ISSN 2545-4366
www.e-mja.finki.ukim.mk

MJA

Macedonian Journal of Anaesthesia

A Journal on Anaesthesiology, Resuscitation, Analgesia and Critical Care

Vol. 4 No 3, October 2020

Journal of the Macedonian Society of Anaesthesiologists
and Macedonian Society of Critical Care Medicine

Publisher:
Department of Anaesthesia and Reanimation, Faculty of Medicine,
"Ss. Cyril and Methodius" University, Skopje, R.N. Macedonia

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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.

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i.v. Paracetamol + NSAID i.v. Paracetamol + rescue medicine	УМЕРЕНА БОЛКА
i.v. Paracetamol + rescue medicine	СЛАБА БОЛКА

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CONTENT

EDITORIAL UDK: UDK: 61:001.891

INTEGRITY IN MEDICAL RESEARCH

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Scientific research in medicine is a fundamental driver of the science's development. From the first autopsies that were secretly performed with the aim of discovering the body structure, until today, research and experiments driven by the desire for knowledge, but also curiosity, have contributed to increasing the huge fund of medical knowledge.

Research in the past, although motivated by noble goals, and driven by the desire to deepen the knowledge about diseases and aid the sick, has often been conducted on vulnerable groups, without regard for their well-being or their rights. Experiences from the events in the concentration camps during the Second World War in Nazi Germany, gave impetus to organize the professional public and the first attempts were made in terms of regulating the scientific research work from an ethical point of view. In 1964, the World Medical Association adopted the Helsinki Declaration: "Ethical Principles for Medical Research Involving Human Subjects" by which signatory states undertake to adhere to the basic ethical principles in the conduct of scientific research in medicine."

The importance and benefit of medical research is also recognized by society, as evidenced by the significant funds and resources donated to scientists and institutions in order to encourage and facilitate research. Unfortunately, not all countries are powerful and rich in funding or at least assisting scientific research, although they are aware of its value and importance. That the state recognizes the importance of research is shown by the fact that doctors have an obligation to publish a number of scientific papers, to participate in congresses in order to be able to renew their license or advance in their academic titles. These imposed formalities, where there are no real incentive and financial support, the motive for research is less about scientific curiosity and the desire to discover something new, to doublecheck certain facts, rather the research process feels like an imposed obligation. That is why we need to talk about the integrity of researchers, the ethical principles and the respect for the basic ethical principles that should guide young researchers.

The integrity of a scientist implies honesty and strong moral and ethical values, from which he does not deviate regardless of the challenges. Intellectual honesty and responsibility for their work are the essence of the scientific profession. In other words, the scientist in scientific research is led by an uncompromising commitment to the truth. The philosopher Francis Bacon, considered one of the founders of modern science, deliberates the scientist to be a seeker of truth, only for the sake of truth.

The integrity of scientific research work means conducting research in a way that allows others to have confidence in the method and the results. There is a great deal of public interest in the latest discoveries, and still great confidence in scientists and institutions. The media greatly contribute to the transmission of sensational discoveries, which are accepted and transmitted without any critical assessment by the professionals. Consider the case of gastroenterologist Wakefield, who together with two colleagues, published a scientific paper in The Lancet in 1998, in which he claimed that the MMR vaccine was the cause of autism. Although the paper was later withdrawn due to several identified shortcomings, including a conflict of interest, it nevertheless caused invaluable damage to the vaccination process and initiated the movement of opponents of vaccines.

Intellectual honesty in scientific research is perceived from the very beginning, at the moment of submitting a proposal for conducting research. Motivated by the desire to obtain a work permit or financial support, one can easily succumb to enriching and exaggerating the results achieved so far, and to the goal and the promises of the expected results. But most misconduct occurs in the research phase and the publication of results. There are several types of misconduct that researchers are subjected to. Inventing or fabricating results is one of the most serious manifestations of dishonesty, which fortunately is not so common. In these cases, the researcher did not do any research, nor did he perform experiments, and published a paper with completely invented results that would confirm hypothesis.

Falsification of results, adjustment of data corresponding to the desired result of the set hypothesis, are more common. It takes a lot of time and effort, with repeated examinations to establish the truth in such cases. How often such irregularities are proven is unknown. The most frequently cited example, at the same time the most naive, is the case that dates back to the 1970 s, when William Summerlin announced that he had successfully transplanted tissue from a black mouse to a white mouse. The commission investigating the case found that he had in fact drawn black spots on white mice with a felt-tip pen. Another interesting case is Dr. Chandra who claimed to have found a multivitamin that has the power to restore the memory lost by dementia. Not only did he invent his own results, but he also invented another author and published a paper in his name confirming his findings.

Plagiarism is the most common way of violating ethical values or misconduct in scientific research work. The classic form of plagiarism is the publication of someone else's scientific work as one's own, or part of the work, without mentioning its author at all. Such cases are becoming less common today, primarily due to the availability of the Internet and the access to many data files of published papers, where similar publications are quickly and efficiently found by crosschecking identical parts of the text.

It is much more common to paraphrase and not cite a particular paper. This means that the author retells the same content in his own words, without stating authorship. It is interesting to note that plagiarism is also considered quoting data from another author, without having insight into the original work, but only quoting from another work.

Plagiarism, acquisition and displaying someone else's work and efforts as your own, has many levels and is rarely seen as a major offense, especially when it comes to only a small copied part. The joke, which is widespread in academic circles, says that copying from one paper is plagiarism, and from several papers it is a scientific paper or dissertation.

Misconduct in scientific research refers to a much larger field of scientific research activity, not just plagiarism, fabrication and forgery of papers. Here, first and foremost, we would mention the appropriate order of citation of the researchers who obtained the results. Very often, the name of the first cited researcher is the one of the manager, the professor, the director, who not only did not dedicate time and effort to the research, but does not event participate in it at all. Young researchers, who often have the greatest burden in conducting research, are listed at the end or not mentioned at all.

Peer review of scientific papers is one of the well-designed tools for verifying the originality of the paper, the work methodology, the results and their discussion. In this way, it is possible to reduce the permeability of those papers that reflect misconduct in the research process. The success of the functioning of these expert commissions depends on the selecting experienced scientists in the field, but the most important thing is their independence. They must not be in any way related to both the research and the individual researchers.

There are still many not-so-striking disregards for the ethical and moral values in the work of researchers. Here are just a few: taking someone else's idea as your own to start a research; concealment and non-transparency in the performance of experiments; election of a benevolent review commission; selection of statistical methods that can confirm the hypothesis, while avoiding the unfavorable ones; non-publication of some of the results that do not support the desired outcome of the research.

Many of these violations and dishonest practices and even scams may be known to other fellow researchers. The procedure for proving misconduct is difficult, time consuming and unpleasant. Most of the colleagues turn a blind eye, do not want to disrupt the quasi-collegial relationship, do not want to be bothered at all with the process of crosschecking the fact and proving the wrong hypotheses. Certain colleagues do not start a discussion due to the belief they hold no professional power, thinking they will not achieve anything. This attitude is also unethical, the silence about the dishonest behavior of another researcher is also dishonest and unethical. The desire not to disturb personal comfort, not to cause inconvenience, unresponsiveness to flagrant violations or misconduct may be the reasons for silence, but it all contributes to disturbing the healthy and ethical atmosphere in the institution where scientific research is conducted. Talking in the hallways, in mutual contact with other colleagues is not a way to improve the atmosphere, on the contrary. In that way, the problem is only relativized, and an atmosphere of mistrust is built, of disrespect for the basic characteristic that everyone who wants to be a scientist should have and that is honesty and respect for moral and ethical values.

As a personal opinion, some authors have stated that fraud and violation of the basic principles of ethics in scientific research work are most common in the field of biomedicine. There is no research on this, nor data on the number of detected frauds compared to other scientific disciplines. But the list of misconduct discovered in the field of scientific research shows that medical experts are really ahead of all other scientists.

This situation is explained by the fact that research in the field of medicine is performed by doctors, whose main professional task is the treatment and care of patients' health. Scientific research is not their primary task, they are forced to divide their time between professional duty as a doctor and research. All this is a great pressure, especially for young doctors who are obliged to do scientific research work, in conditions when they have minimal or no financial support and poor infrastructure. However, despite the difficult conditions in which they are forced to work, not everyone succumbs to the challenge of committing fraud in order to get results more easily. The character of the researcher, the accepted moral values, but also the moral values of the environment have a great influence. The desire for fame, recognition and prominence in the scientific environment, sometimes lucrative motives, are the most common cause of fraud in medical research.

One may not go to jail for violating ethical principles and dishonesty, but the consequences of such actions can be catastrophic for the research doctor. Degradation, shame, moral condemnation, revocation of license, public condemnation, inability to continue working in the field for which he was educated, are just some of the consequences that researchers might suffer from when their dishonest and unethical behavior is exposed.

Ethical values and recommendations are not binding, nor are penalties provided, which is precisely why we should openly talk about and discuss them, so that it becomes part of the researchers' character. Institutions, faculties, laboratories should pay special attention to promote an atmosphere of responsibility and honesty at all levels of scientific research work.

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ORIGINAL RESEARCH UDK: 616.8-009.7-036.81-052

PAIN PATTERNS IN UNCONSCIOUSS CRITICALLY ILL PATIENTS

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ABSTRACT

Critically ill patients may suffer from pain, and it is a challenge to assess pain in patients who are not able to communicate due to their illness. The aim of this study was to analyze pain intensity patterns in one week period after admission to intensive care unit (ICU) and identify period in which patients may have higher need for analgesic drugs. This was an observational study, whereby altogether 30 patients were enrolled. They were assessed with COPT (Critical Care Pain Observation Tool) and BPS (Behavioral Pain Scale) in the first, the 3rd and in the 7th day from admission to the ICU. Patients were assessed in rest, during a non-painful manipulation and during high intensity stimulation. Both COPT and BPS in all 7 days period showed that in rest patients didn't have pain or discomfort, but during high intensity stimulation both scales showed increased pain scores and the highest reactivity to painful manipulations was one week after admission to ICU. Comparing three different patient groups, it was found that trauma patients and surgical patients were more reactive to high intensity stimulation than non-surgical patients.

Key Words: *BPS, COPT, Mechanical ventilation, Pain assessment.*

Introduction

Acute pain is frequently experienced by critically ill patients. Patients could have unwanted physiologic responses to pain, such as increased myocardial oxygen consumption, immunosuppression, hypercoagulability, and persistent catabolism due to the neuroendocrine activation and increased sympathetic tone (12).

It appears that patients in intensive care unit (ICU) tend to receive a large portion of sedation, but a lack of attention has been given towards management of procedural pain. Despite the frequent use of continuous administration of opioids, significant proportion of patients had increases in their level of pain during manipulations that could cause discomfort (1, 2). Continuous sedation and opioid administration are used, but tools to measure pain in sedated patients are not well implemented in everyday practice. Frequent pain assessment is associated with less use of sedative drugs, such as midazolam, as well as shorter duration of mechanical ventilation (MV) and reduced stay in ICU (3, 4).

It is a challenge to assess pain in patients who cannot communicate; therefore, tools like Behavioral Pain Scale (BPS) and Critical Care Pain Observation Tool (COPT) to assess pain level in such patients had been developed. Both scales have been previously validated for mechanically ventilated non-communicating ICU patients (5, 6, 7). COPT has 4 domains while BPS has 3 domains. One of the three BPS domains evaluates upper limb movements. But with COPT there are 2 domains which evaluate body movements and muscles' tension. Other 2 domains in both scales are similar – compliance with MV and facial expressions.

In this study, we evaluated BPS and COPT scores in unconscious ICU patients in 3 conditional states – no active interventions ("at rest"), non-painful intervention (routine oral care) and high intensity stimulation (routine tracheal suction). The aim of this study was to analyze pain intensity patterns during one-week period after admission to ICU and identify a particular time period in which patients may have higher need for analgesic drugs. Secondary aim was to estimate pain patterns in sub-groups of surgical, multiple trauma and non-surgical patients.

Material and methods

This was a prospective observational study done in general ICU in Riga Eastern University Hospital "Gailezers" from 9th of Dcember 2019. to 13the of January 2020. Study protocol was approved by Riga Eastern Clinical University Hospital Medical and Biomedical Research Ethics Committee.

30 patients in total were enrolled. A written informed consent signed by patient was acquired as soon as patient was able to communicate. If patient was not able to communicate and give consent, then it would be taken from a patient's family member. In performing this study there was no deviation from routine standard ICU care.

Inclusion criteria were: 1. Patients who have severely impaired consciousness (GCS 3-8 points); 2. Patients who were unable to report pain; 3. Patients who had MV. MV was performed trough endotracheal tube or tracheostomy tube. Only adult patients (>18 years old) were included.

Exclusion criteria were: 1. Patients with prior central nervous system impairment; 2. Patients with prior paresis; 3. Patients with myopathy; 4. Patients who can report pain; 5. Patients from elective surgery.

While ICU nurses performed standard care for the patients that included oral care and trachea sanation, observations were taken by a single resident doctor. Glasgow Coma Scale (GCS) and Richmond Agitation-Sedation Scale (RASS) were assessed before both procedures. Evaluating GCS verbal response was not measured because of endotracheal intubation. Pain intensity was assessed with COPT and BPS before any procedures – in rest state, then during oral care and afterwards during trachea suction. If there had been any other interventions done, patient had to be at rest for at least 20 minutes before evaluation. Assessment was performed from 10 am to 8 pm.

The COPT consists of 4 domains: facial expression, body movements, muscles' tension and compliance with ventilator for intubated patients or vocalization for patients without endotracheal tube. Each domain is scored between 0 and 2, total score ranges from 0 (no pain) to 8 (maximum pain).

The BPS scale consists of 3 domains: facial expression, movements of upper limbs and compliance with ventilator. Each domain scores from 1 (no response) to 4 (full response). The score ranges from 3 (no pain) to 12 (maximum pain).

According to patients' requirements, ICU physician prescribed analgesics and sedative medication. Routine policy was to keep patients on MV adjusting sedation and analgesia accordingly, with daily interruption of sedation, to assess changes in mental status if appropriate. For sedation, a patient received continuous midazolam infusion and by need it was combined with propofol 50-100 mg/h or thiopental 100-140 mg/h.

