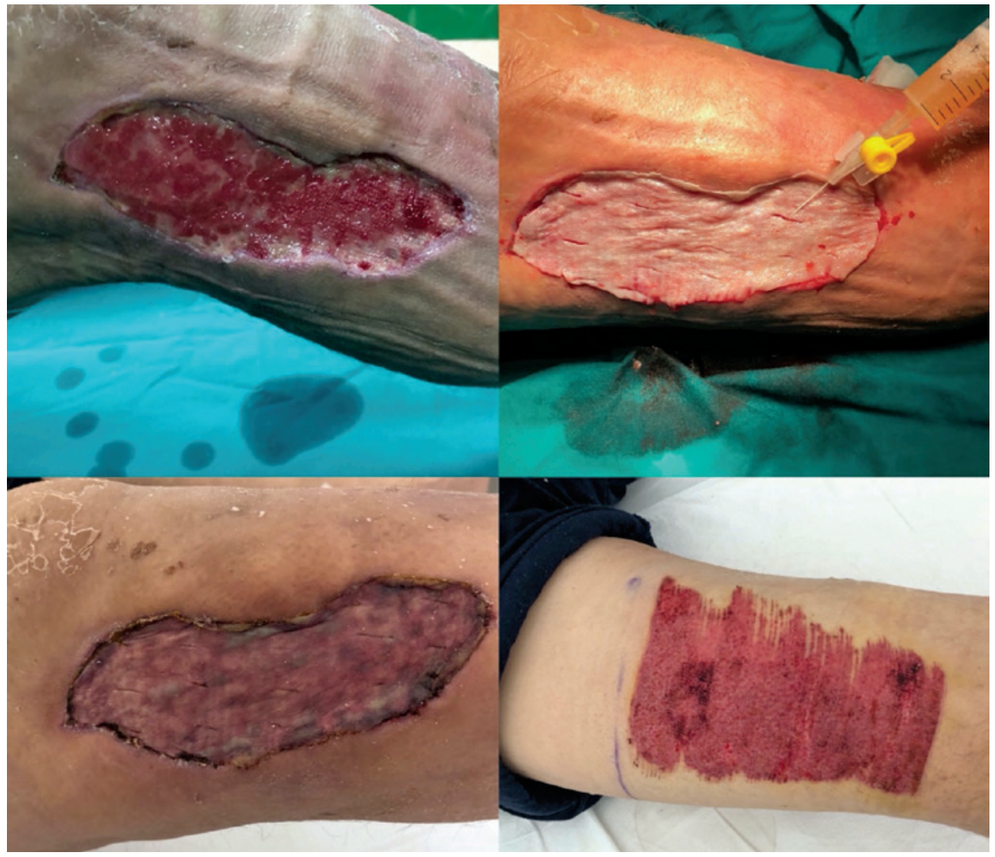
Fifteen ml of blood was taken from the patients via 18 G butterfly needle into an Arthrex ACP double syringe. The syringe was centrifuged in a Hettich Rotofix 32 A centrifuge (Andreas Hettich GmbH & Co. KG, Tuttlingen, Germany) for five minutes at 1500 rpm (= 350 G). The PRP settled in the upper third of the syringe (approx. 5 to 6 ml) and was drawn into the inner syringe. The PRP was transferred into a 10 ml syringe with aseptic technique and was ready for use. Each patient had 15 to 30 mL of blood drawn, depending on the surface of the wound

(calculated in% of TBSA): for 1% to 5% (TBSA) 1 Arthrex ACP double syringe was used and for 5% to 10% (TBSA) 2 Arthrex ACP double syringe were used (22).

Surgical Technique

All patients with NSTI were treated previously with surgical debridement of all necrotic infected tissue, antibiotic therapy and supportive care. The wounds were dressed with antiseptic solution of sodium hypochlorite 0.022% and left to heal by secondary intention. Alternatively, negative wound pressure therapy was used. The debridement was repeated if necessary. The time from initial debridement to skin grafting was approximately 20 days (range from 16 to 40). In all patients the skin graft was taken with electrical dermatome (Integra S Padgett Slimline Dermatome). Skin thickness was 0.4 mm and meshed for graft expansion 1:1.5 ratio. All wounds were dressed with paraffin gauze dressing and gauze saturated with solution of sodium hypochlorite 0.022%.

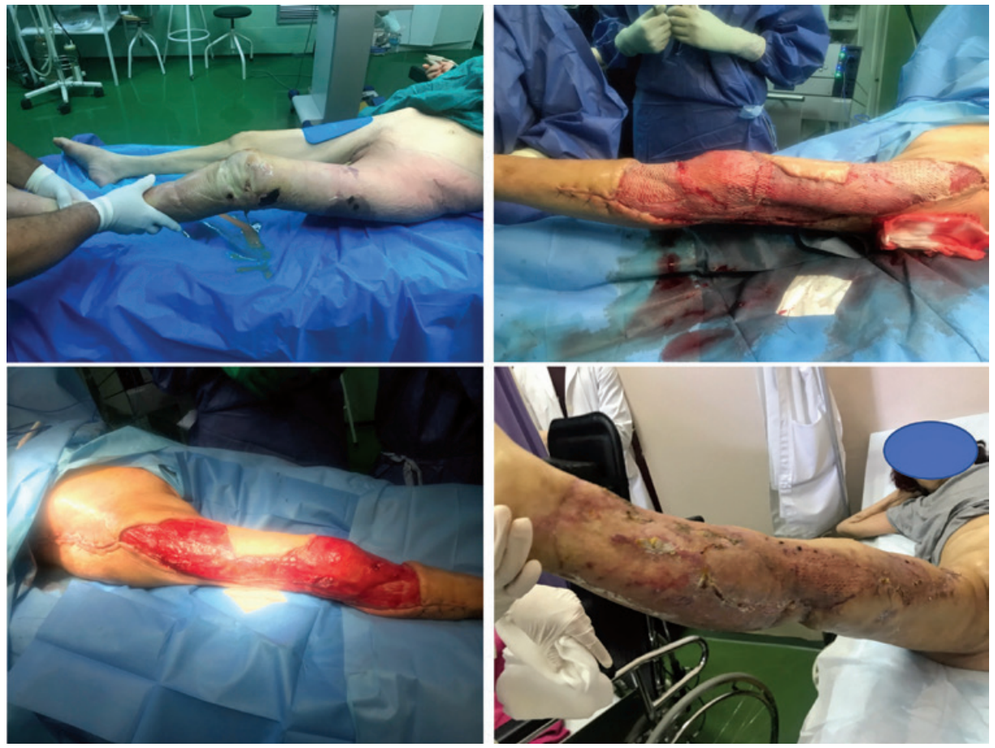
Picture 1.



Top left: Skin defect after debridement, Top right: Technique of STSG and PRP, no sutures are placed; Bottom right: One week after STSG 100% graft take; Bottom left: Donor site after 1 week

In the experimental group PRP was applied on the wound prior to resurfacing with skin graft with no additional fixation. PRP was also applied at the donor site. In the control group the skin graft was sutured with silk sutures/ stepler. The donor site was dressed as described previously.

Picture 2.



Top left: Initial presentation of a patient with NF type 1; Bottom left: Skin defect after extensive debridement; Top right: Wound after STSG and PRP; Bottom right: One month after STSG

Follow-up

All patients were immobilized for 2 days, with elevation of the extremity, appropriate antimicrobial therapy was administered. Analgesic therapy was administered upon patients' request. The wound inspection was done on the fifth day or sooner if indicated (hematoma, infection, odor, pain). The frequency of dressing changes was noted. The end point was the complete healing of the donor and recipient wounds defined as 100% of re-epithelialization and dressing discontinuation. The complications were noted, and additional surgeries for skin grafting.

Statistical Analysis

The data was stored in electronic database (Microsoft EXEL for Mac version 16.4) and were analyzed with Prism 9 for macOS Version 9.0.0 GraphPad Software L.C.C. The results are

displayed as average value and standard deviation. Student t-test was used to confirm statistically significant difference between both groups.

Results

Patients were analyzed for demographics, comorbidities, type of NSTI, localization of the defect. Both groups had similar age distribution, experimental group had average 61.7 with SD of 6.5 and control group had average 57 with SD of 9.76. No significant difference in gender was found (Male vs. Female) in experimental group was 3 vs. 4 and in control was 4 vs. 3. In both groups there was one patient with Type I NF, the rest of the patients had type II NF. The localization of skin defect was similar in both groups: abdominal wall, inguinofemoral region and lower extremity. The most significant comorbidities in both groups was Diabetes mellitus (75.1%) and obesity 57.1%. Smoking was prevalent equally in both groups 5/7 patients (75.1%).

In the PRP group there was an instant adherence of the skin graft in all patients. No migration of the skin graft was reported. In the control group there was one migration of the skin graft in the inguinal area. In the experimental group, the success of STSG was 90.2% and in the control group was 77.2%. In the experimental group there was one patient that had partial necrosis due to secondary infection, but the wounds healed by secondary intention. In the control group, there were 2 patients with partial necrosis of the skin graft which healed by secondary intention and one patient that had more than 90% skin graft necrosis due to secondary infection with Pseudomonas Aeruginosa and needed regrafting. The experimental group had in average 31.07 days for epithelialization of STSG with SD 3.78 and control group has in average 49.64 days for 1epithelialization of STSG with SD 17.47 and P= 0.0169 which is significantly different.

The donor site was analyzed for postoperative pain, wound infection, healing time. In the PRP group, 4 patients were presented with no pain and three patient had mild pain. In the control group 5 patient had moderate pain and 2 patients had severe pain. Pain was statistically significant P<0.0012. The experimental group had in average 16.5 days for 100% epithelialization with SD 4.83 and the control group had in average 25.5 days for 100% epithelialization with SD 3.416 and P= 0.0023, which is significant. The rate of infection of the donor site was higher in the control group – 3 patients, and the PRP only one patient had infection on the donor site. The infection wasn't significant in time of healing of the wound. No adverse effects were reported in both groups.

The experimental group had in average 9.86 postoperative days (post STSG) with SD 2.545 and the control group had in average 13.86 postoperative days (post STSG) with SD 5.113 and P= 0.0067

Discussion

Patients with NSTIs usually have one or more comorbidities that impede wound healing and are strongly associated to skin graft failure. The most significant comorbidities are diabetes mellitus and metabolic syndrome, immunodeficiency, obesity (weight-to-hip ratio greater than

1, cardio-vascular disease, peripheral vascular disease (23,24). Advanced age, lower extremity and smoking are other independent risk factors that can attribute to delayed wound healing and skin graft complications (25). The inguinofemoral region is particularly difficult for skin grafting due to its proximity to the urogenital area and bacterial contamination. In this study the groups were homogenous for demographic factors, comorbidities and localization.

There is a relationship between infection and graft failure: active infection is a contraindication for skin grafting due to catabolic effects of the bacteria and leucocytes on the skin graft, but bacterial colonization on the wound bed without active infection also may adversely affect healing (25). Our results showed that the most common bacterial colonization of the wound was with Acinetobacter sp. and Pseudomonas Aeruginosa. Three of the patients in the control group had complications after initial skin graft uptake with graft dialysis due to infection with Pseudomonas. One of the patients needed regrafting and in other two patients there was partial necrosis and the wound healed by secondary intention.

Chøgsberg et al. showed significant difference in healing of STSGs on leg ulcers colonized with different microbes. They have shown that colonized wounds with Pseudomonas aeruginosa have the most complications (26). In our study P. Aeruginosa was found in all cases of wound complications, but the group was too small to draw conclusions.