Depending on the degree of agitation, patents received fentanyl infusion 0.01-0.05 mg/h which was titrated by ICU staff in accordance to patients' individual needs. Depending on requirements of the patient, non-steroidal anti-inflammatory drugs (NSAID) ketoprofenum of 30 mg 2-3 times daily or dexketoprofenum of 50 mg 2-3 times daily, gabapentin 300 mg 2-3 times daily, paracetamol 0.5-1 g 3-4 times daily, metamizol 1 g 2-3 times daily or ketamine infusion 2-10 mg/h could be administrated. Midazolam sedation maintenance dose in ICU is 0.03-2 mg/h/kg. For statistical analysis we divided patients in 4 groups: those who received midazolam <3mg/h, 3-5mg/h and >5 mg/h, and patients who received midazolam >5mg/h and another sedative agent.

Assessment was performed at 3 time points, firstly, on 30 patients on the first day (the first 24 hours) of admission to ICU, secondly, second assessment on 24 patients took place on the third day (48-72 hours after admission to ICU) and third assessment was performed at seventh day after administration on 13 patients. Before pain evaluation RASS and GCS were assessed. If the patients had been extubated or could actively communicate with body language thereby reporting pain, then they would be excluded from further evaluation. No patient died in this period. Main reasons for exclusion after the first assessment were extubation, gain of ability to communicate pain or transfer to regular ward.

Data were analyzed with SPSS 22 version. Descriptive analysis was used to analyze characteristics related to general health and treatment. Kruskal Wallis Test was used to determine if there were any statistically significant differences in pain scores between patient groups in COPT and BPS.

Results

The results were compiled from measurements taken from 30 patients, which included pain assessment, sedation/agitation assessment by (RASS) and consciousness level evaluated by Glasgow Come scale (GCS). Sedation and analgesic medication were also noted.

Average age of patients was 55 years (IQR 41; 71). Patients were divided in 3 groups according to their diagnosis – nine patients had a surgical diagnosis, 11 patients were diagnosed

with multiple trauma and 10 were non-surgical patients. All patients had MV with Hamilton Medical ventilator mode Adaptive Support Ventilation (ASV).

Results gained from 30 patients evaluated in the first 24 hours are shown in Table 1 (See Table 1).

Table 1. *First measurements in the first 24 hours after admission in ICU (All patients, n=30)*

Scale		Age	GCS	RASS	COPTr	COPTo	COPTt	BPSr	BPSo	BPSt
Median value		55	4	- 4	0.00	0.00	3.00	3.00	4.00	5.00
Percentiles	25	41.75	3	- 5	0.00	0.00	1.00	3.00	3.00	4.00
	75	71.5	5	- 3	0.00	0.00	5.00	3.00	4.00	8.00

COPTr – COPT evaluation during rest, COPTo – COPT evaluation during oral care, COPTt – COPT during tracheal suction, BPSr – BPS during rest, BPSo-BPS during oral care, BPSt – BPS during tracheal suction.

In the first 24 hours there were 9 patients with a surgical diagnosis (See Table 2).

Table 2. *The first 24 hours after admission in ICU in patients with surgical diagnosis. (n=9)*

Scale		GCS(s)	RASS(s)	COPTr(s)	COPTo(s)	COPTt(s)	BPSr(s)	BPSo(s)	BPSt(s)
Median value		5.00	- 3.00	0.00	0.00	3.00	3.00	4.00	5.00
Percentiles	25	3.00	- 4.00	0.00	0.00	2.00	3.00	3.00	4.50
	75	6.00	- 1.50	0.00	0.00	5.50	3.00	4.00	8.00

GCS(s) – GCS in surgical patients, RASS(s)-RASS in surgical patients, COPTr(s) – COPT during rest in surgical patients, COPTo(s)-COPT during oral care in surgical patients, COPTt(s) – COPT during tracheal suction in surgical patients, BPSr(s) – BPS during rest in surgical patients, BPSo(s) – BPS during oral care in surgical patients, BPSt(s) – BPS during tracheal suction in surgical patients.

In the first 24 hours there were 11 patients with a multiple trauma diagnosis (See Table 3).

Table 3. *The first 24 hours after admission in ICU in patients with multiple trauma diagnosis. (n=11)*

Scale		GCS(t)	RASS(t)	COPTr(t)	COPTo(t)	COPTt(t)	BPSr(t)	BPSo(t)	BPSt(t)
Median value		4.00	- 4.00	0.00	0.00	4.00	3.00	4.00	7.00
Percentiles	25	3.00	- 5.00	0.00	0.00	2.00	3.00	3.00	5.00
	75	5.00	- 3.00	0.00	0.00	5.00	3.00	4.00	9.00

GCS(t) – GCS in multiple trauma patients, RASS(t) – RASS in multiple trauma patients, COPTr(t) – COPT during rest in multiple trauma patients, COPTo(t)-COPT during oral care in multiple trauma patients, COPTt(t)-COPT during tracheal suction in multiple trauma patients, BPSr(t) – BPS during rest in multiple trauma patients, BPSo(t) – BPS during oral care in multiple trauma patients, BPSt(t) – BPS during tracheal suction in multiple trauma patients.

In the first 24 hours there were 10 patients with a non-surgical diagnosis (See Table 4).

Table 4. *The first 24 hours after admission in ICU in patients with non-surgical diagnosis. (n=10)*

Scale		GCS(ns)	RASS(ns)	COPTr(ns)	COPTo(ns)	COPTt(ns)	BPSr(ns)	BPSo(ns)	BPSt(ns)
Median value		3.00	- 5.00	0.00	0.00	0.5	3.00	3.00	4.00
Percentiles	25	2.00	- 5.00	0.00	0.00	0.00	3.00	3.00	3.00
	75	4.00	- 3.75	0.00	0.00	2.75	3.00	3.25	5.25

GCS(ns) – GCS in non-surgical patients, RASS – RASS in non-surgical patients, COPTr(ns) – COPT during rest in non-surgical patients, COPTo(ns)-COPT during oral care in non-surgical patients, COPTt(ns)-COPT during tracheal suction in non-surgical patients, BPSr(ns) – BPS during rest in non-surgical patients, BPSo(ns) – BPS during oral care in non-surgical patients, BPSt(ns) – BPS during tracheal suction in non-surgical patients.

Sedation in the first 24 hours admission to ICU is compiled in Table 5 (See Table 5).

Table 5. *Sedation in the first 24 hours (All patients, n=30)*

	Patients	Percent
No sedation	3	10.0
Midazolam <3mg/hour	1	3.3
Midazolam 3-5 mg/hour	12	40.0
Midazolam >5 mg/hour	7	23.3
Midazolam >5mg/hour + another sedative agent	7	23.3

In the first 24 hours 17 patients did not received opioids, 13 patients received fentanil infusion. One patient received gabapentin, one patient received ketamine and 3 patients received non-steroid anti-inflammatory drugs (NSAID's) and 4 patients had paracetamol for analgesia.

During the second assessment which was done 48-72 hours after admission in ICU, 24 patients were evaluated (See Table 6).

Table 6. *The second measurements 48-72 hours after admission in ICU (All patients, n=24)*

Scale		GCS2	RASS2	COPT2r	COPT2o	COPT2t	BPS2r	BPS2o	BPS2t
Median value		5.00	- 3.00	0.00	0.00	3.50	3.00	4.00	6.00
Percentiles	25	4.00	- 4.00	0.00	0.00	2.00	3.00	3.00	5.00
	75	6.00	- 2.00	0.75	1.00	5.00	3.00	4.00	8.00

GCS2 – GCS (48-72 h), RASS2 – RASS (48-72 h), COPT2r – COPT during rest (48-72 h), COPT2o – COPT during oral care (48-72 h), COPT2t – COPT during tracheal suction (48-72 h), BPS2r – BPS during rest (48-72 h), BPS2o-BPS during oral care (48-72 h), BPS2t – BPS during tracheal suction (48-72 h).

In the second assessment there were 8 patients with a surgical diagnosis (See Table 7).

Table 7. *48-72 hours after admission in ICU in patients with surgical diagnosis. (n=8)*

Scale		GCS2(s)	RASS2(s)	COPT2r(s)	COPT2o(s)	COPT2t(s)	BPS2r(s)	BPS2o(s)	BPS2t(s)
Median value		5.50	- 2.00	0.00	0.5	4.50	3.00	4.00	7.50
Percentiles	25	5.00	- 2.75	0.00	0.00	3.25	3.00	4.00	6.00
	75	7.00	- 1.25	1.00	1.75	5.00	3.75	5.50	8.75

GCS2(s) – GCS in surgical patients (48-72 h), RASS2(s) – RASS in surgical patients (48-72 h), COPT2r(s) – COPT during rest in surgical patients (48-72 h), COPT2o(s)-COPT during oral care in surgical patients (48-72 h), COPT2t(s) – COPT during tracheal suction in surgical patients (48-72 h), BPS2r(s) – BPS during rest in surgical patients (48-72 h), BPS2o(s) – BPS during oral care in surgical patients (48-72 h), BPS2t(s) – BPS during tracheal suction in surgical patients (48-72 h).

During the second assessment there were 9 patients with a multiple trauma diagnosis (see Table 8).

Table 8. *48-72 hours after admission in ICU in patients with multiple trauma diagnosis. (n=9)*

Scale		GCS2(t)	RASS2(t)	COPT2r(t)	COPT2o(t)	COPT2t(t)	BPS2r(t)	BPS2o(t)	BPS2t(t)
Median value		4.00	- 3.00	0.00	0.0	4.00	3.00	4.00	7.00
Percentiles	25	4.00	- 4.00	0.00	0.00	2.50	3.00	3.50	5.00
	75	5.50	- 1.50	2.00	2.50	5.50	4.00	5.00	8.50

GCS2(t) – GCS in multiple trauma patients (48-72 h), RASS2(t) – RASS in multiple trauma patients (48-72 h), COPT2r(t) – COPT during rest in multiple trauma patients (48-72 h), COPT2o(t) – COPT during oral care in multiple trauma patients (48-72 h), COPT2t(t) – COPT during tracheal suction in multiple trauma patients (48-72 h), BPS2r(t) – BPS during rest in multiple trauma (48-72 h), BPS2o(t) – BPS during oral care in multiple trauma patients (48-72 h), BPS2t(t) – BPS during tracheal suction in multiple trauma patients (48-72 h).

During the second assessment there were 7 patients with a non-surgical diagnosis (See Table 9).

Table 9. *48-72 hours after admission in ICU in patients with non – surgical diagnosis. (n=7)*

Scale		GCS2(ns)2	RASS2(ns)	COP2r(ns)	COPT2o(ns)	COPT2t(ns)	BPS2r(ns)	BPS2o(ns)	BPS2t(ns)
Median value		4.00	- 4.00	0.00	0.0	2.00	3.00	3.00	5.00
Percentiles	25	3.00	- 5.00	0.00	0.00	2.00	3.00	3.00	5.00
	75	5.00	- 3.00	2.00	0.00	3.00	3.00	4.00	5.00

GCS2(ns) – GCS in non-surgical patients (48-72 h), RASS2(ns) – RASS in non-surgical patients (48-72 h), COPT2r(ns) – COPT during rest in non-surgical patients (48-72 h), COPT2o(ns)-COPT during oral care in non-surgical patients (48-72 h), COPT2t(ns) – COPT during tracheal suction in non-surgical patients (48-72 h), BPS2r(ns) – BPS during rest in non-surgical (48-72 h), BPS2o(ns) – BPS during oral care in non-surgical patients (48-72 h), BPS2t(ns) – BPS during tracheal suction in non-surgical patients (48-72 h).

The use of sedation in patients admitted after 48-72 hours to ICU is compiled in Table 10 (See Table 10).

Table 10. *Sedation in 48-72 hours after admission in ICU (All patients, n=24)*

	Patients	Percent
No sedation	5	20.8
Midazolam <3mg/hour	3	12.5
Midazolam 3-5 mg/hour	11	45.8
Midazolam >5mg/hour	2	8.3
Midazolam >5mg/hour + another sedative agent	3	12.5

48-72 hours after administration, 12 patients did not receive any opioid analgesia and 12 had fentanyl infusion. Three patients received gabapentin, 5 received NSAID's and 1 patient had paracetamol for analgesia.

During the third assessment which was 7 days after admission in ICU 13 patients were evaluated (See Table 11).

Table 11. *The third measurements 7 days after patient admission in ICU (All patients, n=13)*

Scale		GCS3	RASS3	COPTr3	COPTo3	COPTt3	BPSr3	BPSo3	BPSt3
Median value		7.00	- 1	0.00	0.00	5.00	3.00	4.00	7.00
Percentiles	25	5.00	- 2.5	0.00	0.00	3.00	3.00	4.00	6.00
	75	8.00	0	0.00	1.00	6.00	3.00	4.50	7.50

GCS3 – GCS (one week), RASS3 – RASS (one week), COPTr3 – COPT evaluation during rest (one week), COPTo3 – COPT evaluation during oral care (one week), COPTt3 – COPT during tracheal suction (one week), BPSr3 – BPS during rest (one week), BPSo3-BPS during oral care (one week), BPSt3 – BPS during tracheal suction (one week).

7 days after admission to ICU there were 5 patients with a surgical diagnosis (See Table 12).

Table 12. *One week after admission in ICU in patients with surgical diagnosis. (n=5)*

Scale		GCS3(s)	RASS3(s)	COPT3r(s)	COPT3o(s)	COPT3t(s)	BPS3r(s)	BPS3o(s)	BPS3t(s)
Median value		8.00	- 1.00	0.00	0.00	6.00	3.00	4.00	8.00
Percentiles	25	7.00	- 1.00	0.00	0.00	4.50	3.00	4.00	6.00
	75	9.50	1.00	2.00	3.00	6.50	3.00	5.00	9.00

GCS3(s) – GCS in surgical patients (one week), RASS3(s) – RASS in surgical patients (one week), COPT3r(s) – COPT during rest in surgical patients (one week), COPT3o(s)-COPT during oral care in surgical patients (one week), COPT3t(s) – COPT during tracheal suction in surgical patients (one week), BPS3r(s) – BPS during rest in surgical patients (one week), BPS3o(s) – BPS during oral care in surgical patients (one week), BPS3t(s) – BPS during tracheal suction in surgical patients (one week).

7 days after admission to ICU there were 5 patients with a multiple trauma diagnosis (See Table 13).