The outcome of the skin grafting depends on several factors, which should be improved for better outcome: prior to skin grafting the wound bed has to be prepared, the graft fixation technique must be adequate in order to prevent shearing of the graft and migration, and physiological factors which adjunctive therapy is used for (27).

Platelet-rich plasma is used as an adjunctive therapy for augmentation of STSG. Schade and al. evaluated the effect of PRP in complex wounds in patients with medical comorbidities in 13 patients. The wounds were skin grafted, 4 of the patients had negative pressure dressing. Wound healing was achieved in 16 days. The authors concluded that the wound healing time is less when PRP is used (28). In our study we have evaluated the comorbidities in our patients and diabetes mellitus and obesity were the most frequent.

Three studies compare mechanical fixation versus fixation with PRP of split thickness skin graft. In these randomized prospective studies, more than 400 patients with acute and chronic wound from different etiology were enrolled. Results showed that instant adhesion of the skin graft to the surface, lower incidence of complications and better cosmesis of the scar in 3 and 6 months after the intervention in the PRP group. Additionally, they analyzed that the length of hospital stay, and the total cost was lower when PRP was used (29-31). This is similar to our study where instant adhesion of the skin graft was seen and noted in the operating theatre, less postoperative time (from skin grafting do discharge from hospital) and no adverse reactions in the PRP group were reported.

Up to date, there is only one prospective randomized study in which activated PRP is used as an adjunct with STSG for resurfacing of post-infectious soft tissue defects (32). In this study,

twenty seven patients were randomized in two groups: STSG with A-PRP and STSG only. The authors analyzed the complete healing time, complication rate and adverse effects. They suggest that PRP has an antimicrobial effect. They concluded that in the PRP group there is 50% faster wound healing and no side effects. In our study we used PRP on both donor and recipient wounds. There was significant difference in the frequency of wound dressing changes, the infection rate of the donor site and time to complete healing of both wounds.

Although there are many studies about regenerative property of PRP, the antimicrobial effect of platelet-rich plasma has not been analyzed until recently. Zhang and al. reviewed in vitro results, and in vivo preclinical and clinical use of PRP for the treatment of wound and bone infections. They described the mechanism of action of the antibacterial properties of the PRP: several proteins interact with the bacterial outer cell membrane and increase membrane permeability which impedes protein synthesis, synthesis of enzymes and inhibit enzyme activity (33). In vitro, PRP inhibits adherence and growth of several bacteria. Studies have shown that Klebsiella pneumoniae (Gram-negative), Staphylococcus aureus (Gram-positive), and Streptococcus faecalis (Gram-positive) are sensitive to molecules contained within PRP and have synergistic effect with antibiotics and can be considered as an adjunct therapy to treat infection 34-37).

Varshney and al. summarized the studies of different platelet concentrates and compared the in vitro antibacterial efficiency. They concluded that in addition to the well-established regenerative properties, platelet concentrates seem to possess antimicrobial properties too (38).

Donor site wound heals by secondary intention and can have complications such as delayed wound healing, infection, pain and abnormal scaring. Sometimes, it can cause more discomfort and pain than the condition for which the skin grafting was performed. That is why optimal treatment is required in order to achieve wound healing. There are many wound dressings that are used for the donor site wound, but still there is no universal consensus of the ideal wound dressing (39). There are several studies that analyze the effect of PRP on the donor site. All studies report decreased pain and faster wound healing than the control group (40-43).

In our study the patients with PRP on the donor site, reported less pain with dressing changes and overall faster healing time.

Conclusion

Platelet-rich plasma has many properties that aid in wound healing with different mechanisms of action. It has well established hemostatic, adhesive and regenerative effect and it seems that has some antibacterial effect. When combined with STSG, PRP can reduce healing time, and can lower the complication rates. It is safe to use with no adverse effect reported. Further studies are needed with larger number of patients to further validate its efficacy.

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EVALUATION OF NEAR-INFRARED SPECTROSCOPY MONITORING IN SELECTIVE SHUNTING DURING CAROTID ENDARTERECTOMY

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ABSTRACT

Background: Carotid endarterectomy (CEA) is a standard prophylactic treatment of symptomatic and asymptomatic carotid stenosis. CEA can be performed either by conventional or eversion techniques. No matter what technique is used, cross-clamping of the carotid artery increases the risks for cerebr al ischemia and hypoperfusion. Carotid artery shunting used as an alternative method to prevent cerebral hypoperfusion by many clinicians, is not proven as reliable procedure that exposes patients to additional risks. However, literature supports findings of monitoring and vigilance methods that can be used as predictors when shunting is required. The aim of our study was to evaluate near infrared spectroscopy (NIRS) as a noninvasive method for the monitoring of regional cerebral oxygenation (rSO_2) during carotid cross-clamping and its reliability for the requirement of shunting in patients undergoing CEA.

Key Words: Carotid endarterectomy, local anesthesia, near-infrared spectroscopy.

Introduction

Carotid artery stenosis can be treated by different treatment modalities and one of those includes carotid endarterectomy (CEA). Literature reveals that carotid endarterectomy as treatment of choice significantly reduces the risk of ipsilateral stroke in patients with severe and symptomatic carotid stenosis (1). Another treatment approach, like carotid stenting, might be a reasonable alternative to endarterectomy in asymptomatic patients who have high surgical risk, but there is no evidence that carotid stenting is superior to endarterectomy for the prevention of stroke as an end point (2). By indications, when revascularization is considered in symptomatic patients with 50-99% stenosis, it is recommended that CEA should be performed within 14 days of symptoms onset (3). On the other hand, a perioperative risk, especially stroke, is increased when CEA is performed within the first 48 hours (4). However, in "average surgical risk" in patients considered as an asymptomatic with 60-99% stenosis, CEA should be done in the presence of more than one reliable imaging characteristics. This by itself is associated to increased risk of late ipsilateral stroke (5).

CEA is primarily performed for the prevention of stroke in patients with carotid stenosis. Main surgical techniques used for CEA are conventional or eversion techniques, both of them carrying more than 2% risk of stroke and other complications, due to the fact that cross-clamping of carotid artery is required (6). Strategies to maintain adequate cerebral perfusion and prevent cerebral hypoxic/ ischemic injury are numerous and include intracarotid shunt placement, induced hypertension and administration of supplemental oxygen. However, all above mentioned strategies carry risks of varying degrees, as well as different pathophysiological mechanism involved (7).

Literature reports that several methods of assessing the adequacy of cerebral oxygen delivery during the cross-clamp period have been used (7, 8, 9). Novel reports argue that the type of anesthesia is also a factor that contributes to adequate cerebral oxygenation and that different anesthesia techniques emphasize the need for prompt surgical reactions and shunting during CEA (8, 9).

From this point of view, CEA as a procedure can be done under different anesthesia techniques. Various studies have indicated that CEA can be performed either under general or local anesthesia including both epidural and deep skin infiltration. Despite these, the debate of CEA under general or plexus anesthesia is a debate still going on and still no consensus is present. However, more and more clinicians prefer superficial and cervical plexus block in combination as anesthetic choice for CEA (6). This is due to the fact that this aesthesia technique has been shown to be superior in relation to continuous neurological monitoring, accurate cognition level, decreased level of shunting during clamping, less intraoperative hemodynamic changes, shortened surgery time and shorter length of hospital stay (7).

In this context, relatively novel models for the tissue oxygenation monitoring (providing useful information not only about the degree of the tissue oxygenation, but additionally giving view of the microcirculation state), like Near infrared spectroscopy (NIRS) are more often used for monitoring in patients undergoing CEA (10, 11, 12). NIRS is a noninvasive method for monitoring of regional cerebral oxygenation (rSO_2). Studies have reported different degree of drop in the NIRS values as predictors for surgical or medical intervention (above 15%, above 20% and above 30% from the baseline). Despite this, during CEA, it is shown that sensitivity in prediction of cerebral ischemia is present and there is a need for shunting (10).

The objective of the study was to evaluate the values of NIRS (drop of NIRS values for 20% from baseline) in determining the need for selective shunting during CEA in patients undergoing a combination of deep and superficial cervical plexus block. Additionally, we evaluate the intraoperative and postoperative neurological status in CEA patients.

Material and Methods

This retrospective study included analysis of data from patients that underwent carotid endarterectomy for a period of five years beginning February 2015 until February 2020 at the University Clinic for Thoracic and Vascular Surgery in Skopje, Macedonia.

The analysis included all patients with carotid artery stenosis ≥ 70% with conventional or eversion CEA technique under superficial and deep cervical plexus block. All patients under general anesthesia and those patients with severe neurological impairment or dementia were excluded from the study. Standard continuous ECG, invasive artery pressure and pulse oximetry monitoring was applied in all patients.

The first considered as baseline measurement consisted of the arterial blood pressure, heart rate and SpO_2. Boluses of volume fluids or atropine were given to patients with drop in hemodynamic parameters, while the body temperature was regulated with warm blankets.

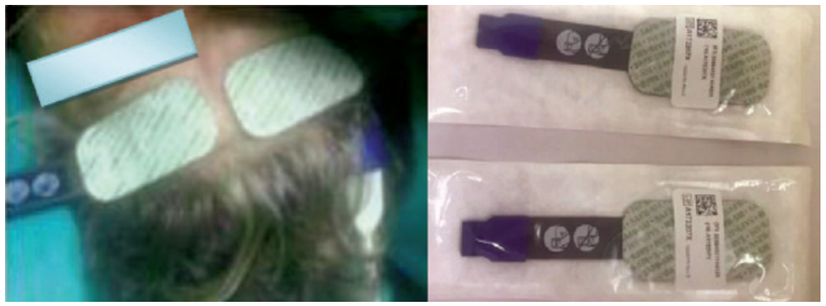
The procedures for anesthesia and CEA surgery were explained to all patients in detail whereby these patients provided their consent to undergo the above mentioned procedures.

Upon the patients' entry into the operating theatre, their neurological assessment was confirmed. The anesthesiologist explained to the patient that a set of questions will be frequently asked during the surgery that includes their name, date, year, children's names, counting backwards, movements and the strength of the limbs etc. to reassess their neurological condition.

The anesthesia was done by landmarks techniques with 0.25% bupivacaine. In all patients we used conventional or eversion CEA technique. All patients were placed on the operating table in the supine position with the head hyperextended and turned away from the operative side.

Two oximeter sensors were applied on the forehead of the patient and rSO_2 values were recorded continuously during the operation (Figure 1).

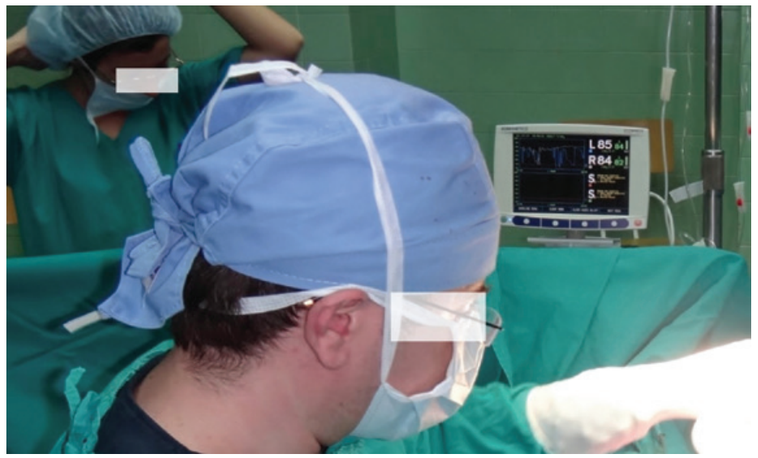
Figure 1. *Forehead placement of the oximeter sensors*



The rSO_2 measurement was performed using the INVOS 5100 C oximeter (Medtronic, Minneapolis, MN, USA). Our strategy was selective shunting.