Table 13. *One week after admission in ICU in patients with multiple trauma diagnosis. (n=5)*

Scale		GCS3(t)	RASS3(t)	COPT3r(t)	COPT3o(t)	COPT3t(t)	BPS3r(t)	BPS3o(t)	BPS3t(t)
Median value		6.00	- 1.00	0.00	0.00	5.00	3.00	4.00	7.00
Percentiles	25	6.00	- 2.00	0.00	0.00	4.50	3.00	4.00	7.00
	75	7.50	0.00	0.00	1.00	5.50	3.00	4.50	7.00

GCS3(t) – GCS in multiple trauma patients (one week), RASS3(t) – RASS in multiple trauma patients (one week), COPT3r (t) – COPT during rest in multiple trauma patients (one week), COPT3o(t)-COPT during oral care in multiple trauma patients (one week), COPT3t(t) – COPT during tracheal suction in multiple trauma patients (one week), BPS3r(t) – BPS during rest in multiple trauma patients (one week), BPS3o(t) – BPS during oral care in multiple trauma patients (one week), BPS3t(t) – BPS during tracheal suction in multiple trauma patients (one week).

One week after admission to ICU there were 3 patients with a non – surgical diagnosis (See Table 14).

Table 14. *One week after admission in ICU in patients with non – surgical diagnosis. (n=3)*

Scale		GCS3(ns)	RASS3(ns)	COP3r(ns)	COPT3o(ns)	COPT3t(ns)	BPS3r(ns)	BPS3o(ns)	BPS3t(ns)
Median value		4.00	- 3.00	0.00	0.0	3.00	3.00	4.00	6.00
Percentiles	25	3.00	- 5.00	0.00	0.00	2.00	3.00	3.00	5.00
	75	4.00	- 3.00	0.00	0.00	3.00	3.00	4.00	6.00

GCS3(ns) – GCS in non-surgical patients (one week), RASS3(ns) – RASS in non-surgical patients (one week), COPT3r(ns) – COPT during rest in non – surgical patients (one week), COPT3o(ns)-COPT during oral care in non – surgical patients (one week), COPT3t(ns) – COPT during tracheal suction in non – surgical patients (one week), BPS3r(ns) – BPS during rest in non – surgical (one week), BPS3o(ns) – BPS during oral care in non – surgical patients (one week), BPS3t(ns) – BPS during tracheal suction in non – surgical patients (one week).

The use of sedation for patients admitted after one week to ICU is compiled in Table 15 (See Table 15.)

Table 15. *Sedation 7 days after patient admission in ICU (All patients, n=13)*

	Patients	Percent
No sedation	3	23.1
Midazolam <3mg/hour	4	30.8
Midazolam 3-5 mg/hour	5	38.5
Midazolam >5mg/hour	0	0
Midazolam >5mg/hour + another sedative agent	1	7.7

After one week, fentanyl infusion was administered to 1 patient, other 12 patients had no more need for opioid analgesia. Five patients received gabapentin, 2 patients received NSAID's for analgesia.

Patients with surgical diagnosis, multiple trauma diagnosis, and non-surgical diagnosis were compared, in order to find statistically significant differences in their level of discomfort measured by COPT and BPS in rest, during oral care and during tracheal suction. Statistically significant

difference was found between sub-groups only during tracheal suction – COPTt (during tracheal suction) H value 7.882, p value 0.019; BPSt (during tracheal suction) H value 10.107, p value 0.006. Surgical and trauma patients were more reactive to high intensity stimulation compared to non-surgical patients (See Table 16).

Table 16. *Summary of Kruskall Wallis test analysis. (n=30)*

	COPTr	COPTo	COPTt	BPSr	BPSo	BPSt
Kruskal-Wallis H	1.090	0.331	7.882	1.090	5.042	10.107
P	0.580	0.847	0.019	0.580	0.080	0.006

COPTr – COPT evaluation during rest, COPTo – COPT evaluation during oral care, COPTt – COPT during tracheal suction, BPSr – BPS during rest, BPSo-BPS during oral care, BPSt – BPS during tracheal suction.

Discussion

When comparing different measurements in time, it was found that the most reactive to high intensity stimulation patients were after one week after administration to ICU. In a different study, which was made in brain injury patients, it was found that during high intensity stimulation which was also tracheal suction pain score with COPT scale reached minimum in 3rd or 6th day, then increased on day 9, and reduced again in day 14 (8). Difference could be due to different patients' groups, as this study enrolled patients with surgical and non-surgical diagnosis and multiple trauma patients. In both studies early increase in reactivity to high intensity stimulation were associated to improvement in consciousness level. GCS and RASS showed improvement in patient's consciousness in time, the same pattern was found in pain scores during high intensity stimulation. Same findings that linked improvement in consciousness level and higher reactivity to high intensity stimulation were in previously mentioned study, which evaluated patterns of pain scores in patients with brain injury, even though the time pattern was different (8).

In our study during all 3 assessments, patients did react to high intensity stimulation (tracheal suction). In the first measurements which were taken in first 24 hours after admission to ICU, patients reacted to tracheal suction with 3 points increase in COPT scale and 2 points increase in BPS. This was the lowest pain intensity during tracheal suction in all 3 measurements. During second assessment, the increase was in COPT 3.5 points and BPS 3 points from the rest to tracheal suction and in one week after admission to ICU pain score showed increase in COPT by 5 points and in BPS by 4 points, which was the largest. Consciousness level could be one of the reasons for this raising in reactivity to painful manipulation, which did improve in each time period when measurements were taken. As mentioned previously, there is a pattern that links improvement in consciousness and pain scores during highly stimulating manipulations. Other reason could be that in time, fewer patients had sedation and less opioids were administered. As both scales showed higher pain levels after time during highly stimulating manipulation, it is necessary that patients receive more short – lasting analgesics during highly stimulating manipulations. Prolonged sedation is associated to longer stay in ICU and in hospital, and an increased in-hospital mortality rate (9). It is a good practice to adjusts and reduce sedation over time and this study showed that there was no baseline pain in all 7 days period for all patients sub-groups, but doing so it is important to monitor procedural pain and to adjust analgesia accordingly. It could be beneficial for those patients, if they would receive more short-lasting opioid bolus or use of topical lidocaine on airways to reduce discomfort during tracheal suction. To find that patients need additional analgesics for painful manipulations, such as tracheal suction which was examined in this study, but also patient turning, catheter placement and other frequently performed manipulations or to find which patient is receiving higher opioid doses than necessary, it is necessary to document patients' pain with validated pain evaluation scale (4, 10, 11).

Comparing 3 different patients' sub-groups, it was found that trauma patients and surgical patients were more reactive to pain than non-surgical patients. All patients in the sub-groups had sufficient baseline analgesia and sedation. These obtained results could be related to initial admission diagnosis to ICU. Overall, nonsurgical patients had more severe neurological damage than surgical or trauma patients.

Conclusion

In all 3 assessments through the first week after admission to ICU patients responded to painful stimuli and the highest reactivity to it was after one week from admission to ICU. While comparing 3 different patients' groups, it was found that trauma patients and surgical patients were more reactive to high intensity stimulation than non-surgical patients.

Acknowledgment and author contribution

There is no conflict of interest.

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HARVESTING BUCCAL MUCOSA UNDER LOCAL ANESTHESIA – FEASIBILITY AND ACCEPTANCE FOR SUBSTITUTION URETHROPLASTY

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ABSTRACT

Background: The management of male urethral strictures is complex. In recent years, open reconstruction using a buccal graft has become the preferred primary treatment modality over repeated minimally invasive options. Hereby we describe the feasibility and safety of buccal mucosa harvest under local anesthetic agent infiltration for urethroplasty.

Materials and methods: We retrospectively analyzed all patients who underwent open urethral reconstruction graft surgery with buccal mucosa harvest under local anesthesia between October 2013 and September 2020. Demographic data of the patients, length of the graft needed for urethroplasty, pain during and after the harvest, donor site complications were considered and analyzed.

Results: During this period 18 male patients with anterior urethral strictures underwent open urethral reconstruction using a buccal mucosa graft harvested under local anesthesia. All procedures were done by a single surgeon, except in three cases were a buccal nerve block was used to anesthetize the soft tissues and periosteum buccal to the mandibular molars. The mean harvested graft length was 4.81 cm (+-2.8 cm) and the mucosa was closed after harvesting. There was no need for general anesthesia. Sixteen patients (88.88%) reported that it was "easy" to maintain the mouth open during the procedure. In all of them except in one, there was no significant pain present during or after the harvest. Only one patient reported a donor site hematoma after the procedure that required gauze packaging.

Conclusion: Buccal mucosa harvest under local anetshesia is feasable, save and acceptable for the patients who underwent urethroplasty for urethral stricture disease.

Key Words: *Buccal mucosa, local anesthesia, reconstructive, urethroplasty*

Introduction

The management of male urethral strictures is complex. In recent years, open reconstruction using a buccal mucosa graft has become the preferred primary treatment modality over repeated minimally invasive options (1). Various urethroplasty techniques have been described including dorsal or ventral onlay, dorsal inlay, combined dorsal inlay plus ventral onlay, double buccal mucosa graft, Kulkarni's urethroplasty and two-stage urethroplasty (1-3). The inherent properties of buccal mucosa that favors early imbibition and good acceptance rate have earned buccal mucosa the status of "gold standard" tissue for substitution urethroplasty (4).

The harvest of buccal mucosa has been traditionally done under general anesthesia with preferably nasopharyngeal or oropharyngeal intubation. Many centers have accepted the "two surgeons approach" where otorhinolaryngologist is simultaneously harvesting the buccal mucosa to shorten the operation and thus the anesthesia time (5-6). However, since the introduction of buccal mucosa urethroplasty in 2013 in our center, all buccal mucosa harvest has been done by a single urologic surgeon mostly under general anesthesia.

The regional anesthetic techniques have many advantages that are well documented and outweigh the risks that may be associated to general anesthesia.[6-8]. In other to avoid the risk that may be associated to general anesthesia, we have harvested the buccal mucosa under local anesthetic agent infiltration in some patients. Hereby we report our experience on the feasibility, safety, and acceptance of buccal mucosa harvest for urethroplasty under local anesthesia.

Materials and Methods

We analyzed all patients who underwent open urethral reconstruction with buccal mucosa harvest under local anesthesia between October 2013 and September 2020. Demographic data of the patients, length of the graft needed for urethroplasty, information on previous repair, location of the stricture, donor site complications were considered and data were analyzed.

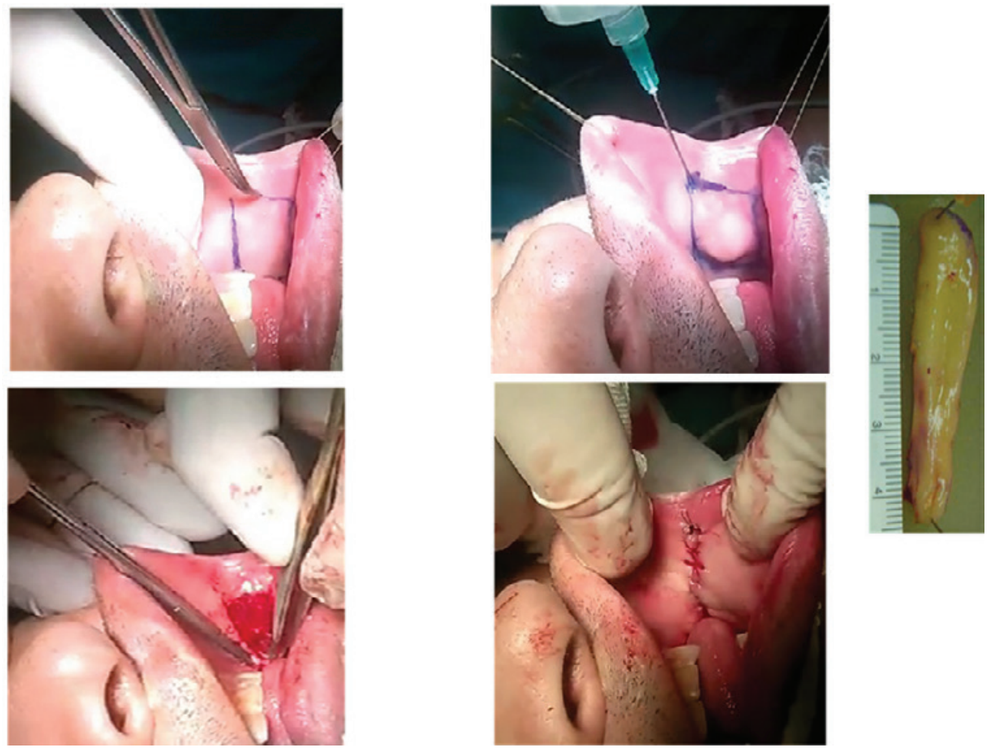
Preoperative Evaluation

A detailed history and physical examination were performed in all patients. Basic biochemical evaluation, urine culture and retrograde urethrogram was done. The later showed us in the most of the cases the anatomy and exact location of the urethral stricture. In all patients a preoperative cystoscopy was performed. Informed consent was obtained in all patients.

Surgical Technique

Surgical exposure for the urethroplasty was determined based on location of the stricture. However, all of them had buccal mucosaharvest under local anesthesia. The patient was placed in lithotomy position following spinal anesthesia for bulbar stricture disease. A silk-0 suture on an atraumatic needle was applied to the dorsal aspect of the glans for retraction. The urethral stricture was assessed and exposure was done as previously described (2,12). The preparation of the head and neck was done to expose the mouth for proper access to the donor site. Two stay stitches were placed on upper and lower lip for retraction and better exposure of the inner chick. Simultaneously, the patient was asked to open his mouth as wide as possible and the Stensen's duct opening was identified, noted, and avoided. The desired length of the buccal mucosa was marked out with a marker before infiltration (Figure 1 A). The cheek mucosa was infiltrated with 5 – 10 mL of 2% lidocaine with 1% adrenaline under the surface of the mucosa to be harvested, depending on the length of stricture to be repaired, using 23gauge needle (Figure 1B). After waiting for about 2 minutes, to allow for effective anesthesia of the area, a rectangularshaped piece of mucosa graft was excised avoiding the underlining buccal muscles (Figure 1 C). The patient was allowed to rest, by closing the mouth and swallow intermittently. Hemostasis was secured with pressure and suture ligation. No electro-cautery was used. The graft bed was closed with 5/0 PDS suture (Figure 1D) and a gauze pack applied which was removed two hours after the urethroplasty was done. In addition, an ice pack was applied on the outer side of the chick to decrease the postoperative edema. The graft was then prepared by trimming the sub-mucosal fat before being used for the urethral reconstruction.

Figure 1



Intraoperative images showing the technique and location of local anesthesia. A. The desired length of the graft is marked, B. The cheek mucosa was infiltrated with 5 – 10 mL of 2% lidocaine with 1% adrenaline under the surface of the mucosa, C. A rectangularshaped piece of mucosa graft was excised D. Donor site closure with 5/0 PDS.

In three patients a buccal nerve block also known as the (long buccal) was used to anesthetize the soft tissues and periosteum buccal to the mandibular molars. The buccal nerve block has a high success rate due to the buccal nerve's location just under the soft tissue and not within the bone. The landmarks are the mandibular molars and the mucobuccal fold. The target area and injection site is located distal and buccal to the most distal molar in the arch on the anterior border of the ramus. The bevel of the needle should be towards the bone and inserted at a depth of 1-3 mm with the buccal soft tissue lateral and taut. After negative aspiration 3 ml Lidocaine 2% was applied.

Results

During this period, 18 male patients with anterior urethral strictures underwent open urethral reconstruction using a buccal mucosa graft harvested under local anesthesia. The mean age of the patients was 55 years (42 – 70). All procedures were done by a single surgeon (OI) except in three cases were a buccal nerve block was used by an attending anesthesiologist (AD). The mean harvested graft length was 4.81 cm (+-2.8 cm) and the mean operative time of buccal mucosa extraction was 22+-5.6 min. There was no need for general anesthesia.

The most of the urethral strictures were located in the penile and bulbar parts of the urethra accounting for 12 (66.6%) and 5 (27.7%) respectively, with only one (5.5%) in the membranous region. Ten patients (55.5%) reported previous surgeries, optical urethrotomies in seven patients (38.8%) and urethroplasties in three (16.6%).

Sixteen patients (88.88%) reported that it was "easy" to maintain the mouth open during the procedure, whereas only two (11.1%) reported difficulties to maintain the mouth open. In all cases two stayed stitches on upper and lower lip facilitated the donor site exposure. In all cases, except in one, there was no significant pain present during the harvest. Using the numeric rating scale (NRC) to assess pain, two hours after the harvest no pain was present in all patients. The same was true when patients were asked the next day or 24 hours after the surgery. Only one patient reported a donor site hematoma after the procedure that required gauze packaging. In the early postoperative period, the most of the patients found it difficult to open the mouth especially in the first two days. However, the third day sixteen patients (88.8%) were able to open their mouth properly without difficulties. All patients were able to drink water on the day of the surgery and it took 2 days before thay could start taking soft food and normal diet. There was no report of postoperative swelling or numbness of oral cavity.

Only one patient reported inner chick hematoma one month after the surgery due to anticoagulant therapy that was managed by maxillofacial surgeon. There was no report of any change in salivation following the buccal mucosa harvest and no oral infection was reported. Interestingly, all patients admitted that the perineal and/or penile wound was more painful when compared to the oral wound. The most of the patients (94.4%) were willing to repeat the buccal mucosa harvest under local anesthesia, if necessary. Only one reported discomfort and painful experience.

Discussion

Urethral stricture is a common disease. The surgical approach is based on the stricture location, length and etiology (3). In recent years, open reconstruction of the urethra with free buccal mucosa graft emerged as a preferred technique of surgical management of stricture disease (9). The qualities of buccal mucosa, its histological properties, as well as easiness of handling have been comprehensively elucidated (10).

Traditionally for buccal mucosal graft urethroplasty, nasal or oral endotracheal intubation anesthesia is recommended for harvesting the graft from the oral cavity. In this study, a technique of graft harvesting under local anesthesia using 2% lidocaine solution with 1% adrenaline is described in patient with spinal anesthesia. Vasoconstrictor and local anesthetic infiltration prevents bleeding and, respectively, provides intraoperative analgesia. This method requires a cooperative patient, but saves the morbidity of general anesthesia. When graft harvesting, care must be taken not to damage the Stensen's duct. Furthermore, we recommend that coagulation not to be used. Sufficient hemostasis can be achieved by compression, leaving a soaked swab in the chick pouch for 2 hours after the harvest. In addition, an ice pack should be applied on the outer side of the chick to decrease the postoperative edema. Of note, in our institution the same technique is used for all buccal mucosa urethroplasties including the ones under general anesthesia. By doing so, we minimize the patient's discomfort postoperatively. However, with this study we show that this technique is feasible, safe and acceptable in patient who underwent urethroplasty in spinal anesthesia.

There are only two reports where spinal anesthesia is combined with local infiltration for buccal mucosa harvesting (11, 12). Ajape et al has described 102 patients that underwent urethroplasties with buccal mucosa harvest under local anesthesia and concluded that it is feasible and safe (12). Our observation is in agreement with these reports. In addition, when asked, 17 out of 18 patients would repeat the local anesthesia harvest if necessary suggesting good acceptance rate ofthis procedure.

Conclusion

In conclusion, our observation led further support to the feasibility, safety and acceptance of buccal mucosa harvest under local anesthesia. A larger randomized and prospective study is needed to confirm these findings.

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CASE REPORT UDK: 616.447-006.55-089.87

PRIMARY HYPERPARATHYROIDISM INDUCED BY AN ECTOPIC ADENOMA, INITIALLY PRESENTED AS BROWN TUMOR OF THE TIBIA

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ABSTRACT

The classic manifestation of unchecked, advanced hyperparathyroidism is the brown tumor, a non-neoplastic giant cell osteomedullary lesion.

We report a case of, these days rarely seen manifestation of advanced hyperparathyroidism, brown tumor due to an ectopic mediastinal parathyroid adenoma. A 63-years-old woman presented with an expansile osteolytic lesion of the right tibia on the radiographic images. Because of the suspicion of primary or secondary bone tumor, bone scintigraphy was performed. The bone scan was indicative of metabolic bone disease. Furthermore, laboratory investigations were obtained that revealed hypercalcemia, hypophosphatemia, increased level of alkaline phosphatase, and parathyroid hormone. Subsequently, ultrasound of the neck was performed, but no enlarged parathyroid glands were detected, so the patient underwent dual-phase 99mTc-methoxy-isobutyl-isonitrile (MIBI) parathyroid scintigraphy using a hybrid SPECT/CT gamma camera. The MIBI scan showed ectopic hypermetabolic parathyroid tissue in the anterior mediastinum, as well as an additional appearance of focal radiotracer uptake in the sternal end of the right clavicle, suggesting the presence of a brown tumor. After thorough clinical workup, the diagnosis was in favor of primary hyperparathyroidism and the patient underwent surgical resection of the ectopic parathyroid gland with gamma-probe guidance, later histopathologically confirmed it to be a parathyroid adenoma. Postoperatively her PTH level dropped and the electrolyte status normalized within 6 months.

Osteolytic brown tumors can easily imitate bone malignancy and should be evaluated with caution. The use of intraoperative gamma-probe guidance could support the complete removal of the parathyroid adenoma tissue ensuring the surgical and therapeutic success for the patient.

Key Words: *brown tumor, ectopic parathyroid adenoma, MIBI scintigraphy, primary hyperparathyroidism.*

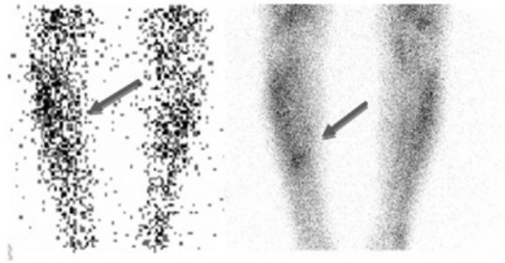
Introduction

Primary hyperparathyroidism (PHPT) is a condition in which one or more of the parathyroid glands become overactive and secrete excess amounts of parathyroid hormone (PTH), thus presenting with disturbances mainly in the calcium homeostasis. It is the most frequently present in middle-aged women (1). About 80% – 85% of the cases of PHPT are caused by a solitary benign parathyroid adenoma, but rarely it might be related to a chief cells hyperplasia or parathyroid carcinoma (2). Ectopic parathyroid adenomas report for approximately 1 – 3% of all parathyroid tumors and the most of them develop in the anterior mediastinum (3). The classic manifestation of unchecked, advanced hyperparathyroidism is the brown tumor, a non-neoplastic giant cell osteomedullary lesion. It presents as a component of a metabolic bone disease also known as *osteitis fibrosa cystica* (OFC) *(generalisata)* or Recklinghausen's disease of bone (4). Cases of large hyperfunctioning parathyroid adenomas found in an ectopic mediastinal location, presenting simultaneously with OFC, have been rarely described. Here we present a case of a female patient with PHPT caused by an ectopic mediastinal parathyroid adenoma. Interestingly enough, the first clinical manifestation of the disease was a painful bone lesion initially suspected for malignancy, but later proved to be part of metabolic bone disease.

Case Report

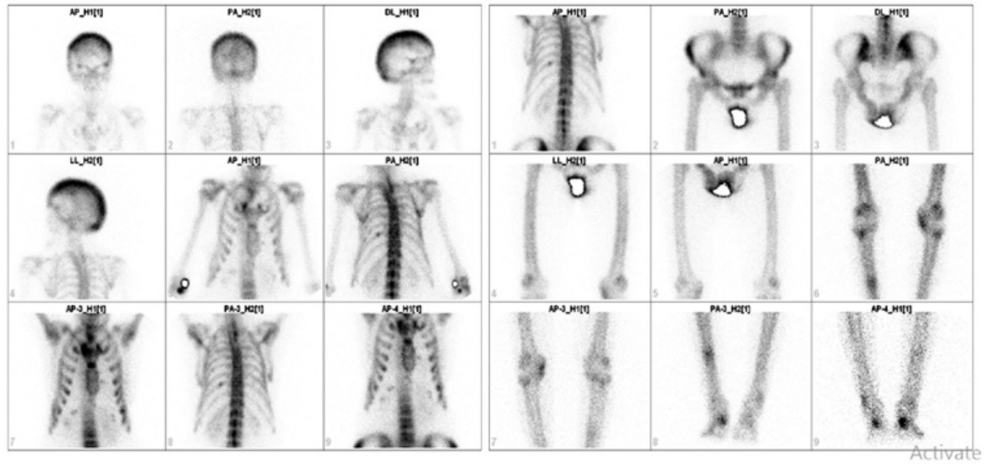
A 63-year old woman was referred to an orthopedic surgeon because of swelling accompanied by intensifying pain in the anterior right lower leg. She had a history of osteoporosis and complained of muscle weakness in the lower limbs and walking problems for the past several months. Moreover, she denied having sustained any trauma or fracture and there was no significant past or family medical history. On physical examination, apart from the redness and swelling localized in the anterior part of the right lower limb, the patient presented severe thoracic kyphosis. The X-ray revealed a well-defined expansile osteolytic lesion in the diaphysis of the right tibia, measuring 15×40mm. The presence of the osteolytic lesion gave rise to an initial diagnosis of a primary bone tumor or metastatic bone disease, and she was referred to our nuclear medicine department for a radionuclide bone scan. The patient underwent three-phase bone scintigraphy performed with a planar gamma camera *(Mediso, Nucline)* with general-purpose collimator and 128×128 matrix, at 1 minute, 5 minutes, and 3 hours after i.v. application of 740 MBq of technetium-99 m methylene diphosphonate (^{99m}Tc-MDP). The blood flow and blood pool phase images of the lower limbs demonstrated slightly increased vascularity in the middle third of the right tibia (Figure 1).

Figure 1. *Blood flow and blood pool phase (anteroposterior view) images of bone scintigraphy of lower limbs, demonstrating slightly increased vascularization and perfusion in the middle third of the right tibia.*



Late phase bone scintigrams showed generalized increased radiotracer uptake throughout the skeleton with prominent calvaria, costochondral junctions as well as focal increased uptake in both sacroiliac joints, the middle third of the right tibia, both knees, and feet, with reduced renal activity suggesting metabolic bone disease ("metabolic superscan") (Figure 2).

Figure 2. *Late phase static bone in anteroposterior and posteroanterior views, indicative of a "metabolic superscan"*



Laboratory blood test was obtained and revealed: PTH, 1612pg/mL (15 to 65pg/mL); serum alkaline phosphatase, 867U/L (38 to 125U/L); total calcium, 3.4 mmol/L (2.1 to 2.5 mmol/L); ionized calcium, 1.84 mmol/L (1.3 to 1.6 mmol/L); serum phosphate, 0.4 mmol/L (0.8 to 1.4 mmol/L). Thyroid hormonelevels were within normal laboratory range reference. Neck ultrasound (US) demonstrated a normal-sized thyroid gland with an inhomogeneous isoechoic structure and a solitary nodule of 14 mm in diameter located in the right lobe. There were no signs of enlarged parathyroid glands. Couple of days later dual-phase^{99m}Tc-methoxy-isobutyl-isonitrile (MIBI) parathyroid scintigraphy of the neck and upper thorax was performed. Early single-photon emission computed tomography (SPECT) images were obtained 10 minutes after i.v. injection of 740 MBq of^{99m}Tc-MIBI followed by hybrid SPECT/computed tomography (CT) acquisition

at 2 hours (using Optima NM/CT 640GE Healthcare dual detector/4-slice CT gamma camera, LEHR collimator, 120 views, and matrix size 128×128). The images revealed a single anterior mediastinal nodule consistent with an ectopic parathyroid adenoma (Figure 3) with an additional appearance of focal radiotracer uptake in the sternal end of the right clavicle, suggesting the presence of a brown tumor (Figure 4).