Patients were given 80 IU/Kg heparin intravenously and the activated clotting time (ACT) was checked and maintained within a range 200-250 s. Intermittent heparin boluses were administrated as required during the operation. The anesthesiologist constantly communicated with the patient during the operation. At the same time, the cerebral oxygenation was monitored with the NIRS oximeter INVOS 5100C (Figure2).

Figure 2. *Intraoperative monitoring with INVOS 5100C oximeter*



A decision to perform shunt depended upon completion of the test clamping of the internal carotid artery. The conscious patients were assessed for signs of cerebral ischemia, decreased motor and cognitive response parallel with the rSO2 monitoring decrease in values ≥ 20% from the baseline on both the ipsilateral and contralateral brain hemispheres. Criterion for shunting was set when rSO_2 values decreased by more than 20% of the baseline values.

In all patients we analyzed, demographic and clinical data like age, gender, side and type of the CEA procedure, level of intraoperative neurological impairments, hemodynamic instabilities (drop or rise of blood pressure and heart rate more than a 20% from the baseline). Additionally, the presence of other comorbidities, need for shunting regarding the type of CEA, baseline values before carotid clamping and decrease of rSO2 after clamping, as well as postoperative complications were evaluated.

For statistical data analysis we used Fisher's exact test with level of significance $p < 0.05$.

Results

During the five-year period CEA was performed in 75 patients. Right side CEA was done in 52%, while left sided CEA in 48% of the patients. We displayed baseline demographic and clinical characteristics of the patients (Table 1).

Table 1. *Baseline demographic and clinical characteristics of the patients*

Variables	No (%)
Age (years)	69.5±6.2 (Mean±SD)
Male	49 (65.3)
Female	26 (34.7)
Right carotid artery stenosis	39 (52)
Left carotid artery stenosis	36 (48)
Neurological changes during carotid clamping	4 (5.3)

Both CEA techniques were used, conventional and eversion CEA. Our strategy was selective shunting. A statistical analysis shows that there is no statistically significant difference between the type of CEA technique and patients that received a shunt. We showed the type of CEA technique we used, as well as the need for shunting according to the CEA technique (Table 2).

Table 2. *Selective shunting in relation to CEA technique*

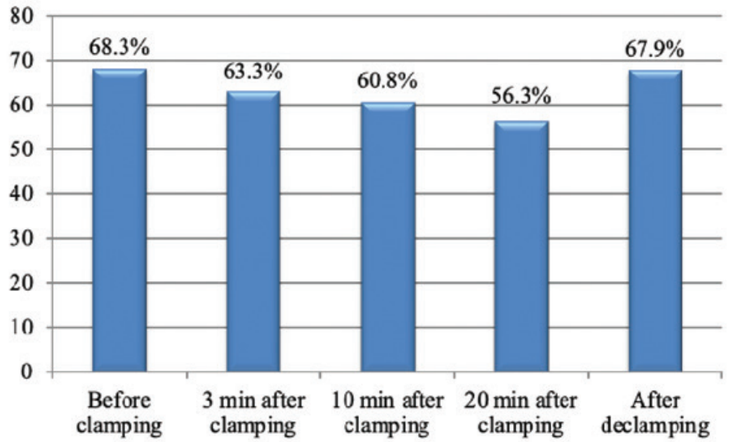
CEA technique	Shunting	Non-shunting	Total	p*
	No (%)	No (%)	No (%)	
Conventional	3 (4)	37 (49.3)	40 (53.3)	0.618
Eversion	1 (1.3)	34 (45.3)	35 (46.7)	
Total	4 (5.3)	71 (94.7)	75 (100)	

**Fisher's exact test*

Conventional carotid endarterectomy was performed in 40 patients (53.3%). During the conventional CEA we used great saphenous vein patch. Eversion carotid endarterectomy was performed in 35 patients (46.7%). The comorbidities: hypertension, Diabetes mellitus and generalized arteriosclerosis were present in 42 patients (56%). A total of 49 patients (65.3%) had smoking habits.

Carotid clamping duration was 15 to 35 minutes in all patients (mean duration of 22.5±7.6 minutes). Mean baseline rSO_2 values before carotid clamping, rSO_2 values 3, 10, 20 minutes after clamping and rSO_2values after carotid declamping are displayed (Figure 3).

Figure 3. *Mean rSO_2 values during the CEA*



During the carotid clamping there was a drop in rSO_2 values for more than 20% from the baseline values on the ipsilateral side in 4 patients (5.3%). All 4 patients developed neurological changes (motor or consciousness impairment, weakness of extremities) intra-operatively and therefore an intraluminal carotid shunt was done. One patient postoperatively developed temporary articulation disorder due to nerve traction.

Discussion

Carotid endarterectomy carries the risk of cerebral ischemia due to necessity of carotid artery cross-clamping. Although CEA purpose is to reduce the risk of stroke, the operation by itself can increase the risk of stroke from 5% to 10%. Temporary shunting reduces the time frame as blood flows to the brain is interrupted during the cross-clamping. This, on one hand, reduces the risk of perioperative stroke occurrence, but on the other hand may result in arterial wall damage which also increases the risk of stroke (16). There are three shunting strategies: routine shunting, when the surgeon inserts a shunt in every patient, selective shunting, when the surgeon only uses a shunt in patients with an inadequate blood supply to the brain, and various methods of cerebral monitoring are used to determine the need for shunting, and third strategy is without shunting (17). We prefer the strategy of selective shunting.

We used both CEA techniques, conventional and eversion CEA. In the literature, there is still no consensus for what CEA technique is superior in regards to conventional or eversion CEA technique (18). Some of the advantages of eversion CEA include shorter surgery time, no need for patch angioplasty and usage of synthetic materials and reduced incidence of restenosis. However, the need for more extensive dissection, more prone to shunting, difficult approaching when not well experienced surgeon is working, and increased incidence of postoperative hypertension, are its main disadvantages (19). Whichever technique is used care must be taken to remove all of the debris from the intimal surface of the artery in order to prevent postoperative emboli occurring (20).

During conventional CEA we used great saphenous vein patch. During CEA, patching with autologous venous tissue is the most commonly used option. Prosthetic patching materials commonly used are expanded polytetrafluoroethylene (PTFE) and Dacron, a polyester fiber. For many years backwards bovine pericardium has been a popular option for a biomaterial patch (21). Patch closure in CEA is correlated to reduction in the incidence of postoperative restenosis. More widespread use of patching should be considered to improve long-term durability (22).

In our study, CEA in all patients was performed in cervical plexus block and no need for conversion to general anesthesia occurred. Some surgeons prefer this type of anesthesia so they rely heavily on intermittent neurological checks as a pathway to assess perfusion. Neuroglial, motor, speech, and cognitive assessments are ideal for use, but their usage is bit impractical. However, such surgeons control the contralateral motor response testing. Despite this, some factors like language barriers, aphasia, and confusion related to past strokes limit the efficacy of this type of intraoperative assessments (23). Any of these impairments excluded patients from study.

Several methods to assess the need for shunting in order to optimize hemodynamics and hypoperfusion are present. Many studies have identified patients at ischemic risk and assessed the need for shunting using carotid artery stump pressure measurements, transcranial Doppler, intraoperative electroencephalographic measurements, neurological assessment in awake patients, and cerebral oximetry (24).

We used NIRS for monitoring of rSO_2 during the operation and anesthetist also controlled the vigilance of the patient in order to assess the brain perfusion. The human brain has high oxygen consumption and small changes in oxygen supply make it very sensitive to produce some signs of these. Successful treatment for low brain levels of oxygenation during or after surgery relies on early detection of cerebral hypoxia (25). Cerebral oximetry using NIRS has been developed to detect cerebral hypoxia in order to prevent hypoxic brain injury (26). Some studies have found that the triple assessment method (combination of NIRS, transcranial Doppler and awake testing) in detecting cerebral ischemic symptoms during CEA had the best outcome (27).

Our criteria for shunting was drop in rSO_2 values≥20% from baseline values. Only 4 patients (5.3%) in our study received a shunt. Samra et al. used the same criterion. In patients undergoing CEA in cervical plexus block, they found that a relative decrease of ≥ 20% from the pre-clamping rSO_2 values had a high negative predictive value, *i.e.*, if rSO_2 did not decrease, ischemia was unlikely, but a low positive predictive value, *i.e.*, a decrease in rSO_2, may not always indicate cerebral ischemia (28). Moritz et al. reported that a 20% relative rSO_2 decrease from baseline maximized both the sensitivity (83%) and specificity (83%) for the risk of hypoperfusion under local anesthesia (29). Mendonça et al. reported shunt using in 3 cases (2.4%) due to signs and symptoms of cerebral ischemia after carotid artery clamping in patients undergoing CEA in superficial and deep cervical plexus block (30). Mille et al. argued that a relative decrease in $rSO_2$of <20% from preclamping to early cross clamp value had a high negative predictive value. This means that if rSO_2 does not decrease more than 20%, ischemia due to hypoperfusion is not occurring and a shunting is not necessary. Furthermore they suggest that a relative decrease for more than 20% does not always indicate or does not always have correlation to intraoperative neurological complications. They evaluated the reliability of NIRS during CEA under general anesthesia (31). For Ritter et al., cerebral oximetry and a cutoff value of ≥ 19% drop in rSO_2 has a high sensitivity and specify compared to awake testing (32). Pedrini et al. found that NIRS is a reliable monitoring technique during CEA under general anesthesia using a cutoff of 255 or a cutoff of 20% for prolonged hypoperfusion (33).

Some authors applied shunt if the reduction in the rSO_2 values after cross-clamping in the ipsilateral side exceeded 15% or less. Kondov et al. in their study observed a drop of > 15% in rSO_2values on the ipsilateral side in 7% of the patients undergoing CEA during general anesthesia. Furthermore, they have noticed significantly increase of rSO2 values on the contralateral side after cross-clamping compared to baseline in the group where shunting was not done and a statistically significant reduction in values of the rSO_2 on the contralateral side in the patients that required an Internal carotid artery shunt (34). Inčiūra et al. showed that the 10% decrease of the values of rSO_2 in awake patients correlated to clinical cerebral ischemia signs. However in their study they have used one more parameter – stump pressure and their findings were matched well with the stump pressure for cut-off value of ≤40 mmHg (35). On the other hand, Wang et al. revealed that NIRS monitoring results were consistent with findings of transcranial

Doppler monitoring values and a 12.3% decrease of rSO_2 should be adopted as a threshold for intraoperative cerebral hypoperfusion (36).

A possible explanation for different cut-off values is the use of different NIRS oximeters and different generations of the same type of oximeter. Probably, each device should be tested individually. Some authors concluded that NIRS is a safely and a reliable cerebral monitoring technique, but could not identify the cut-off value. Rigamonti et al. tried to find the cut of value of the NIRS in awake patients. Their findings could not identify an rSO_2 threshold that can be used as a predictor alone for shunt placement due to low sensitivity and specificity (37). A contrary to this, Botes et al. confirmed that transcranial cerebral oximetry compared to EEG, is a practical and non-invasive monitoring system with a high sensitivity (100%), but a low specify (38). Pennekamp et al. similar to our study concluded that NIRS may lead as a suitable parameter to exclude patients for unnecessary shunt use and be a predictor for the usage of the selective shunting (39). The same conclusion as in the above mentioned studies was confirmed in the study of Cho and Jang. In this context they concluded that NIRS usage is a safe and reliable monitoring tool cerebral perfusion in terms of postoperative stroke and neurologic symptoms (40).

Conclusion

A drop in near-infrared spectroscopy values of almost more than 20% is a good marker of the need for shunting during cross-clamping in patients undergoing carotid endarterectomy. This is a reliable indication that can identify patients who are at risk of cerebral hypoperfusion during this period. Using a threshold of more than 20% decline in rSO_2 from the baseline during the clamping period helps to prevent unnecessary shunting during CEA.

Limitations and Benefits

Our study has several limitations, firstly – this is a retrospective study and secondly the patients' data were collected from several surgeons that have been conducting the addressed interventions. Thirdly, the sample size of patients is modest thereby not yielding a strong evidence of significance.

This study is the first to be conducted in Macedonia and encourages the vascular faculty to embark on future larger randomized studies proving the objectivity and reliability of NIRS monitoring during the CEA procedure.

Conflict of interest: none.

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HETEROTOPIC PANCREAS IN THE HEPATOBILIARY TRIANGLE

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ABSTRACT

Heterotopic pancreas is migration anomaly characterized by anatomic separation from main pancreas, the most commonly located in upper gastrointestinal tract. The basic histological features of heterotopic pancreas are identical to orthotopic pancreas. Hereby, we describe a case of 55-years-old female that was admitted for elective laparoscopic cholecystectomy. After routine dissection and cholecystectomy, the pathological analysis of the retrieved specimen described heterotopic pancreas in the structure that was regarded as Lund's nodule during the dissection. The ectopic pancreatic tissue comprised of lobules of exocrine pancreatic acini and ducts without any communication to the gallbladder lumen and no islet of Langerhans cells. The heterotopic pancreas was classified as type 2 by Heinrich classification. The incidence of heterotopic pancreas was low, clinical features were atypical, and the preoperative diagnosis was difficult. Because of the risk of pancreatitis, malignant alteration or bleeding, the same should be removed whenever found on exploration.

Key Words: *hepatobiliary triangle, heterotopic pancreas, Lund's nodule.*

Background

Heterotopic pancreas, also known as ectopic pancreas, pancreatic choristoma or pancreatic rest, represents congenital anomaly with distinctive separation of the vascular and ductal continuity between orthotopic and ectopic pancreas.

Hepatobiliary or Calot's triangle, firstly described by Jean Francois Calot in 1891, is defined as anatomic space delineated by cystic duct, common hepatic duct and inferior surface of the liver (1). The cystic artery lies within the boundaries of the Calot's triangle. Lymph node, called Lund's node or Mascagni lymph nodeis situated in the proximity of the cystic artery within the boundaries of Calot's triangle and is important anatomical landmark during laparoscopic cholecystectomy (2).

Case Report

55-years-old female patient, with history of chronic cholecystitis, confirmed ultrasonographically, was admitted to our department for elective laparoscopic cholecystectomy. On admission, the physical examination showed normal sinus rhythm and normal blood pressure. The laboratory results were also within normal parameters. After pneumoperitoneum of 12 mmHg was established, routine exploration of the peritoneal cavity was performed. Upon exploration, the gallbladder was identified and routine dissection was performed. The structures of the Calot's triangle were identified. The cystic duct and the cystic artery were identified and, after the posterior view of safety was obtained, the artery and the duct were clipped and divided. Firm, yellow and round structure with diameter of approximately 1 cm was identified within the perimeter of the triangle and at that moment it was regarded as Lund's node. Typical cholecystectomy was performed and the retrieved specimen was sent for pathology. On macroscopic examination, the gallbladder measured 10 cm in length and was 3.5 cm wide. The wall thickness ranged from 0.3 to 0.5 cm. On cutting open, the mucosa was velvety flattened and single yellow stone 0.7 cm in diameter was found in the lumen of the gallbladder. The region of the neck was carefully examined and firm, yellow nodule with diameter of 1.2 cm was isolated. On microscopic examination, the nodule showed well-demarcated ectopic pancreatic tissue comprised of lobules of exocrine pancreatic acini and ducts without any connection to the gallbladder lumen and no islet of Langerhans cells. The heterotopic pancreas was classified as type 2 by Heinrich classification.

Figure 1. *H&E stain demonstrating heterotopic pancreatic tissue located in pericholecystic fat (x5)*

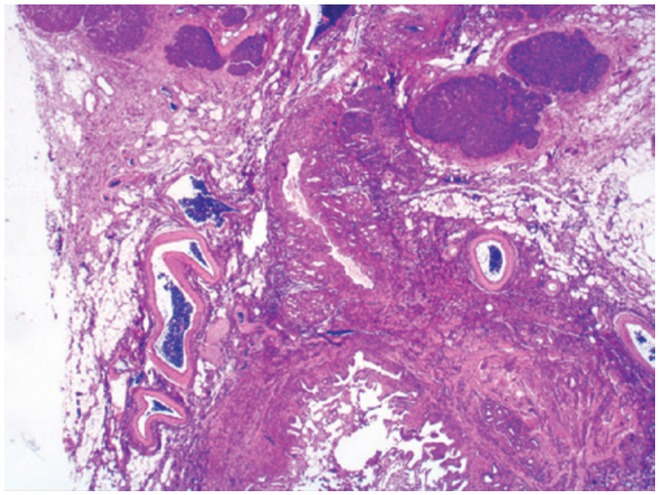


***Figure 2**. H&E stain of gallbladder mucosa with pancreatic tissue (x5)*

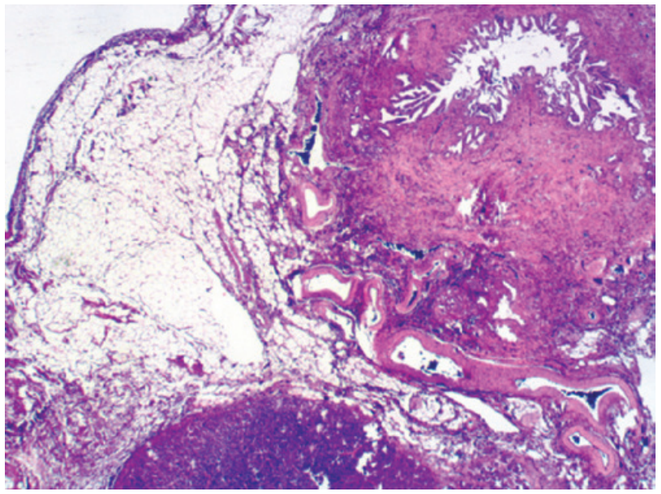
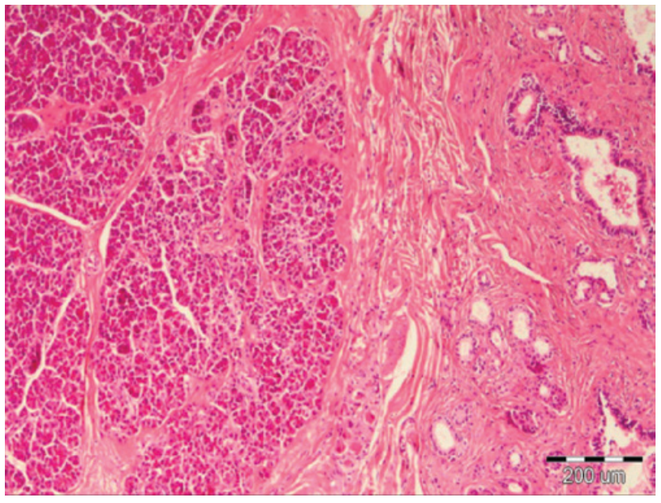


***Figure 3**. H&E stain of pancreatic acini with ducts (x40)*



Discussion

Beside the misplacement theory, there are other theories regarding the embryological basis of heterotopic pancreas, such as metaplasia theory and the omnipotent cell theory (3). Basic hypothesis of the metaplasia theory is migration of endodermal tissue into submucosa and its transformation into pancreatic tissue. Basic hypothesis of the omnipotent cell theory is that endodermal cells differentiate into pancreatic tissue.

Considering the classification of pancreatic congenital anomalies into three categories: fusion, migration and duplication anomalies, heterotopic pancreas is considered as migration anomaly,

where, according to the most plausible misplacement theory, droplets of pancreatic tissue are misplaced throughout developing gastrointestinal tract (4). The main hallmark of heterotopic pancreas is anatomic separation from the main pancreas.

Due to the asymptomatic nature of heterotopic pancreas, the real incidence is difficult to determine and some authors suggest incidence as high as 0.6 to 5.6% in autopsies (5). The most common location is upper gastrointestinal tract (stomach, duodenum and proximal jejunum) while location in liver, gallbladder or biliary tree is less common, comprising 1% of all reported locations (6).

Basic histological features of heterotopic pancreas are identical to orthotopic pancreas. According to the histological features, heterotopic pancreas can be classified into 3 distinctive types: type 1: 1-heterotopic tissue consisting of all the components of normal pancreatic tissue, including acini, ducts and islet cells; type 2: 2-heterotopic tissue consisting of acini and ducts with no islet cells; and type 3: 3-heterotopic tissue consisting of ducts only. This classification was suggested by Heinrich in 1909 and later was modified by Fuentes in 1973 (7).

Three parameters correlate to presence or absence of symptoms: location, size and growth pattern. Heterotopic pancreas of the biliary tree is very rare and there are no available reports that evaluate these parameters in this specific location. In case of gastric presentation, it is considered that size larger than 1.5 cm is more likely to produce symptoms (8). Heterotopic pancreas that involves the mucosal surface is more prone to produce symptoms. In our case, we report nodule 1.2 cm in diameter that is completely detached from the gallbladder. The size and growth pattern in our case provide explanation for absence of symptoms related to heterotopic pancreas. Meticulous analysis of the history of the patient can provide only symptoms that can be correlated to chronic cholecystitis, not heterotopic pancreas. Pathological classification of the nodule as Heinrich type 2 heterotopic pancreas provides further explanation for the asymptomatic nature of the lesion.

During the dissection, there were no macroscopic characteristics that would have differentiated the heterotopic pancreas from regular Lund's nodule. One of the main disadvantages of laparoscopy is the absence of tactile evaluation during the dissection, and the true nature of the nodule was established only after microscopic evaluation. Since heterotopic pancreas has histological characteristics of orthotopic pancreas, pancreatitis, hemorrhage and malignant transformation may occur (9).

Malignant transformation of heterotopic pancreas is defined by location within or in the vicinity of heterotopic pancreas, direct transition between carcinoma and pancreatic structures, while the non-malignant tissue must include acini and ducts (10).

One of the characteristics of heterotopic pancreatitis is mild nature and moderate elevation of the pancreatic enzymes. Explanation can be found in the small volume of the inflamed tissue. Acute pancreatitis can result in pseudocyst formation that can reach significant proportions.

Conclusion

The incidence of heterotopic pancreas is low, clinical features are atypical and the preoperative diagnosis is difficult. Because of risk of pancreatitis, malignant alteration or bleeding, it should be removed whenever found on exploration.