Figure 3. *Delayed images of parathyroid dual-phase scintigraphy with ^{99m}Tc-MIBI: coronal, sagittal and transversal CT, SPECT, and SPECT/CT fusion images localizing the ectopic mediastinal parathyroid gland (arrow).*

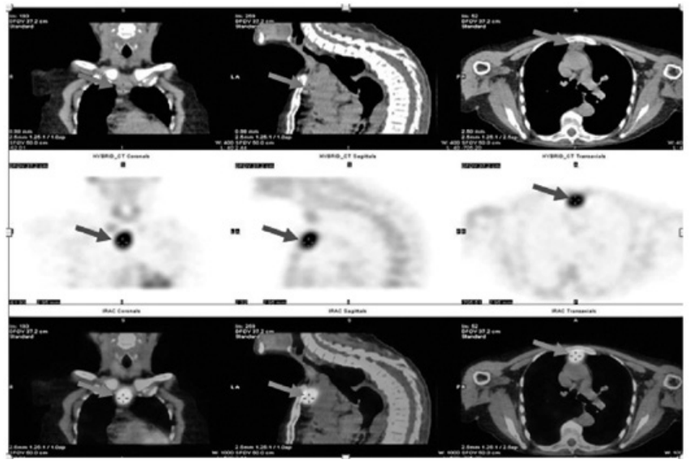
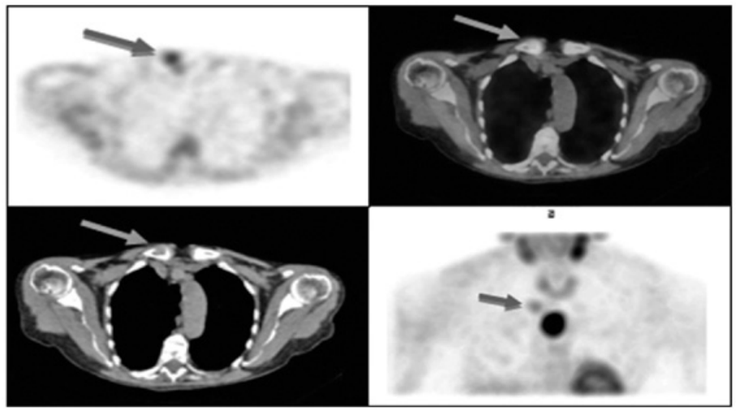
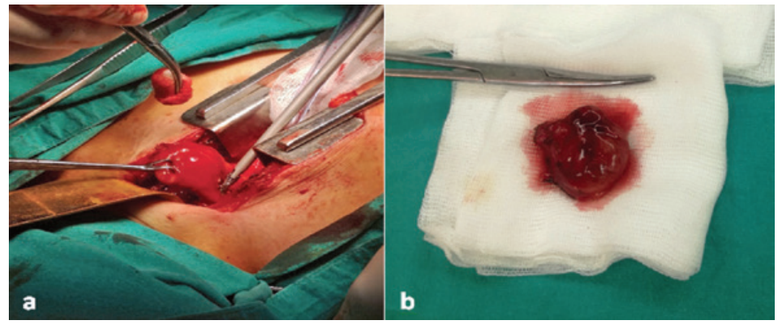


Figure 4. *Delayed images of parathyroid dual-phase scintigraphy with ^{99m}Tc-MIBI: maximum intensity projection view and axial projections of CT, SPECT, and fused SPECT/CT showing focal uptake of the tracer in the sternal end of the right clavicle suggestive of a brown tumor (arrow).*



As a result of the strongly suspicious biochemical parameters (hypercalcemia, hypophosphatemia, increased levels of alkaline phosphatase and PTH), as well as the report of the ^{99m}Tc-MIBI scan, a diagnosis of PHPT was confirmed and the patient underwent surgical resection of the ectopic parathyroid gland. A video-assisted transcervical approach combined with gamma-probe guidance was used to explore the mediastinum. For this reason, 2 hours before the surgery 110 MBq of ^{99m}Tc-MIBI was i.v. administered to mark the parathyroid adenoma. Due to the deeply seated mediastinal localization of the adenoma, a hemi sternotomy was performed. The gamma-probe was inserted directly over the location of the adenoma as suggested by the SPECT/CT imaging. Once the specimen was removed, an ex vivo counting rate was performed and as expected it was much higher than the background or that of the surgical bed, ensuring the complete removal of the ectopic tissue. The surgical specimen was well-circumscribed with a size of 35×30×15mm (Figure 5).

Figure 5. *Intraoperative view of the ectopic parathyroid gland (a). The smaller size of the giant parathyroid adenoma measured 35×30×15mm (b).*



On histopathological examination, the tumor consisted mainly of chief cells and the definitive diagnosis was ectopic parathyroid adenoma. On post-operative follow-up, serum alkaline phosphatase, serum calcium, and serum PTH levels fell gradually and returned to normal values in 6 months after the surgical procedure.

Discussion

The parathyroid glands are two pairs of glands derived embryologically from the third and fourth branchial pouches. From there they descent towards their final anatomical position, which is on the posterior aspect of the lateral lobes of the thyroid gland (5). Approximately 1-3% of the population has atypically placed parathyroid glands due to faulty glandular tissue migration during embryologic life. Ectopic parathyroid glands are mostly found inside the mediastinum (3). In a review conducted by Clark from 64 mediastinal parathyroid tumors, 81% were located in the anterior mediastinum (6). Phitayakorn R et al. in a review of 231 cases with verified hyperparathyroidism, showed a 16% prevalence of ectopic glands, with 5 of 23 (22%) parathyroid glands located in the anterosuperior mediastinum (7). Mendoza V et al. also presented data of 145 cases with PHPT in a five years period in which ectopic parathyroid glands were found in 9% of the cases. Interestingly, severe bone disease occurrence was reported among these patients (8). The

normal parathyroid glands have subcentimeter size, ranging from 4-6 mm in length, 2-4 mm in width, and 1-2 mm in thickness (9). The size of the parathyroid adenomas is variable usually, it is <2cm in patients with primary hyperparathyroidism (10). In our case, the parathyroid adenoma measured 35×30×15mm, which is a relatively small size for a giant parathyroid adenoma, comparing to other reported cases (11,12,13).

PHPT occurs when a problem arises in one or more of the parathyroid glands leading to excess production of PTH and subsequent hypercalcemia. The involvement of the skeletal system and the kidney is the most commonly seen. Symptoms in clinically manifest disease are usually vague and hard to spot, are often protean, and may lead to misdiagnosis. Characteristic skeletal manifestations like brown tumors, are a result of the abnormal osteoclastic activity causing bone resorption and fibrous replacement of the bone tissue. They can occur at any location of the skeleton and they often do not cause noticeable symptoms until they are quite large (14). The prevalence of brown tumors has been reported to be 0.1% (15). In our case, the performed bone scan, suggestive of metabolic bone disease, followed by high PTH, as well as an elevated level of total and ionized calcium and abnormally low phosphate in serum, were factors indicative for PHPT. The osteolytic right tibial lesion was more consistent with OFC; thus excluding bone malignancy (primary or metastatic). US, CT, magnetic resonance imaging, and ^{99m}Tc-MIBI scintigraphy are the most commonly used imaging tests for detecting abnormal parathyroid glands, among which ^{99m}Tc-MIBI SPECT scintigraphy has the highest sensitivity. One advantage of this imaging method over the US, is its ability to diagnose ectopic mediastinal parathyroid glands, whereas the US is less expensive and radiation free (16). Moreover, Neumann et al. analyzed dual-isotope SPECT and SPECT/CT in PHPT and showed that while the sensitivity appeared to be similar, the specificity for SPECT/CT was 96% compared to 48% for SPECT (17). Wong et al. performed a meta-analysis of 24 studies and revealed a higher sensitivity of SPECT/CT compared to both SPECT and planar imaging (18). In any case, for effective clinical outcome of the parathyroid adenoma associated PHPT, proper coordination between the nuclear medicine physician, the surgical team and the pathologist is a crucial factor. In a previous report by Ristevska et al. minimally invasive radio-guided surgery was considered as an effective technique for parathyroid adenoma resection (19). Similarly, Dogan et al. gave special importance to gamma-probe usage during surgery for proper localization of ectopic parathyroid tissue, resulting in successful treatment (20). A study by Rubello et al. including 102 patients, demonstrated the advantages of radio-guided surgery especially in lesions located in the upper mediastinal, supporting again the use of this method (21).

We report a case of nowadays rarely seen metabolic bone disease as the first sign of primary hyperparathyroidism caused by a giant ectopic parathyroid adenoma. Furthermore, we emphasize the important role of radionuclide imaging procedures as the key to confirming primary hyperparathyroidism, detecting an ectopic parathyroid adenoma, as well as identifying osteolytic brown tumors which can easily imitate bone malignancy and should be evaluated with caution. The use of intraoperative gamma-probe guidance could support the complete removal of the parathyroid adenoma tissue ensuring the surgical and therapeutic success for the patient.

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CASE REPORT UDK: 616.132.2-089.853:618.5-089.888.61

POSTPARTUM SPONTANEOUS CORONARY ARTERY DISSECTION: A RARE CAUSE OF ACUTE CORONARY SYNDROME IN YOUNG WOMEN

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ABSTRACT

Spontaneous coronary artery dissection (SCAD) is one of the rarest causes of acute coronary syndrome and myocardial ischemia, as well as sudden cardiac death, with a total prevalence of 0.2% worldwide, predominantly in the young female population, with an average age of 43 years and no previously known cardiovascular risk factors.

This is a rare case of a 38-years-old woman with no previous history of cardiovascular disease. She was hospitalized 1 month after cesarean section, presented with severe chest pain.

After the initial preoperative clinical exams, she was referred to Cath lab for invasive procedure. Coronarography findings showed pLAD stenosis 99% TIMI flow=3 (Dissection), mLAD stenosis 99% TIMI flow=3 and coronary artery by-pass surgery (CABG) was recommended. After couple of days, CABGx1 (LIMA to LAD) was made.

Through this case, the accurate diagnosis and individually based treatment in these patients is presented.

Key Words: *Myocardial infarction, Pregnancy, Spontaneous coronary artery dissection.*

Introduction

Spontaneous coronary artery dissection (SCAD) is a rare nonatherosclerotic cause of acute coronary syndrome (ACS), including sudden cardiac death, with a prevalence of 0.2% in the world, particularly in young females, with previously not known cardiovascular risk factors (1, 2). SCAD myocardial infarction is caused by lack of myocardial blood flow due to partial or complete occlusion of the coronary artery from a vessel wall tear and hematoma (3). Diagnosis, treatment, and future care of SCAD patients can be challenging. Women with SCAD present with typical signs and symptoms of ACS such as chest pain, ST-segment elevation myocardial infarction, non – ST-segment elevation myocardial infarction, and sudden cardiac death. Although SCAD patients may present with chest pain and other ischemic symptoms, the initial electrocardiogram and troponin levels may be normal. Serial evaluations are advised in those with concerningsymptoms (4, 5).

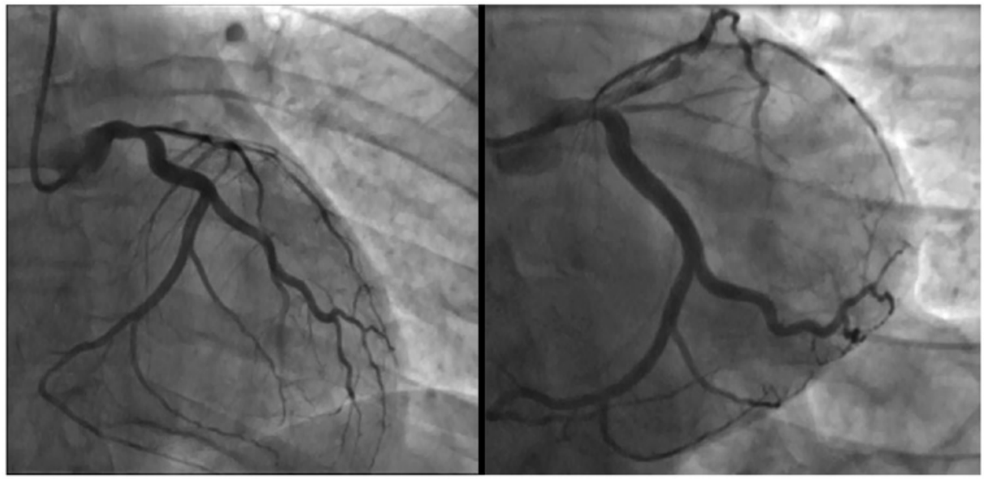
Case Report

38-years-old woman with no previous history of cardiovascular disease was hospitalized one month after cesarean section, after she presented with severe chest pain. She was previously treated for acute pericarditis for 2 weeks with anti-inflammatory and antibiotic therapy, and due to high values of D-dimmers, by the recommendation of a transfusiologist she received low molecular weight heparin continuously after delivery, until 5 days before admission. The results of her clinical examinations are following:

- ECG: sinus rhythm HR 83bpm, ST segment elevation in leads V1-V3, negative T wave in lateral and precordial leads.
- Laboratory examination: elevated biomarker of myocardial injury (high sensitivity Troponin I-289ng/L).
- Echocardiography: normal left-ventricular dimensions and volumes, with mildly reduced systolic function (LVEF 47%), hypokinesia of the apex and IVS.-Coronarography: pLAD stenosis 99% TIMI flow=3 (Dissection), mLAD stenosis 99% TIMI flow=3. Recommended CABG (Fig. 1,2)

Figure 1 *(pLAD 99% stenosis+dissection)*

Figure 2 *(mLAD99% stenosis)*



Treatment included double antiplatelet, anticoagulant, statins and antihypertensive therapy, and the patient was transferred for cardio surgery.

After the initial preoperative clinical exams, CABGx1 (LIMA to LAD) was made. The patient was stable postoperatively, with echocardiographic findings of normal left-ventricular dimensions and volumes, with slightly improved systolic function (LVEF 53%), hypokinesia of the apex and IVS and GLS (global longitudinal strain)-16.8%. The postoperative follow-up after 1 month and after 6 months showed normal left ventricular systolic function, without any new symptoms or complications.

Discussion

SCAD is an epicardial dissection of a coronary artery that is not associated to atherosclerosis or trauma, and is not iatrogenic. The etiopathogenesis of which is still poorly understood, preferentially affects the healthy and young population, especially females. The mechanism of myocardial injury is different from the typical occlusion that occurs with atherosclerotic plaque rupture or intraluminal thrombus, and is the result of intimal disruption or intramural hematoma formation that obstructs flow through the coronary artery (1). The first case was recorded in 1931 by Pretty, and the greatest progress on this condition and theme has been made in the past 5 years (2).