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CASE REPORT UDK: 616.131-007.63:616.24-008.24

PROGRESSIVE DYSPNEA IN PATIENT WITH DILATATION OF MAIN PULMONARY ARTERY AND ITS BRANCHES

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ABSTRACT

Dilatation of the pulmonary artery (PA) can cause compression of the surrounding structures. We are presenting a rare case of dilatation of the main pulmonary artery and its branches with tracheobronchial compression and consecutive atelectasis of the right upper lobe segment. A 73-years-old woman was referred to cardiac examination because of the progressive dyspnea and detected dilated pulmonary artery on chest radiography. A dilatation of the main pulmonary artery and its branches was revealed on the echocardiography, which was later confirmed by the computerized tomography (CT) angiography. On CT angiography there was also detected tracheobronchial tree compression with a consecutive atelectasis of the right upper lobe segment. Because of the progressive dyspnea and CT angiography findings, the patient was referred to a cardiac surgeon for further treatment, but she was rejected because of the high operative risk.

Key Words: atelectasis, progressive dyspnea, pulmonary artery dilatation, tracheobronchial tree compression.

Introduction

The pulmonary artery (PA) is in a spatial relationship with the trachea, the two principal bronchi, the left main coronary artery (LMCA) and the left recurrent laryngeal nerve (LRLN), and its dilatation can cause compression of the surrounding structures. The right pulmonary artery lies anterior to the right principal bronchus, and the left pulmonary artery lies superior to the left principal bronchus. Dilatation of the PA can cause compression of the trachea and/or the two principal bronchi, such as in our case. Despite the mechanical obstruction of the bronchial tree, shortness of breath can occur as a result of many other reasons that require further investigations for establishing the differential diagnosis. Progressive dyspnea can also occur as a result of diseases related to the cardiovascular system, such as congenital and valvular heart diseases, different stages of heart failure, cardiomyopathies, coronary artery disease. Pulmonary hypertension from different etiology may also be the cause of progressive dyspnea, especially during exertion.

Our presentation refers to a rare case of dilatation of main pulmonary artery and its branches with tracheobronchial tree compression and consecutive atelectasis of the right upper lobe segment.

Case Report

A 73-years-old woman was referred to cardiac examination due to progressive dyspnea and detected dilated pulmonary artery on chest radiography, performed before the cardiac examination. She was treated as chronic obstructive pulmonary disease (COPD) for several years, with poor response to bronchodilator therapy. The patient also had arterial hypertension, which was well-controlled with medication. On physical examination, she had wheezing, prolonged expiration bilaterally and absent breathing in the upper part of the right lung. The patient was referred to echocardiography.

The two-dimensional transthoracic echocardiography (TTE) revealed dilatation of the main pulmonary artery with dimension of 34 mm at the level of the valves and more pronounced dilatation after the valves with dimension of 53 mm. There was also dilatation of the branches of the main pulmonary artery. The right pulmonary artery was with more pronounced dilatation of 29 mm than the left pulmonary artery with a diameter of 19 mm. (Image No. 1 (a, b)).

Image 1a. Image 1b.

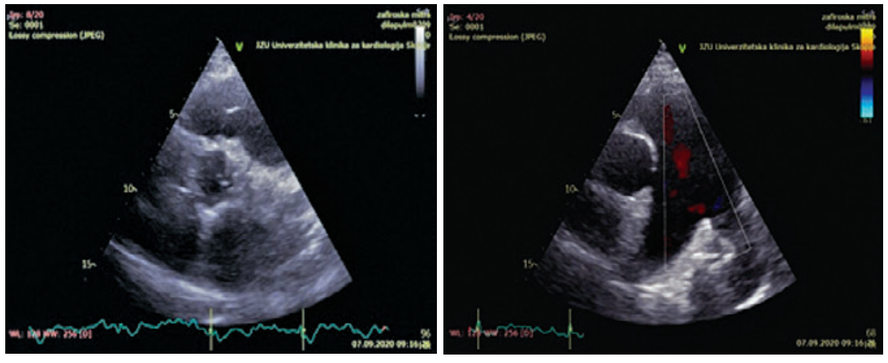

***Image No. 1**. TTE, parasternal short axis view with dilatation of the pulmonary artery at the level of valve (1a), and visualization of the upper part of pulmonary artery and branches showing dilatation of all segments (1b).*

Moderate functional pulmonary regurgitation, due to dilatation of the pulmonary artery, was detected on the Color Doppler echocardiography. The severity of the pulmonary regurgitation was estimated according to the American and European Guidelines with the usage of several integrated parameters, such as vena contracta width, velocity of the regurgitant jet on continuous wave Doppler (CW) and density of the regurgitant jet (1, 2). On the parasternal short axis view (PSAX) we estimated: the diameter of vena contacta – 5 mm, the velocity of the regurgitant jet on CW Doppler – 4,3 m/s, the regurgitant jet was with intermediate density.

According to the European and American Guidelines, all measured parameters in our case graded the pulmonary regurgitation as moderate. (Image No. 2 (a, b)).

Image 2a. Image 2b.

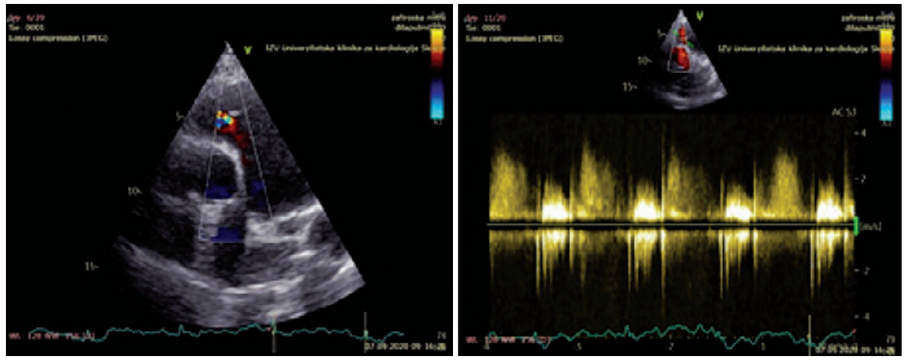

***Image No 2**. TTE, parasternal short axis view, color Doppler imaging showing vena contracta of the pulmonary artery (2a), and CW Doppler of the pulmonary valve with pulmonary regurgitation (2b).*

The right heart cavities were slightly enlarged, but the right ventricular function was normal. The left heart cavities were with normal dimensions and the left ventricular function was normal. Heart structural and functional disorders that could lead to dilation were ruled out with echocardiography and for the discovery of the underlying cause for PA dilatation the patient was referred to CT angiography of the chest.

64-slice CT scan with administration of intravenous contrast was performed. The images obtained from the mediastinal and lung window were analyzed. Images obtained from the mediastinal window revealed significantly dilated main PA, measured at the level of bifurcation with a diameter of 58 mm, with mainly dilated right PA with a diameter of 40 mm, less dilated left PA with a diameter of 30 mm and detected king at the proximal segment of left PA. Images obtained from the lung window showed external compression of the trachea and the two principal bronchi, predominantly to the right principal bronchus and superior lobar branch with present atelectasis of the anterior segment of the right upper lobe. There was no filling defect present that ruled out pulmonary embolism.

Image No3

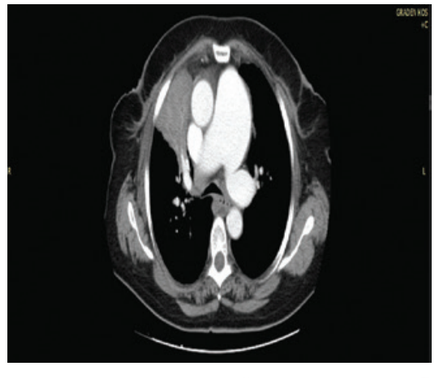

***Image No. 3**. CT scan – mediastinal window, showing significantly dilated main PA (d=58mm), mainly dilated right PA (d=40mm), less dilated left PA (d=30mm) with king of the proximal segment of left PA.*

Image 4a.

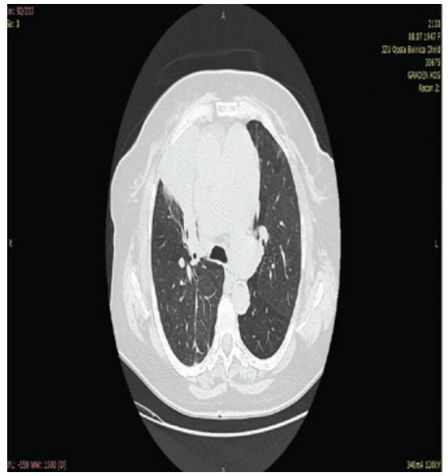

Image 4b.

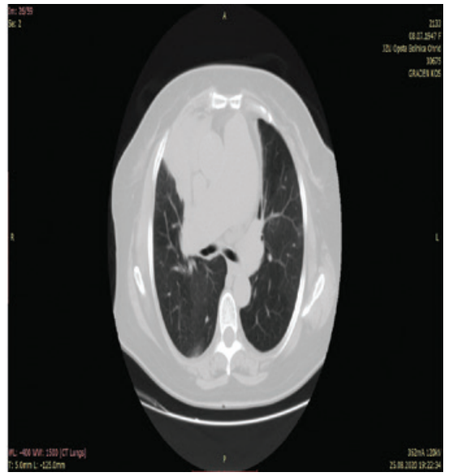

***Image No 4**. CT scan – lung window, showing external compression of the trachea (4a) and two principal bronchi, predominantly to the right principal bronchus (superior lobar branch) and atelectasis of the anterior segment of the right upper lobe (4b).*

Discussion

The most common etiology for PA dilatation is pulmonary hypertension (PH), but there is also another wide spectrum of underlying causes for PA dilatation, such as increased or turbulent blood flow in patients with congenital heart diseases (ASD, VSD, patent ductus arteriosus, valvular pulmonic stenosis), rheumatologic and vasculitic diseases (M. Behçet, Takayasu arteritis), connective tissue disease (Marfan Sy.), infections (tuberculosis, syphilis), trauma or idiopathic dilatation of pulmonary artery, as shown on Table 1 (3).

Table 1. *Known causes of dilated pulmonary artery (3)*

Pulmonary hypertension	**Rheumatologic/vasculitis**
Pulmonary arterial hypertension	Behçet disease
Thromboembolic disease (acute or chronic)	Hughes-Stovin syndrome
Eisenmenger syndrome	Takayasu arteritis
High altitude	
Schistosomiasis	**Connective tissue disease**
	Marfan syndrome
Increased or turbulent blood flow	Loeys-Dietz syndrome
Left-to-right shunting	Ehlers-Danlos syndrome
Patent ductus arteriosus	Cystic medial necrosis
Atrial septal defect	**Infectious**
Ventricular septal defect	Tuberculosis
Valvular pulmonic stenosis	Syphilis
Arteriovenous malformation	Bacterial
Congenital	**Trauma**
Infectious	Blunt
Hereditary hemorrhagic telangiectasia	Penetrating
	Idiopathic

In our case, the dilatation of the pulmonary artery was probably idiopathic, because all causes for dilatation were excluded and all the criteria for idiopathic dilatation of pulmonary artery published by Deshmukh M. et al. (Table 2), were fulfilled, because the dyspnea and the impairment of the respiratory function were due to the extrinsic compression of the trachea and the bronchi from the dilated pulmonary artery (4).

Table 2. *Criteria for idiopathic dilatation of the pulmonary artery (4)*

Deshmukh et al. (1960)
(1) Simple dilatation of the pulmonary trunk with or without involvement of the rest of arterial tree
(2) Absence of abnormal intracardiac or extracardiac shunts
(3) Absence of chronic cardiac or pulmonary disease
(4) Absence of arterial diseases such as syphilis, arteriosclerosis or arteritis
(5) Normal pressure in the right ventricle and pulmonary artery

The dilatation of the pulmonary artery can be asymptomatic or it can manifest symptoms due to the compression of surrounding structures: left main coronary artery, left recurrent laryngeal nerve or tracheobronchial trunk. The wide range of symptoms are: chest pain, left ventricular dysfunction, arrhythmias or sudden cardiac death, if the left main coronary artery is compressed, hoarseness due to paralysis of the left vocal cord, if the left recurrent laryngeal nerve is compressed, wheezing or dyspnea if the compression is at some level of the trachea or the principal bronchi (5). Also, it can result in dissection or rupture of the arterial wall (6).

Normal dimensions of the PA obtained from echocardiography are: 15-25 mm of the main pulmonary artery, 8-16 mm of the right pulmonary artery and 10-14 mm of the left pulmonary artery (7). Normal dimensions of the main pulmonary artery obtained from CT angiography, according to the Framingham Heart Study, were 26.9 mm for women and 28.9 mm for men (8). In our patient there were measured enlarged dimensions of all segments of the pulmonary artery and its branches, on TEE, bigger on CT scan with repercussions of adjacent structures.

The dilatation of pulmonary artery, the most frequently is detected on chest X-ray, because this method is the first line diagnostic method in patients with dyspnea. On chest X-ray the mediastinal structures and/ or hilar structures can superimpose the PA and because of that the measurement is less accurate.

Echocardiography is a method to rule out conditions that may cause dilatation of the pulmonary artery and it is a useful method for accessing the dimensions of the main pulmonary artery and its branches, the morphology of the pulmonary valve, the severity of pulmonary regurgitation if present, as well as the right ventricular function. Another method of visualization, such as CT is useful to establish the diagnosis. With CT angiography, using a contrast, we can obtain more accurate measurements and better differentiation of two nearby objects, versus echocardiography, where the assessment of PA is more difficult and the measurement is less accurate. With CT we

can also detect changes in the tracheobronchial tree and lung parenchyma, such as in our case, with compression of the trachea, the bronchi and atelectasis of the right upper lobe segment.

That was the reason for the small difference in the measured dimensions, especially at the level of the branches, in the images obtained from echocardiography and CT angiography.

Tracheobronchial compression as a result of a dilated pulmonary artery is a rare condition, subsequently lobar collapse, such as in our case – with segmental lobar collapse due to the compression, is even rarer. In article published by Cureus, from year 2019, it had been reported only 10 cases of bronchial compression from dilated PA in adults, found from the literature review (9).

Tracheobronchial compression is a rare condition in adults and more common condition in children, because younger individuals have more elastic airways which are more susceptible to compression (10). In adults, the respiratory symptoms caused by tracheobronchial tree compression, when the reason for the compression is from vascular etiology, are the most common due to aortic aneurysms (11).

The therapeutic option in adult patients, is surgical reconstruction of the pulmonary artery (arterioplasty). Airway stenting is less invasive, but adults are not suitable patients for endobronchial stenting, because there is a risk of wall erosion (12).

Because of the progressive dyspnea and the urgency due to the segmental lobar collapse, the patient was referred to a cardiac surgeon for further treatment. Unfortunately, our patient was rejected from operation because of high operative risk.

Conclusion

Our case is one of the few reported in the literature with significant dilatation of the pulmonary trunk and its branches, which leads to tracheobronchial compression and consecutive atelectasis.

With the usage of two-dimensional color Doppler echocardiography, dilatation of the PA and its branches was detected, with moderate pulmonary regurgitation, and the same was confirmed by CT angiography of the chest. On the CT angiography a compression of the trachea and the two principal bronchi was also detected, predominantly to the right principal bronchus, that lead to consecutive atelectasis of the right upper lobe segment. Symptomatic patients should be referred to a cardiac surgeon for further treatment decision.

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TOCILIZUMAB, CHLOROQUINE AND OZONE THERAPY – TREATMENT FOR SEVERE COVID-19

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ABSTRACT

The coronavirus disease 2019 (COVID 19) in some patients is characterized by severe acute respiratory syndrome (SARS) and multiple organ failure (MOF), that has a rapid progression and is very difficult for treatment. The following report presents a severe case of COVID-19 respiratory infection, where a combination of treatment modalities was used. This case study aims to emphasize the use of chloroquine, anti-interleukin 6 receptor inhibitor-tocilizumab and major ozone autohemotherapy for treatment of severe COVID-19 infection.

Key Words: *chloroquine, COVID-19, ozone therapy, tocilizumab.*

Introduction

The coronavirus disease 2019 (COVID 19) that is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been spreading rapidly since December 2019 and became a pandemic since March 11. COVID 19 has affected more than 62 311 483 people worldwide and 1 453 467 of them died. This data is from 29 November 2020 (1).

The pathogenic mechanism of COVID-19 still remains unclear and at the present time there is no specific antiviral therapy and the vaccination in some countries has just started.

Some of the patients develop severe acute respiratory syndrome SARS and multiple organ failure (MOF) (2,3). This is usually associated to a cytokine storm developed because of over activated immune response. This immune response is characterized with high levels of cytokines including IL6, TNFα, interferon ϒ, IL1, IL12, IL 8 (4-7).

The data we present suggest that a combination of chloroquine, anti-interleukin 6 receptor inhibitor-tocilizumab and major ozone autohemotherapy, stops the progression of inflammatory cascade and achieves good outcome.

Case Description

A 37-years old male patient with a medical history of psychiatric disease (bipolar disorder) was presented with a dyspnea and dry cough. The symptoms had started one day earlier. He had a normothermia and negative epidemiological anamnesis for COVID on hospital admission. His vitals were normal, (AP 135/75 mmHg, heart rate 85/min, respiration rate 20/min) except he had an oxyhemoglobin saturation of 85%.

On the first chest X ray, the picture showed a bilateral pneumonia with ground glass opacity and nodular shadowing in the peripheral and lower parts of the lung. On the second admission day, a real-time polymerase chain reaction (RT-PCR) assay nasopharyngeal swab was taken, which turned out to be negative for SARS-CoV-2. He was started on antibiotics Ceftriaxone and Azithromycin and given oxygen therapy with a face oxygen mask, 5-10 L O_2/min. But over the next week his condition worsened. A new chest X-ray was made and it showed a progression of the pneumonia.

Seven days after the admission, due to respiratory failure (SAT 70%, spO2 45 mmHg, pCO2 45 mmHg, respiratory rate 50/min), he received a noninvasive CPAP ventilation. After two days he could not tolerate the CPAP ventilation, so he was intubated, sedated and put on a control mechanical ventilation. All laboratory values relevant to COVID 19 were examined during treatment (Table 1). Meanwhile a second swab for COVID 19 was taken, which also turned out to be negative. A serology test showed a presence of IgM and IgG antibodies against SARS CoV 2. After that he was started on chloroquine, and 800 mg of tocilizumab was given in a single dose. Values of IL6, before and after tocilizumab were examined (Table 2). Meanwhile a computer tomography (Photo 1) was performed where a typical ground glass pattern for COVID 19 was found.

Table 1. *Laboratory findings in this patient*

	21.04	24.04 (intubation)	27.04	30.04	1.05	2.05	3.05 (extubation)	4.05	5.05	6.05	7.05
CRP		201		10	20.3	13.6	5.9	3.3	4	3.14	1.8
LE	8.1	15.4	11.9	8.7	7.6	8.9	9.6	9.9	8.4	7.6	10.3
ER	6.3	5.26			4.3		3.9	4.15	4.43		5.38
HBG	14	15.1	13.3	12.1	12.9	12.8	11.9	12.5	13.3	14.2	15.6
HCT	42	46.2		35.8		36.9	34.5				47
TR		321	264	196	196	222	215	197	207	198	218
AST		54	38	49	54	45	49	40	31		25
ALT		58	32	39	51	49	56	57	55		53
LDH		628	625								
PROCA		0.11	0.11					0.04			
DDI		19.98		12.36	4.34		4.34	6.08	4.4	4.86	4.98
UREA			9.9	5.6	4.9	4.3	6.5	6.2	6.1		7.3
CREAT			49.5	39.2	39	48	49	46	49		65
GLY			3.5	4.6	4.7	5.4	3.8	4	3.8	4.7	4.7
ALB								31.8	35.7	40.1	
AMILAZA									211	203	199
LIPAZA									994	851	854

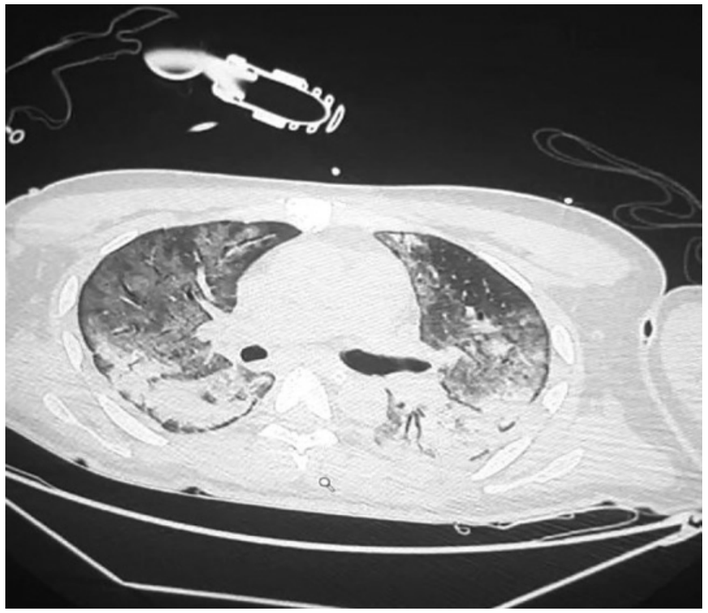
After 12 days on mechanical ventilation and five days after the tocilizumab was given, he was extubated. A control chest X-ray of the lungs showed a regression of the bilateral pneumonia. He was released home after being one month in a hospital.

Table 2. *The values of IL6, before and after tocilizumab.*

	24.04.2020 (Before tocilizumab)	28.04.2020 (After tocilizumab)	Reference range
IL 6	39,92 AU/ml	1064 AU/ml	< 7 AU/ml

Raising of the IL6 level after the administration of tocilizumab is expected, due to the binding of the tocilizumab to the IL6 receptor cites

Photo 1. *CT scan when the patient was intubated*



Discussion

Ongoing clinical trials are performed at the moment in order to find out which drug has the most potential for treating COVID 19, but so far there has not been a clear satisfactory results in large randomized clinical trials (8, 9).

Clinical exacerbation to severe COVID 19 is usually due to hyperactive immune response which results in an inflammatory storm. COVID 19 patients may develop secondary hemophagocytic lymphohistiocytosis (sHLH), an under recognized hyperinflammatory syndrome characterized by a fulminant hypercytokinemia with a development of ARDS and multiple organ failure (10).