SCAD has specific risk factors, comorbidities, and different diagnostic, therapeutic, and prognostic implications compared to atherosclerotic coronary heart disease. There are previously established associated conditions, such as extracoronary vascular abnormalities, coronary tortuosity, connective-tissue diseases, family history, migraines, and potential triggers such as extreme emotion/exertion and pregnancy/postpartum. As a cause of acute coronary syndrome, SCAD is present in 0.1-0.4% worldwide, in the few registers among which the most significant is the Mayo clinic from 2010 with 150 patients, of which 82% were women, 45% had no cardiovascular risk factor or known primary disease. The most common predisposing factors are delivery and fibromuscular dysplasia, while in the male population the predisposing factors are considered to be intense emotional stress, extreme physical exertion and the use of sympathomimetics (2, 3).

The clinical presentation in >50% of patients is with a typical manifestation of chest pain, STEMI and elevated troponin in the blood, while the diagnosis of SCAD is made by coronary angiography. The lesion is the most often in the middle and distal segment of the LAD and its lateral branches.

The diagnosis of SCAD is made at the time of coronary angiography. Findings can be graded into three types:

Type 1

The classic description is of a longitudinal filling defect, representing the radiolucent intimal flap. There is often contrast staining of the arterial wall with appearance of a double lumen.

Type 2

Diffuse long smooth tubular lesions (due to intramural haematoma) with no visible dissection plane that can result in complete vessel occlusion. Lesions are typically >30mm in length with an abrupt change in vessel diameter between normal and diseased segments. There is no response to intracoronary nitrates and there are no atherosclerotic lesions in other coronary segments.

Type 3

Multiple focal tubular lesions due to intramural haematoma that mimic atherosclerosis. An intravascular ultrasound (IVUS) or optical coherence tomography (OCT) at the time of angiography should be used to diagnose intramural hematoma secondary to SCAD (4).

Initial treatment is standard for ACS patients, including dual antiplatelet therapy, heparin, B blocker for preservation of the true lumen and prevention of platelet occlusion. Thrombolytic agents should not be used due to an increased risk of bleeding and extension of intramural haematoma.

Conservative treatment is recommended in hemodynamically stable patients, who usually resolve spontaneously, while those with hemodynamic instability, left main stem involvement, or complete occlusion, require immediate coronary revascularization. PCI is the preferred re-vascularisation strategy, but it is associated to significant challenges and has reported success rates of <50%. Coronary angiography provides poor visualisation of intramural haematoma, and intravascular imaging with OCT or IVUS is recommended in all PCI cases. OCT has superior resolution to IVUS: it can confirm guidewire position in the true lumen, can detail the site of intramural haematoma and intimal tear, can facilitate appropriate vessel sizing and can optimise stent expansion. CABG is considered for patients with left main stem dissections or when PCI has been unsuccessful or is not technically feasible. In-hospital results following CABG for SCAD are excellent, with a reported mortality of <2%. Follow-up angiographic studies have shown high rates of graft occlusion, possibly due to competitive flow in the native vessel or technical difficulties with distal graft anastomosis (9, 10).

Conclusion

Spontaneous coronary artery dissection is an important cause of acute coronary syndrome, especially in young female population without any cardiovascular risk factors. The pathophysiology and treatment are different from those in acute coronary syndrome caused by plaque rupture and erosion. The most of coronary spontaneous dissections resolve spontaneously with a recommendation for conservative treatment in uncomplicated cases.

In patients presenting with persistent chest pain or in whom hemodynamic instability is present, with left main stem involvement, as well as complete occlusion, coronary revascularization is necessary. PCI results are suboptimal in these patients and should be performed using intravascular imaging and the possibility of on-site surgery due to the increased risk of complications. Although the long-term prognosis is excellent, the risk of recurrent SCAD is significant, with an average recurrence rate of 5% per annum.

Well-designed, large, nation-wide, prospective studies are required on this unique condition.

The AHA and ESC scientific statements on recognizing and optimizing management need to move from expert-based recommendations to evidence-base medicine. Depending on the needs of the individual patient, incorporation of a multidisciplinary team including specialists in cardiology, vascular medicine, genetics, psychiatry, pain management, neurology, cardiac rehabilitation, radiology, and obstetrics can facilitate personalized care.

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ORIGINAL RESEARCH UDK: 614.253.8-054.7(497.715)"2019"

HEALTH WORKERS' ATTITUDES, KNOWLEDGE AND PRACTICE TOWARDS MIGRANT-PATIENTS

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ABSTRACT

Purpose: This study is aimed to examine the attitudes and knowledge of different groups of health professionals and their work with migrant patients, as well as to identify contributory factors and barriers.

Materials and Methods: The study is designed as a descriptive-analytical cross-sectional study, conducted in 2019 on a representative sample of 30 health workers in Gevgelija General Hospital, which examined the attitudes, knowledge and practice of health professionals when working with migrant patients, using of an instrument – a structured questionnaire for assessing attitudes (Dias, Gama, Cargaleiro & Martins, 2012).

Results: The results of this study reveal that physicians are more likely to have negative attitudes towards migrant patients compared to nurses for all examined attitudes. Among health professionals, the older ones expressed less positive attitudes than the younger ones. Male health workers are more likely to agree with the views expressed in the study. Spearman's correlation coefficient suggests that as the number of migrant patients increases, so does the agreement, and vice versa (R=0.482, R=576, R=0.387, respectively).

Conclusion: Development strategies are needed that prevent negative attitudes and stereotypes in healthcare professionals in providing health services to migrants, in order to enable the improvement of the ability and knowledge of healthcare professionals to work with culturally diverse population, to be culturally sensitive, to obtain positive health outcomes in the migrant population.

Key Words: *attitudes, healthcare, healthcare professionals, knowledge, migrants.*

Introduction

Migration flows have resulted in growing cultural heterogeneity among European population. Since the beginning of 2015, the Republic of North Macedonia has continuously faced an influx of increasing number of refugees and migrants, who from the territory of the neighboring Republic of Greece enter our territory in organized groups. The dynamics of the refugee crisis during this period continuously tested the state's readiness to fully respect the guarantees of basic human rights under national legislation, as well as the obligations of international agreements and instruments, and at the same time to deal with the influx of refugees and migrants (Kalajdjiev, 2018).

The right to health is one of the most basic and important rights that must be guaranteed to all people, including refugees and migrants. This right is internationally recognized and is provided by many binding instruments (O'Donnell C. A, 2016) (Universal Declaration of Human Rights, 2020) (Z, 2018) (Convention on the Elimination of All Forms of Discrimination against Women, 1979). It is accepted that the involvement of the migrant population in the basic institutions of society, especially in the health care system is the key to positive integration (Organisation for Economic Co-operation and Development: International Migration Outlook: SOPEMI – 2008 Edition. 2008, Paris, 2008) (A & Azambuja Martins L, 2011). Numerous national efforts have been made in recent decades to adapt to European regulations in order to improve access to and use of Republic of North Macedonia migrants' health services according to the status they enjoy in the country. Currently, all asylum seekers and persons under international and temporary protection, according to the Law on International and Temporary Protection (Law on international and temporary protection, 2018) have the right to basic health services, until a permanent solution is reached. Persons with recognized refugee status enjoy the same rights as the citizens of Republic of North Macedonia. According to the Law on Foreigners (Law on foreigners, 2018) and the Law on Health Insurance, (Law on health insurance, 2015), those who do not have a residence or work visa or who do not pay social security, have to pay the full amount for the issued health services.

A quick and efficient response in a country is a complex challenge that requires a lot of resources, especially when the host country is in an economic crisis or is not fully prepared to deal with the problem (WHO, 2015).

In the context of cultural diversity, what is worrying is how to improve the delivery and quality of health care for culturally diverse populations. Recent research has shown that migrants often use health services and tend to receive lower quality health care than the general population (Dias S, 2008) (Schneider EC, 2002) (Smedley BD, 2003).

Inequalities in the quality of health care may be the result of a combination of patient-level factors, healthcare and services (Phillips KA, 2000). In particular, the healthcare worker-patient documented role plays an important role in patient care (Anderson LM, 2003). Interaction between healthcare professionals and migrants is influenced by socio-demographic and cultural

background, healthcare expectations, language barriers and communication difficulties (Ferguson WJ, 2002) (Karlsen S, 2007). In addition, research suggests that the healthcare-patient relationship may also be mediated by the healthcare workers' own beliefs, perceptions, and attitudes toward migrants (Hamilton M, 2008) (Garcia Campayo J, 2006).

Despite the potential impact of healthcare professionals' attitudes, knowledge and practice on migrants, there is a lack of research in this area. The surveys mainly consist of qualitative studies, with a limited number of participants, while quantitative research is scarce (Michaelsen J, 2004) (Abbott S, 2007).

In addition, several studies have focused on the patients' side in the healthcare-patient relationship, while perceptions and attitudes of healthcare professionals are not yet well explored.

Facing the flow of refugees and migrants was a difficult task for Republic of North Macedonia. Its strategic position in the refugee and migrant crisis as a country at the first entry put it in an unenviable position and turned it into a refuge for all migrants and refugees who, for whatever reason, were not allowed to continue their journey along the route (HCHR, 2018).

However, as a country that has signed and ratified the most of the international binding instruments, Republic of North Macedonia is obliged to provide a quick humanitarian response to the current situation, aiming to maximize the human rights of migrants and refugees on its territory (HCHR, mhc.org.mk, 2016).

On December 25th, 2019, the Assembly of Republic of North Macedonia brought a decision to continue the crisis situation on the Southern and Northern border of the country until June 30, 2020. This was the ninth extension of the Decision on the existence of a crisis situation due to the increased volume of entry and transit of migrants through the territory of the country, which was first adopted in August 2015 (Republic of North Macedonia, 2019).

Purpose

The aim of this study was to examine the attitudes and knowledge of different groups of health professionals and their work with migrant patients and to identify contributory factors and barriers. It also provides information on the perception of health professionals, their knowledge and competencies to work with migrants.

Study design, materials and methods

The study is designed as a descriptive-analytical cross-sectional study, which examines the attitudes, knowledge and practice of healthcare professionals towards migrant patients.

The data for this research are collected through evidence synthesis, documents from relevant sources for access to health care that are subject of research, as well as publications and other documented material.

Public information from the following state institutions was used: Ministry of Labor and Social Policy, Ministry of Interior, Ministry of Health, Crisis Management Center, Red Cross and IOM.

The survey was conducted over a two months period, November-December 2019, on a representative sample of 30 health workers at Gevgelija General Hospital, a health facility that provides health services to migrants from Vinojug Transit – Reception Center.

Surveys of health workers were conducted with a specially designed instrument (Dias, Gama, Cargaleiro & Martins, 2012) – a structured survey questionnaire under European and national legislation on migrants' rights and access to health care, which included closed questions on demographic characteristics, professional experience, knowledge and competencies of healthcare professionals in working with migrant patients, as well as attitudes towards this group (Paksoy, 2017) (Dias S., 2012).

The research included health workers who are employed in the selected health institution and who wanted and were able to answer the survey questionnaire. The participation of health professionals in the study was voluntary, anonymous and confidential.

Statistical analysis: The data obtained from the research were analyzed with the statistical program SPSS for windows 23.0.

The Cronbach's alpha coefficient for the 6 questions in the Questionnaire was 0.817, suggesting a conclusion of a high degree of internal consistency in the respondents' answers to all the questions in the questionnaire.

The Shapiro Wilk's test was used to test the normality in data distribution.

Quantitative traits are represented by an arithmetic mean value with a standard deviation, and a medial mean, qualitative traits are shown by absolute and relative numbers.

Bivariate analysis was performed to compare the analyzed groups (by health profile, by gender, by age). Pearson Chi-square test and exact test were used to compare groups in terms of quality marks, and Mann-Whitnney test was used to compare these groups in terms of quantitative features. Spearman's Rank correlation coefficient was used to examine the correlation between the number of migrant patients and the questionnaire claims.

The values of $p<0.05$ were taken as statistically significant.

Results

The study included 30 health professionals, 15 nurses/ technicians and 15 doctors/ physicians, who differed significantly in terms of gender structure ($p=0.00019$). In the group of nurses/ technicians 93.3% (n=14) were female respondents, while in the group of doctors the majority were male respondents 73.3% (n=11) (Table 1).

Both groups of health workers differed significantly in age ($p<0.001$). The doctors were significantly younger than the nurses/ technicians.

Table 1. *Gender and age structure of health care workers and migrant patients*

Variable	Total n (%)	Nurse n (%)	Doctor n (%)	p value
Gender				
Male	12 (40)	1 (6.67)	11 (73.33)	χ^2 =13.89 p=0.00019 sig
Female	18 (60)	14 (93.33)	4 (26.67)	
Age				
25 – 34 years	5 (16.67)	0	5 (33.33)	p<0.001 sig
35 – 44 years	3 (10)	3 (20)	0	
45 – 54 years	7 (23.33)	7 (46.67)	0	
55 – 64 years	15 (50)	5 (33.33)	10 (66.67)	
Number of patients: refugees and migrants				
0 – 5	17 (56.67)	11 (73.33)	6 (40)	p=0.093 ns
6 – 10	10 (33.33)	4 (26.67)	6 (40)	
15+	3 (10)	0	3 (20)	

The results of the research showed that doctors more often than nurses agree with all 6 views of the questionnaire, but as statistically significant their answers were confirmed, i.e. statements on three questions (p=0.013), (p=0.033), (p<0.001) (Table 2).

This distribution surprises a high percentage of surveyed nurses who do not know whether migrants follow the rules of the health system (33.3%).

With the statement When refugee patients come to my service, they behave like victims "strongly agree" only doctors (53.3%), and "strongly disagree" only nurses (26.7%), (Table 2).