Therefore, there is a reason behind a treatment strategy that ameliorates this condition. Tocilizumab is a recombinant anti-human IL-6 receptor monoclonal antibody. It binds to IL6

receptor sites and therefore inhibits signal transmission (11). This drug had been used to treat rheumatoid arthritis (12), juvenile arthritis, giant cell arthritis and cytokine release syndromes caused by chimeric antigen receptor T cell therapies (11, 13). Tocilizumab is well tolerated by these patients with some side effects of leukopenia, increase in liver enzymes and bacterial infections (11, 12). There are few case reports and case series studies published about tocilizumab use in COVID 19, where a positive effect was reported (14-19). But also a caution should be taken when applying an immunomodulatory drug such as tocilizumab (20).

Chloroquine and hydroxychloroquine have both antiviral activity and immunomodulatory effects (21). Hydroxychloroqine has a less toxic profile (reduced ocular toxicity and less drug interactions) and it has more potent in vitro activity against SARS-CoV-2 (22). A randomized control trial performed by Gautret et al., showed that patients who were treated with hydroxychloroquine, were 70% virologically cured compared to 12.5% in the control group (23). Opposite results (absence of reduction of viral clearance) were recently described by another French group (24).

Ozone therapy is an alternative treatment modality that appeared these last months as a supportive therapy for SARS-CoV-2 (25). The mechanism of action of ozone therapy was investigated by Bocci. He found that ozone therapy improves oxygen utilization, oxygen delivery, blood rheology and induces immunomodulation and intrinsic antioxidant system in the body (26, 27). Also ozone has a direct virustatic effect by oxidizing the sulfhydryl groups in cysteine spikes in the coronavirus (28).

We treated this patient with chloroquine, tocilizumab, ozone therapy, antibiotics and supportive therapy. Chloroquine and azithromycin were started first, but there was not a significant improvement for few days. After five days of this therapy, tocilizumab was given and ozone therapy was started. Improvement of the clinical condition was observed few days after the tocilizumab and ozone therapy were given. Which of these treatment modalities had the most to do with the improvement it stays unknown.

Conclusion

The severity of COVID 19 and the lack of proper treatment, has brought an off label use of certain drugs or therapies such as tocilizumab and ozone therapy. This case report represents just one case where unproved treatment was used, with a good outcome. Further control randomized studies need to confirm and establish the use of these treatment modalities.

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IT'S TIME TO REVISE THE TREATMENT OF ACUTE PAIN IN THE EMERGENT SETTINGS

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Introduction

In March 2020 the European Society for Emergency Medicine published the new Guidelines for pain management in emergent situations (1). According to those guidelines, it is obvious that a new dimension – "advancement in pain treatment in emergencies" is added in the work of the Pre/In-Hospital emergency services, as well as for anesthesiologists, as a need for closer intersectional collaboration within the Staff in the emergency services. The main anesthesiology goal is to cope with the pain in pre-, per-, and postoperative period, while the anesthesiologists are responsible for pain management in the emergent settings and in specialized pain treatment services and clinics.

The aim of this review is to actualize the problem of pain, particularly acute pain and its treatment in emergent settings, with an overview to the new guidelines. The focus will be on implications of untreated acute pain in further treatments, with a tendency to help the EMS providers to follow the pain management guidelines.

From a medical and human point of view, pain relief has great importance. The presence of pain announces an upcoming illness. This is an unpleasant sensation and is the first symptom that compels the patients to ask for medical treatment. Pain develops as a result of many diseases, disorders, and conditions in casualties, as after an accidental situation, trauma, burning, heart attacks, postoperative state, malignancy, impaired circulation, and other similar conditions which need corresponding analgesia. It shows a wide variety of feelings and appears as dull, achy, stabbing, shooting, burning, or a pins-and-needles sensation. In general, pain can be acute (physiological) and chronic (pathological). In all those categories, the most often in the emergencies, they are referred to as the complying of acute pain (2).

There are evidences that in the Pre-hospital emergency services (PHES) and in Emergency Departments (ED), the patients who suffer from pain are not treated properly, and the analgesia is insufficient ("oligoanalgesia") (3,4). The reasons for such situation are multi-factorial. One of the possible reasons is the lack of doctors in the Emergency team. In some countries, the PHES are recognized only as a facility for transportation, they are using light analgesic drugs and they are not prepared for "real" pain management. In the EMS equipment the strong analgesic drugs are not stocked and the staff (doctors, nurses, and the providers) is insufficiently educated to treat pain. Also, some of the doctors feel fear of using opioids, because of the abuse, or from the development of the other side effects connected with its use (5).

This situation is almost the same in the most of the countries in Europe. There are only a few countries that developed guidelines for pain treatment in Emergencies. Between them is the French Society for Emergency Medicine, the guidelines in Nederland, UK, and Ireland. What is interesting is that those recommendations differed one to the other. They recommend the use of regional analgesia, the use of the simple assessment tests as visual analgesic scale (VAS), and they realize documentation of the severity of the pain and the pain treatment (at least three times-on arrival, after intervention, and at the end of the medical visit). The use of IV morphine is recommended for the treatment of severe pain or as a part of multimodal analgesia (6). The situation in our country is as follows – there are no guidelines for treatment of the pain conditions in emergencies; the main emergent providers are part of the PHES and their area of work is the transportation of the emergent cases. The hard opioids as morphine are used only for myocardial infarction (MI). The trauma patients receive only weak analgesics (Tramadol), except if they are transported from a provincial hospital to the main trauma center when the transport is done by an anesthesiologist. In the emergency departments (ED) as part of the hospitals, the pain is treated by the anesthesiologists. Only the Medical Center and the City Hospital in Bitola have ED led by the specialized doctors of emergency medicine. The new program for specialization emergency medicine is promising a better situation in the future.

Looking to the recent situation in emergencies the authorities in Europe conclude that the pain in emergency situations was not treated sufficiently. With the aim to make some changes in this field the European society of Emergency medicine order a project and under it auspices the European pain initiative, a body who prepared the "Guidelines for the management of the acute pain in emergent situations was developed" (1).

Pathogenesis of Pain

Pain as a medical problem is still in the middle of many professional debates. It is the first self-defense mechanism signaling for impairment or damaging the tissue. According to the definition from the International Association for the Study of Pain (IASP), it is an unpleasant sensation with emotional experience indicating injury, damage, or potential future damage of the tissue (7). As a sensory symptom, the pain can be acute or chronic. The existence of the pain from the physiological aspects is a positive event that is announcing a problem for possible further damage of the tissue and at the same time is pushing the person for prompt reactions to avoid the noxious stimulus.

The last decade was marked by plenty of new facts about the physiological and psychological basis of pain and its transmission, modulation, and plasticity. A huge number of new receptors and neurotransmitters were developed, and the concept of the body's adaptation to the pain became clearer. The perception of pain as a complex event is not completely understood still. In general, the perception of the pain depends on several concomitants mechanisms: I-pain sensitivity; II-transduction; III-transmission (8).

In normal homeostasis the nerves' terminals in the tissue and organs are inactive receptors (nociceptors). They are activated by mechanical, thermal, and chemical stimuli (noxious stimuli) from the injured tissue where the process of transduction starts. In the place of the damaged tissue, the cells crack, and from the mast cells and neutrophils are released chemical substances. They activate the primary afferent fibers, which are inclusive of the unmyelinated C-fiber and myelinated Aσ-fiber. In the neurons, the chemical noxious stimuli are transformed into electrical energy necessary for the mechanisms of transduction. When this action is completed, it advances to the mechanism of the transmission. It compromises an activity in which the electrical impulses are sent to the spinal cord, where the primary afferents are terminated. C fiber activity increases. Here they synapse with the cells of the dorsal horns at the second-order neuron. At the synapses, the electrical energy transduces as chemical events. The dorsal horn cells are involved in the process of nociception. They are the main relay where the neurotransmitters (glutamate) bind to the receptors (AMPA, NMDA, GABA-A, and others) which take an important role in the modulation of the pain. In the dorsal horn of the spinal cord, it is also created the fast nociceptive withdrawal reflex where the nociceptive signals are transmitted to the interneuron (9, 10).

The released neurotransmitters and neuropeptides enable the action potentials to ascend to the thalamus and midbrain. The pain information from the dorsal horns cells travels to the brain through two main tracts: the spinothalamic tract (preserved and localized the pain) and the spinoreticular tract (involved in descending inhibition of the pain). The spinomesencephalic tract goes from the spinal cord and is synapsing in the periaqueductal gray meter in the midbrain (involved in the modulation of the pain) (11). Descending pathways descend in the dorsolateral fasciculus and synapse in the dorsal horn inhibitory tracts; they are coming mainly from areas in the brainstem (periaqueductal grey matter, the raphe nuclei, and the locus coeruleus) tracts. During its pathway, the pain undergoes modulation in several levels, segmental (the primary afferent neuron and dorsal horn), supra-segmental and cortical. Modulation is a process of inhibition vs. amplification of the pain signals. In this process are included Excitatory substances as excitatory amino acids (EAA), acetylcholine (Ach), Glycine, substance P (sP), Oxytocin, CRH, and the Inhibitory substances as Serotonin, Noradrenalin (NE), and gamma-aminobutyric acid (GABA) (12).

For perception of the noxious stimuli and forming the memory of the pain, the middle and higher levels of the brain are responsible for. Modulation and perception are the components of the plasticity of the pain.

Acute Pain in Emergency Situations

Acute pain appears as a rapid response to trauma, injury, or illness. It has a fast onset and short duration. By its quality, the suddenly appeared acute pain is sharp and severe. If it is treated properly it occurs for a short period of time (less than 3 months) and stops when the underlying cause is removed. The persistence of acute pain is a situation when the self-defending mechanism acts serving to inform the person of dangers, and to take some actions in order to avoid the underlying

conditions. Somatic and visceral pain is distinguished by its ability to localization of the source of the pain, which is characteristic of the nociceptors in peripheral tissues (skin and muscle-somatic) (13).

The etiology for acute pain is different, but it is caused by something specific, such as burns, trauma, infection or cuts, broken bones, surgery, bee stings, dental work, and childbirth (14). Acute pain range from mild to severe and derives from combined effects of stimulated nociceptors, local inflammation, systemic stress response mediators and psychological factors. The most important action is to remove the potentially harmful noxious stimulus if it is directly related to soft tissue damage, and to start immediately to treat the pain. Acute pain is the most common type of pain that goes away when it is treated.

The severity of the pain depends on several factors: the number of stimulated receptors, the duration of the stimulus and the number of mediators released locally (10). Acute pain can be minor acute pain, moderate and severe. Acute pain must be appropriately treated; otherwise, it can easily become chronic pain.

Management of Pain in Emergency Setting according to the Last Guidelines

Nowadays, the treatment of pain has several aspects, including neurobiological, clinical, and behavioral. From the practical reasons, in the management of acute pain, it is accustomed to use the WHO pain relief ladder (1986) for cancer pain. It proposed a "step by step" approach which understands the escalation of the drugs from non-opioid to opioid analgesics (15). The main goals of pain management are early recognition, effective treatment, monitoring and documentation. In the recent guidelines, the focus is put on efficient pain relief as "a right for all patients and presents an integral part of the ethics in medicine" (16).

The most important part of the treatment and at the same time responsible for its effectiveness is the assessment of the pain. The quality and the severity of the pain are assessed immediately at the beginning of the casualty, and it continues during the stay in the emergency settings. A comprehensive assessment permits to identify the different physical, psychological, social and spiritual aspects of the pain.