Table 2. *Analysis of the examined claims regarding the profile of the healthcare worker*

Variable	Total n(%)	Nurses n(%)	Doctors n(%)	p value
Some refugee patients are aggressive and dangerous				
Agree	11 (36.67)	4 (26.67)	7 (46.67)	p=0.29 ns
Disagree	10 (33.33)	6 (40)	4 (26.67)	
Strongly disagree	7 (23.33)	5 (33.33)	2 (13.33)	
Don't know	2 (6.67)	0	2 (13.33)	
Refugee patients take advantage of the social benefits that the state offers them				
Strongly agree	9 (30)	2 (13.33)	7 (46.67)	p=0.19 ns
Agree	9 (30)	7 (46.67)	2 (13.33)	
Disagree	6 (20)	3 (20)	3 (20)	
Strongly disagree	4 (13.33)	2 (13.33)	2 (13.33)	
Don't know	2 (6.67)	1 (6.67)	1 (6.67)	
Refugee patients are more claiming than the general population				
Disagree	29 (96.67)	14 (93.33)	15 (100)	p=1.0
Strongly disagree	1 (3.33)	1 (6.67)	0	
Refugee patients often dramatize and exaggerate their problems				
Strongly agree	4 (13.33)	0	4 (26.67)	p=0.013 sig
Agree	10 (33.33)	4 (26.67)	6 (40)	
Disagree	10 (33.33)	5 (33.33)	5 (33.33)	
Strongly disagree	6 (20)	6 (40)	0	
Frequently refugees do not respect the health services' rules				
Strongly agree	11 (36.67)	6 (40)	5 (33.33)	p=0.033 sig
Agree	7 (23.33)	1 (6.67)	6 (40)	
Strongly disagree	7 (23.33)	3 (20)	4 (26.67)	
Don't know	5 (16.67)	5 (33.33)	0	
When refugee patients come to my service, they behave like victims				
Strongly agree	8 (26.67)	0	8 (53.33)	p<0.001 sig
Agree	5 (16.67)	5 (33.33)	0	
Disagree	8 (26.67)	4 (26.67)	4 (26.67)	
Strongly disagree	4 (13.33)	4 (26.67)	0	
Don't know	5 (16.67)	2 (13.33)	3 (20)	

p (exact test)

When we analyzed the claims from the questionnaire as average scores, the results showed that they are higher in the group of doctors for all 6 claims, but statistically significant was only for the question "Migrant/ refugee patients often dramatize and exaggerate their problems" (3.60 ± 1.2 versus 2.13 ± 1.2; p=0.005), (Table 3).

Table 3. *Scores analysis like average scores*

Variable	Profile of education mean ± SD		p-level
	Nurse	Doctor	
Some refugee patients are aggressive and dangerous	2.20 ± 1.2	2.93 ± 1.2	Z=1.55 p=0.12 ns
Refugee patients take advantage of the social benefits that the state offers them	3.40 ± 1.2	3.73 ± 1.4	Z=0.93 p=0.35 ns
Refugee patients are more claiming than the general population	1.0 ± 0.3	1.07± 0	Z=0.31 p=0.75ns
Refugee patients often dramatize and exaggerate their problems	2.13 ± 1.2	3.60 ± 1.2	Z=2.82 p=0.005sig
Frequently refugees do not respect the health services' rules	2.53 ± 1.3	2.93 ± 0.9	Z=0.83 p=0.41 ns
When refugee patients come to my service, they behave like victims	2.80 ± 1.4	3.0 ± 1.6	Z=0.39 p=0.69 ns

Strongly agree – 5
Agree – 4
Don't know – 3
Disagree – 2
Strongly disagree – 1

Z (Mann-Whitney U Test)

The analysis of the questionnaire regarding the gender of the respondents showed that male health workers more often than women agree with the claims presented in the questionnaire, but a statistically significant difference was confirmed for two claims (p=0.017, p<0.001, consequently), (Table 4).

Table 4. *Analysis of examined claims gender-based*

Variable	Total n(%)	male n(%)	female n(%)	p value
Some refugee patients are aggressive and dangerous				
Agree	11 (36.67)	7 (58.33)	4 (22.22)	p=0.14ns
Disagree	10 (33.33)	2 (16.67)	8 (44.44)	
Strongly disagree	7 (23.33)	3 (25)	4 (22.22)	
Don't know	2 (6.67)	0	2 (11.11)	
Refugee patients take advantage of the social benefits that the state offers them				
Strongly agree	9 (30)	6 (50)	3 (16.67)	p=0.23 ns
Agree	9 (30)	2 (16.67)	7 (38.89)	
Disagree	6 (20)	1 (8.33)	5 (27.78)	
Don't know	4 (13.33)	2 (16.67)	2 (11.11)	
Strongly disagree	2 (6.67)	1 (8.33)	1 (5.56)	
Refugee patients are more claiming than the general population				
Strongly disagree	29 (96.67)	12 (100)	17 (94.44)	
Disagree	1 (3.33)	0	1 (5.56)	
Refugee patients often dramatize and exaggerate their problems				
Strongly agree	4 (13.33)	4 (33.33)	0	p=0.017 sig
Agree	10 (33.33)	4 (33.33)	6 (33.33)	
Disagree	10 (33.33)	4 (33.33)	6 (33.33)	
Strongly disagree	6 (20)	0	6 (33.33)	
Frequently refugees do not respect the health services' rules				
Agree	11 (36.67)	4 (33.33)	7 (38.89)	p=0.12ns
Disagree	7 (23.33)	3 (25)	4 (22.22)	
Don't know	7 (23.33)	5 (41.67)	2 (11.11)	
Strongly disagree	5 (16.67)	0	5 (27.78)	
When refugee patients come to my service, they behave like victims				
Agree	8 (26.67)	8 (66.67)	0	p<0.001 sig
Strongly agree	5 (16.67)	0	5 (27.78)	
Strongly disagree	8 (26.67)	3 (25)	5 (27.78)	
Disagree	5 (16.67)	1 (8.33)	4 (22.22)	
Don't know	4 (13.33)	0	4 (22.22)	

p (exact test)

For all claims from the questionnaire, higher average scores were obtained from the male respondents, that shows that they are more in line with the claims of the female respondents, but such analysis as statistically significant confirmed the difference in the average score between male and female respondents only for one claim (3.08 ± 1.4 versus 2.50 ± 1.2; p=0.01), (Table 5).

Table 5. *Average score for all claims of questionnaire*

Variable	Gender mean ± SD		p-level
	male	female	
Some refugee patients are aggressive and dangerous	2.92 ± 1.4	2.33 ± 1.1	Z=0.38 p=0.7 ns
Refugee patients take advantage of the social benefits that the state offers them	3.92 ± 1.4	3.33 ± 1.2	Z=1.1 p=0.27 ns
Refugee patients are more claiming than the general population	1.0 ± 0	1.1 ± 0.2	Z=1.35 p=0.18 ns
Refugee patients often dramatize and exaggerate their problems	3.67 ± 1.3	2.33 ± 1.3	Z=0.25 p=0.8 ns
Frequently refugees do not respect the health services' rules	3.08 ± 0.8	2.50 ± 1.2	Z=2.54 p=0.01 sig
When refugee patients come to my service, they behave like victims	3.08 ± 1.4	2.78 ± 1.6	Z=1.25 p=0.22 ns

Strongly agree – 5
Agree – 4
Don't know – 3
Disagree – 2
Strongly disagree – 1

Z (Mann-Whitney U Test)

With the exception of the claim "Refugee patients are more claiming than the general population", the age of healthcare workers had a significant impact on their compliance with all other 5 claims (p=0.0001); (p=0.048); (p<0.0001); (p=0.0002); (p=0.0003).

In all these claims, the health workers from the oldest age group had the highest average scores, i.e. they mostly agreed with these claims (3.60±0.7, 4.07±1.3, 4.1±0.7, 3.60±0.6, and, 4.0±1.1, consequently.

The post-hoc analysis table shows the significant differences between the age groups in relation to the scores of the analyzed claims (Table 6).

Table 6. *Analysis on significant differences between age groups on scores for analized claims*

	Age groups				
	25 – 34	**35 – 44**	**45 – 54**	**55 – 64**	
	mean ± SD				
Some refugee patients are aggressive and dangerous	1.60±0.5	1.0±0	1.71±0.5	3.60±0.7	H=22.2 p=0.0001 sig 1 vs 4 p=0.02 2 vs 4 p=0.005 3 vs 4 p=0.012
Refugee patients take advantage of the social benefits that the state offers them	2.40±0.5	3.0±1.7	3.57±0.9	4.07±1.3	H=7.9 p=0.048 sig 1 vs 4 p=0.049
Refugee patients are more claiming than the general population	1.0±0	1.0±0	1.14±0.4	1.0±0	H=3.4 p=0.33 ns
Refugee patients often dramatize and exaggerate their problems	2.0±0	1.0±0	1.57±0.5	4.1±0.7	H=23.6 p=0.0000 sig 2 vs 4 p=0.0034 3 vs 4 p=0.0017
Frequently refugees do not respect the health services' rules	2.0±0	2.33±1.1	1.57±0.8	3.60±0.6	H=19.5 p=0.0002 sig 1 vs 4 p=0.032 3 vs 4 p=0.00087
When refugee patients come to my service, they behave like victims	1.40±0.5	1.0±0	2.43±0.8	4.0±1.1	H=18.6 p=0.0003 sig 1 vs 4 p=0.007 2 vs 4 p=0.011

1= (25-34 г.), 2= (35-44 г.), 3= (45-54 г.), 4= (55>г.), H (Kruskal-Wallis test)
post – hoc Z (Mann-Whitney test)
Strongly agree – 5
Agree – 4
Don't know – 3
Disagree – 2
Strongly disagree – 1

In our study, we analyzed the correlation between the number of migrant patients and the claims analyzed in the questionnaire. Statistically significant difference was obtained among the number of migrants with the three claims (Table 7), (p=0.007), (p=0.008), (p=0.034). According to the values of Spearman's correlation coefficient, all these correlations are positive, i.e. direct, which suggests the conclusion that with the increase in the number of migrant patients, the agreement with the stated claims increases, and vice versa (R=0.482, R=576, R=0.387, consequently), (Table 7).

Table 7. *Correlation between numbers of migrant patients with analyzed claims*

N migrant patients	Some refugee patients are aggressive and dangerous	Refugee patients take advantage of the social benefits that the state offers them	Refugee patients are more claiming than the general population	Refugee patients often dramatize and exaggerate their problems	Frequently refugees do not respect the health services' rules	When refugee patients come to my service, they behave like victims
Spearman–R	0.221	0.482	0.158	0.576	0.287	0.387
p value	0.24 ns	0.007 sig	0.41 ns	0.008 sig	0.124 ns	0.034 sig
N	30	30	30	30	30	30

Discussion

The results of this study reveal that in certain segments, positive attitudes of health professionals towards migrant patients have been established. This may be partly the result of national efforts to promote the integration of the migrant population, such as several Action Plans for Dealing with Migrants, but as a key document is the draft Strategy for Integration of Refugees and Foreigners in Republic of North Macedonia 2017 – 2027 [29] (MLSP, 2017) and the Action Plan for its implementation, it contains key segments of integration, with predetermined tasks and a period for their implementation, as well as bodies that will perform evaluation. This confirms that developed strategies should promote access and use of health services in order to contribute in reducing health inequalities. The adoption of new legislation, largely adapted to the European one, through the Law on Foreigners and the Law on Temporary and International Protection and the Constitution of the Republic of Macedonia establishes the right that all persons on the territory of Republic of North Macedonia have access to health services and the right to quality health care.

The results suggest a variation in the attitudes of health care workers towards migrants. Several participants have probably been reluctant to answer these questions, as migration policy and the prevention of discrimination are currently the biggest political and social problems under constant monitoring by the UNHCR and the Helsinki Committee.

The survey also found that a significant proportion of health professionals report negative attitudes toward migrants, which is consistent with other research (Van Ryn M, 2000).

Republic of North Macedonia lacks published studies on the attitudes of healthcare professionals towards migrant patients. Attitudes are a complex phenomenon and can vary depending on the different groups of migrants (Van Ryn M, 2000). In this regard, future research should investigate the extent to which healthcare professionals differ in their socio-demographic characteristics.

This research examines whether the demographic characteristics and professional experience of healthcare professionals influence the attitudes towards migrant patients. Gender effects were observed in certain segments, male gender workers more often agreed with negative attitudes towards migrants, unlike some research (Michaelsen J, 2004), (Ward C, 2008). Significant age-related trend has been observed in physicians: the older physicians are, less positive their views are. Older generations tend to be less tolerant and have stronger negative attitude towards migrants for greater adherence to conservative values, while younger people tend to adhere to be more tolerant in social norms, showing greater openness to diversity and positive attitudes toward migration and attesting to it, Migrations in previous studies (Dias S., 2012), (Lages M, 2006). Results are important because unfavorable attitudes towards migrants can have serious implications, especially for migrant users and access to services. Previous studies have shown that people with lower level of education may be less tolerant and reveal a negative attitude towards migrants, which was not the case in this study (Kleemans M, 2009), (Pitkänen P, 2002).

Recent research has pointed to a lack of contact theory in resolving the nature of contact between people with different status and its implications (Escandell X, 2009). Namely, instead of reducing the conflict, contact between different groups can actually increase the tension (Jolly SK, 2009), (Brown LM, 2001).

Similar to that, our results may reveal difficulties in interacting by the health care worker-patient. In another study, health professionals described that interaction with migrant patients was often difficult and that providing care generated feelings of work overload, anxiety, and frustration (Dias S R. R., 2010) as noted by other authors. However, the experiences of healthcare professionals in meetings with migrants and their impact on attitudes need to be further examined. Attitudes towards migrants and negative stereotypes are related to the characteristics of health professionals, professional experience and lack of knowledge and competencies to deal with cultural diversity (Betancourt JR, 2003), (Hudelson P, 2010). Stereotyping and prejudice of health care workers towards migrants affect the behavior of interacting with these patients and making medical decisions, especially in terms of diagnosis and treatment (Eshiett M, 2003), (Peek ME, 2010). Patients themselves perceive these attitudes and their reaction may reflect dissatisfaction, disrespect for treatment and reduced use of services, which adversely affects treatment outcomes (Scheppers E, 2006). What really gets in the way of the first contact with migrant patients are the language barriers and the lack of health information for patients, which further complicates the work of health professionals. The introduction or implementation of the PHR (Personal health record) (IOM, 2018) as unified document containing a detailed medical history, mandatory in each country, would significantly facilitate the provision of health services and increase the quality of services. In Republic of North Macedonia, migrant care is a recent experience for healthcare professionals. The most of the respondents believe that they have moderate or low competence to work with migrants and believe that specific training is important for performance. This may be an indication that health personnel is motivated to improve their competencies, and therefore interventions should be maximally supported to improve them.

Conclusion

In the conducted research, the presented evidence strengthens the need for development of strategies that prevent negative attitudes and stereotypes in health professionals in providing health services to migrants and enable improvement of the ability and knowledge of health professionals. Improving the interaction of healthcare professionals with migrant patients can contribute to quality healthcare delivery. In this regard, it is crucial to improve the competencies of healthcare professionals to work with culturally diverse population, to be culturally sensitive, in order to obtain positive health outcomes in the migrant population. The language barrier that runs through, prevents the adjustment of health procedures, which in return affects the rapid benefits of effectively responding to the needs of the migrant population.