Assessment

To take an anamnesis is the first step which helps tremendously, where the patient must describe the pain in details. The received information helps in understanding pathophysiology and in the classification of the pain as nociceptive or neuropathic. To assign the appropriate management, it is important to discover: the origin of the pain, the states in which the pain is more intensive, the quality of the pain, the route of propagation of the pain and the degree and the intensity of the pain (17).

There are several methods that help in the evaluation of the severity of the pain. According to the EUSEM Guidelines, Categorical scales, Numerical scale, Visual analog scale, the functional activity scale (FAS) and some assessments in special situations (pediatric and geriatric with cognitive impairments) are recommended.

Non-pharmacological Therapies in Acute Pain

The Chapter 4 in these guidelines is dedicated to the non-pharmacological therapies in acute pain. It explains that these therapies are used as stand-alone method or as a part of the multi-modal therapy, and have limited use in ED. They are used in general to relax the patients and to decrease fear and anxiety. It includes: psychological treatment, transcutaneous electrical nerve stimulation (TENS), Chiro-practice, acupuncture, and similar techniques. At the end of this Chapter a list of the currently available evidences about their use in the treatment of acute pain in emergencies is presented (18).

Pharmacological Therapy in Acute Pain

The pharmacological therapy of acute pain elaborated in the Guidelines is supported with the currently available clinical evidences. Clinical evidence is based on randomized clinical trials, other studies, descriptions and expert opinions, and is ranged on levels from IA to IV.

In normal conditions, the analgesic management in ED starts with the *administration of the different analgesic drugs*. Agents advised in the Guidelines are:

NITROUS OXIDE

It is a very old anesthetic inhaled gas, with a rapid onset and offset of effects which is very well known to the anesthesiologists. It has analgesic properties and is suitable for self-analgesia as inhaling the gas by mask in adults and children older than 5 years. Its common use is with oxygen in mixture 50/50, for childbirth, following the first package of trauma patients, reposition of fractured bones and so on. The main advantage of its use is that it does not mask the injury and its application does not have any side effects (19).

PARACETAMOL

Paracetamol (acetaminophen) is the most commonly used analgesic drug for mild to moderate acute pain. It can be administered orally or IV. The onset of the effect for oral form is slow, so the intravenous way is more appropriate. The maximum recommended doses are 4000 mg/24 h, or 80/kg BW/24 h. It is used in combination with opioids. As a spearing agent, it shows a decrease of the need for opioids (20). It should be used in precaution in patients with liver diseases.

NONSTEROID ANTI-INFLAMMATORY DRUGS (NSAIDs)

The NSAIDs (ibuprofen, diclofenac, ketorolac and naproxen) are suitable drugs for the treatment of mild and moderate acute pain in emergent occasions. Their analgesic effect is due to inhibition of the cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2) enzymes. They have analgesic, antipyretic and anti-inflammatory effects (21). When they are used in combination with opioids they decrease their requirements.

According to the recommendations, the administration of NSAIDs (or IV), is not permitted the first three days of soft tissue injuries (22). But it was shown also that acute pain due to soft tissue injury can be treated successfully with topical NSAIDs (the most commonly diclofenac administered via patches, plasters, and gels) (23).

NSAIDs must be used with precaution in patients with renal diseases and gastrointestinal problems and they are contraindicated in gastrointestinal bleeding and uncontrolled hypertension.

METAMIZOLE

Last decades, Metamizole as an analgesic agent was under a deep scoop. Its use was restricted in many countries in the world because when it was taken for longtime it provoked a life-threatening agranulocytosis. But today the Clinical evidence are changed and it was shown that for renal colic and acute pancreatitis, the use of Metamizole produces effective pain relief (24, 25, 26).

OPIOIDS

It was proven that the most suitable and the most effective pain relief for moderate to severe acute pain in emergency settings is with opioids. Weak opioids (codeine or tramadol) are used for moderate pain and for severe pain strong opioids (morphine and fentanyl). They can be administered via oral and other parenteral routes (IM, Iv, IN, SL, SC and others).

The main adverse effects are nausea, vomiting, urinary retention and respiratory depression. The patient should be monitored in accordance to the protocols.

In the moderate pain, if it is not relieved by the NSAIDs, it is recommended the use of *Codeine*. It is suitable for children >12 years and adults. It is valuable as tablets or suspensions for oral administration (27).

Tramadol is a weak analgesic drug. Its use is convenient for moderate to severe pain. Its formulation is as tablets for oral administration or as ampoules for parenteral application (IM, IV).

When the pain is very severe *Morphine, fentanyl, sufentanil* in target doses, with continuous monitoring are used. They are used as oral prescription, sublingual, nasal and parenteral (28, 29).

KETAMINE

It is recommended to use ketamine in low doses. It is an effective analgesic drug and when it is used in combination with other analgesics shows an opioid-sparing effect. Its formulation is as suspension, intranasal or parenteral way of application (30, 31).

METHOXYFLURANE

Methoxyflurane is an inhalational anesthetic that can be used as an analgesic in emergencies for the relief of moderate to severe pain. It was used as analgesic agents in Australia and New Zealand, and its use was approved in some European Countries (32).

It is very well tolerated by conscious patients with trauma because produces a rapid, effective analgesia. It is recommended for self-administration. The patient is handing the inhaler until the access for other routes for drug administration are established (33).

NERVE BLOCADES

The use of nerve blocs is a safe and opioids sparing method of analgesia in emergencies. Because of the development of anaphylaxis, lidocaine in the ED is currently limited, other local anesthetics are preferable. The local analgesics produce proven analgesic efficacy with a low risk. The method is an invasive procedure that needs special education. It is recommended with a slight sedation (34).

The Implications of Untreated Pain

The main goal of the acute pain treatment is to provide a pain relief with minimal sufferance from the pain or to reduce the pain with minimal side effects. The second goal of the acute pain management is to prevent the acute pain to become chronic.

Insufficient analgesia can also provoke many negative effects to the human health. The experience of pain is tied to emotional, psychological and cognitive factors. It is connected to delayed recovery, healing of the wounds, infections and more important, psychological disturbances. The list of the negative effects of the continuous presence of pain is very long. Between the most important will be mentioned the changes in the immunity, post-traumatic stress disorders, and the implications in hormonal and metabolic functions. The proper control of the acute pain prevents a constant stimulation of neurons and their pathological changes which is maladaptive and no protective leading to chronic pain (35).

In addition, the reaction to pain is complex and individual. Because of individual variation, acute pain management plans should be tailored according the needs of each patient. The magnitude, the severity of the illness and the degree of patients' discomfort, all take part in the formation of the individual's experience to pain (36). Different physiological and psychological phenomena in the body produce modifications of the quality of the pain. The memories of pain episodes, the patients' reactivity to pain, families' and friends' support, religions, personal defense skills, and therapeutic strategies are the most frequent reasons for these modifications (37). The levels of education, culture and tradition have an important part in the formation of the pain experience.

Conclusion

Acute pain is often present in the emergency situations. There is a need for the improvement of the awareness about this problem. The new guidelines offer the possibilities for uniformed and more efficient treatment of acute pain in emergencies. There is also valuable literature where the professionals can easy find the information about the acute pain. For the emergent providers this is a quick method for learning what is promising an increase of the knowledge in this field. The education of the staff is one of the main activities that should be taken in the future.

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HOMAGE TO PROF. VLADIMIR N. ANDONOV

An unfinished conversation

This homage is dedicated to our respected professor Vladimir N. Andonov.

Now, when he is not between us, we are sad, trying to summarize all benefits left behind his personality.

Professor Vladimir Nikola Andonov was our teacher, and for sure I can say, he was more than a teacher! He shared with us his knowledge, he gave to us a part of himself, and he learned us to the attitude of a proud anesthesiologist.

With his character of a strong person, he encouraged us to cope with all misadventures in our profession. In our country, he established a unique, very respectable school of Anesthesiology, Resuscitation and Intensive Care. His pupils were very well accepted in all medical centers around the world, working as locum-tenens, or for longer substitution. Some of them today are working in Medical Centers in Europe and in the USA.

He was a visionary person; his documents for development of the profession in the field of cardio anesthesia, transplantation and neuro-anesthesia written in 1980-es are still actual today. With his sense for the profession, he established the first Clinic of Anesthesiology, Resuscitation and Intensive Care, which was recognized by the immense prosperity.

He wanted to make long conversations with us, about the profession, about our private lives, about our views on life and interpersonal relations. He found a hearty word for everybody of his staff. He was doting on music, and spend many hours in discussion about some music performance. His organization ability was encircled with his written edition. He established the cycles of books edited as "Urgent conditions in medicine": Shock and CPR, Practice in Urgent medicine, Death and dying. His last book named as: "The influence of music in recovery" stayed unedited.

During the preparations of all these books we have many hours of conversation, with many suggestions made by him. These conversations never ended. Even when he was very old, he wanted to say: come on to talk, we have so many things to say each to other.

One of his phrases about our profession will stay for all generations of anesthesiologists in Macedonia: "Hurry lentamente! Hurry and think".

He will stay in our memories as a special person and we will sorrow for him!

May He *Rest In Peace* & *Rise In Glory!*

Prof. Marija Sholjakova

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

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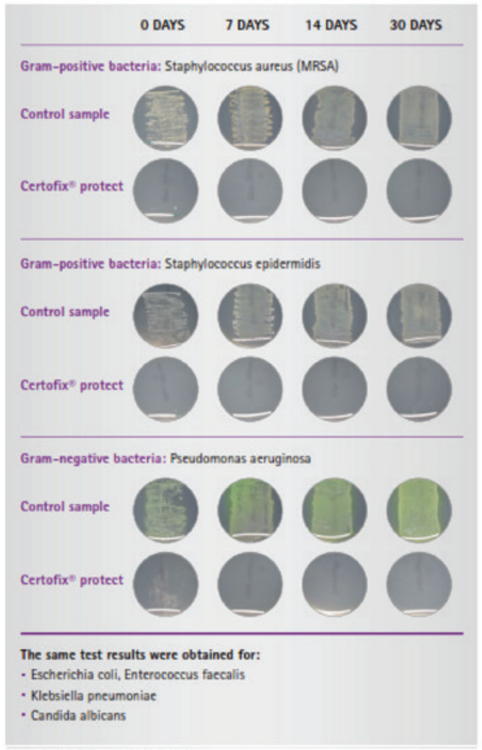

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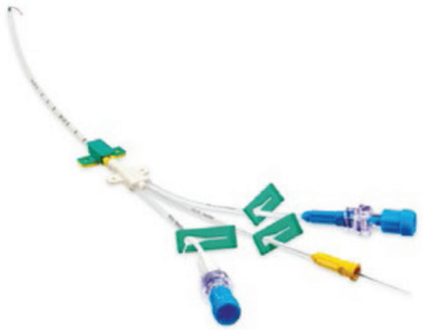

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J. Brunke, T. Riemann, I. Roschke, 30 days antimicrobial efficacy of non-leaching central venous catheters (Poster 063), Critical Care 2016,Volume 20 Suppl 2

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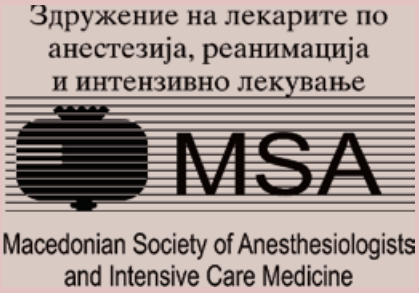
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