In order to achieve an ideal treatment for this category of patients, it is necessary to increase the diversity of the workforce at all levels of the healthcare organization, i.e. a multidisciplinary team that will reflect the cultural diversity of the community service.

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ORIGINAL RESEARCH

UDK: 616.831-006.484-085.227
616.831-006.484-085.849.1

PROGNOSTIC VALUE OF MOLECULAR MARKER ON OUTCOME IN PATIENTS WITH HIGH-GRADE GLIOMA-SINGLE INSTITUTIONAL EXPERIENCE

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ABSTRACT

High-grade glioma (HGG) are among the most frequent primary brain tumors. Prognosis in HGG depends on histology, age, performance status, and other patient and tumor related factors. The 2016 revision of the WHO Classification of CNS Tumors introduced molecular characterization of HGG with possible impact on prognosis. Analysis of a total of 49 patients with HGG with known MGMT methylation status and IDH1 and IDH2 mutation has been done. All patients underwent surgery, followed by concurrent chemoradiotherapy and adjuvant chemotherapy with temozolomide. Median follow up of all patients was 21.3 months (6.2-52.1 months). The Median Disease-free survival (DFS) was 20.3 months, and the median overall survival (OS) was calculated as 21.8 months. Patients has been stratified according to MGMT methylation status and IDH1 and IDH2 mutation status. DFS and OS have been compared between groups. The assessment shows 2-years DFS and OS were 45.5% and 54% for methylated and 40.4% and 47.8% for unmethylated patients. 2-years DFS and OS were 75% and 86% for IDH1 mutated patients and 34.12% and 47.1% for IDH1 unmutated patients. Two-years DFS and OS were 56% and 83% for IDH 2 mutated patients and 28.8% and 40.9% for IDH2 unmutated patients. There were suggestions for favorable prognostic factor for both MGMT methylation and IDH1 and IDH2 mutation, but we did not show any statistically significant difference of DFS and OS between MGMT methylated and unmethylated patients and between IDH1 and IDH2 mutated and unmutated patients due to small specimen and relatively short follow up.

Key Words: *Chemoradiotherapy, Glioma, Molecular Characterization.*

Introduction

The high-grade glioma are relatively rare type of tumors with an incidence of about 1.6 on 100,000 population. It is estimated that there will be around 300,000 new cases annually, with around 250,000 diseases specific deaths worldwide (1).

Patients' treatments are usually multimodal and depend on tumor localization, tumor size, patients' age, and patients' performance status. The survival rate largely depends on the histology of the tumor and applied treatment modality (2 – 4).

The introduction of contemporary multimodality treatment that includes various modern surgical approaches, modern radiotherapy using three-dimensional conformal techniques and techniques derivates combined with temozolomide chemotherapy, extended the survival scenarios of patients on average for about 14 months for glioblastoma patients, WHO Grade IV, and around 5 years for patients with WHO Grade III glioma (5).

The revision of the WHO classification of malignant brain tumors in 2016 led to mandatory molecular classification, which could have an impact on patients' survival rate (6 – 8). Today, it is also clear that some patients who have a tumor with different molecular characterization could have more benefit from chemotherapy treatment (9).

Until recently, brain tumors diagnostics have been almost solely based on morphology and immunohistochemically staining for relatively unspecific markers. Although specific molecular markers have been known for longer than a decade, molecular biomarkers were not included in the WHO classification until the last revision (6).

Today, the classification of diffuse glioma rests on the integration of morphology and molecular results. Also, for many other CNS tumor entities, specific diagnostic, prognostic, and predictive biomarkers have been detected and continue to appear as significant in the clinical settings (10).

It is now clear that mutations of isocitrate dehydrogenase (IDH) genes, in IDH1 – R132H mutation and in IDH2 K129R mutation, have a definite effect on prognosis and may be predictive of radiation therapy and chemotherapy response (11,12).

Molecular characterization of glioma has been implemented in our institution in 2016, and this paper shows the initial results of the predictive value of MGMT methylation, IDH1, and IDH2 mutation in our series of patients.

Material and methods

Total of 49 patients with High-Grade Glioma (8 patients with WHO grade III and 41 with Who Grade IV tumors) have been referred to the University Clinic of Radiotherapy and Oncology (UCRO) in Skopje, North Macedonia in the period January 2016 – December 2018 with the intention to be treated. The institutional ethical committee approved all procedures on patients, and all patients signed informative consent before the start of the treatment. Surgical treatment had been performed before referral to UCRO, and postoperative histology has been verified by qualified neuropathologists. Only patients with verified histological findings of High-Grade Glioma (WHO Grade III and IV), which include the following histological types: glioblastoma, anaplastic astrocytoma, anaplastic oligodendroglioma, and anaplastic oligoastrocytoma (6) were included in this study. In addition to morphological pathohistological findings, molecular analysis of IDH1, IHD2, and MGMT mutation has been performed on all histological specimens using Multiplex ligation-dependent probe amplification (13).

The initial workup of the patients consisted of biochemical blood analysis, total blood count, a collection of preoperative and postoperative imaging, and scoring of patients according to ECOG/WHO Performance Status Scoring System (14). The patients with ECOG/WHO performance scores equal to or larger than 3 have been omitted from this analysis due to different treatment intent and treatment strategies.

After the initial evaluation, the patients have been treated according to an institutional protocol for postoperative chemoradiotherapy, which consisted of radiotherapy using three-dimensional conformal radiotherapy (3D-CRT) or Intensity Modulated Radiotherapy (IMRT) together with concurrent chemotherapy with temozolomide, followed by adjuvant chemotherapy with temozolomide in the duration of a total of 6-12 cycles.

Thermoplastic immobilization mask has been molded individually for all patients, and CT simulation scans with 2.5 mm axial slices were acquired in the treatment position. Preoperative or/and postoperative MRI images were co-registered with CT simulation scans. The gross tumor volume (GTV) was contoured as the contrast-enhancing lesion on T1-weighted MRI or the post-operative cavity on CT. The clinical target volume (CTV) was a 1.5-2 cm margin around the GTV, which was expanded to include the edema and adjusted to anatomic barriers. The planning target volume (PTV) was generated with a 3-5 mm isotropic margin expansion. Planned dose of adjuvant radiotherapy (RT) was 60 Gy in 30 fractions, 2 Gy per fraction, over six weeks with 3D-CRT or IMRT technique. All patients were planned for chemotherapy with temozolomide, 75 mg/m^2 taken orally every day, throughout the radiation process followed by 150-200 mg/m^2 for 5 consecutive days every four weeks in the duration of 6-12 cycles. Treatment plans were generated with Varian Eclipse Version 10 (Varian Medical Systems) treatment planning system. Dose-volume parameters for all treatment structures (target and organs at risk) were documented, and the criteria for plan acceptance were according to QUANTEC guidelines (15).

The patients were followed up according to the institutional protocol of follow up, which comprises of physical examination and blood examination – every month, contrast-enhanced brain MRI every 3-4 months. The criteria for the progressive disease were according to revised RANO/EANO criteria (16). Diseases progression and overall survival has been quantified as a time interval in months from date of diagnosis of disease or date of conformed histological finding to date of confirmed progression for disease-free survival (DFS) or date of lethal outcome for overall survival (OS). The detailed patient characteristics have been shown in **Table 1**.

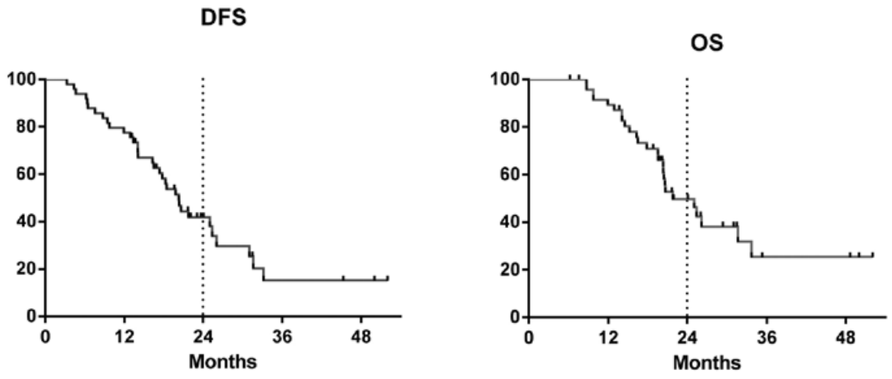
Table 1. *Patients' Characteristics*

Gender	Male	Female
	30	19
WHO Grade	III	IV
	8	41
Performance status	0,1	2,3
	26	23
Type of Surgery	Total Resection	Subtotal Resection
	37	12
IDH1	Wildtype	Mutated
	39	10
IDH2	Wildtype	Mutated
	39	10
MGMT (met)	Unmethylated	Methylated
	30	19
Age at diagnosis	≤50	>50
	13	36

Results

The Median follow-up of all 49 patients was 21.3 months (range from 6.2 to 52.1 months). The median time to progression (recurrence) was 20.3 months, and median survival was calculated as 21.8 months using the Kaplan Meir method (17).

Figure 1. *Median disease-free survival (DFS) – 20.3 months and median overall survival (OS) – 21.8 months*

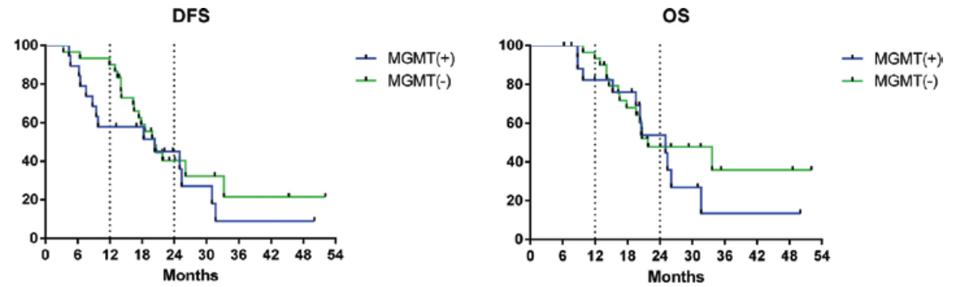


Survival analysis using the Kaplan Meir method has been done on two parameters for disease free survival (DFS) and overall survival (OS). A comparison of survival has been calculated using Mantel-Cox and Gehan-Breslow-Wilcoxon (log-rank) tests (18,19).

Survival analysis for both DFS and OS has been done for patients with MGMT promoter methylated and unmethylated patients. All 49 patients were with MGMT methylation determined status. Nineteen patients were with methylated MGMT and 30 with unmethylated MGMT.

Disease-free survival (DFS) was 20.32 months for MGMT methylated and 20.29 months for unmethylated MGMT patients, and Overall Survival (OS) was 25 months for MGMT methylated and 21.75 months for MGMT unmethylated patients **(Figure 2)**.

Figure 2. *Two-years Disease-Free Survival (DFS) and Overall Survival (OS) in MGMT methylated and unmethylated patients: 45.5% and 54% for methylated and 40.4% and 47.8% for unmethylated patients.*

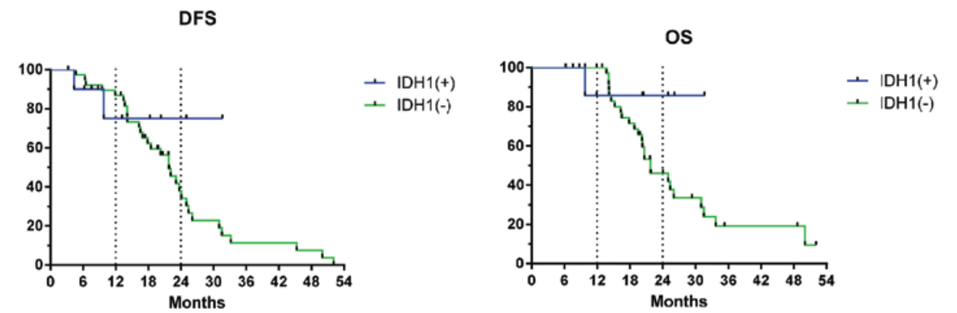


Two-year DFS was 45.5% for methylated and 40.4% for unmethylated patients and 2-year OS was 54% for methylated and 47.8% for unmethylated patients. Log-rank (Mantel-Cox) test of comparison of survival was non-significant (p=0.3513).

Also, IDH status was known for all patients. R132H mutation of the IDH 1 gene was detected in 10 patients, and 39 were IDH1 wild-type gene. R172K mutation of the IDH2 gene was detected in 11 patients, and 38 were IDH2 unmutated (wildtype gene).

Disease-free survival (DFS) was unreached for IDH 1 mutated patients and 21.75 months for IDH1 unmutated patients. Overall Survival (OS) was unreached for IDH 1 mutated patients and 21.75 months for IDH1 unmutated patients. Two-year DFS was 75% for IDH 1 mutated patients, and 34.12% for IDH1 unmutated patients, and 2-years OS was 86% for IDH 1 mutated and 47.1% for IDH1 unmutated patients. The Log-rank (Mantel-Cox) test of comparison of survival was non-significant (p=0.1205) **(Figure 3)**.

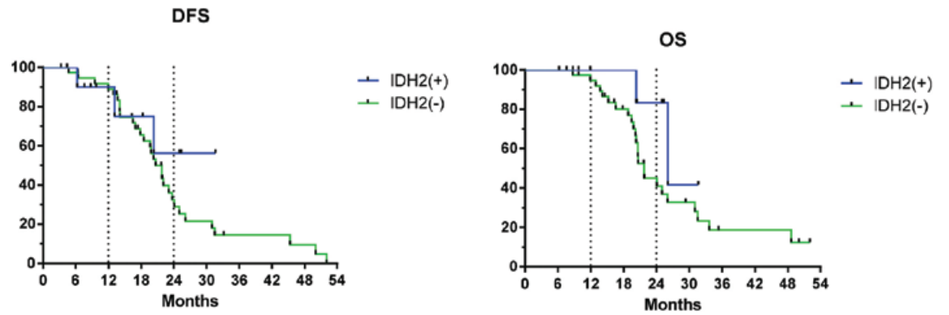
Figure 3. *Two-years Disease-Free Survival (DFS) and Overall Survival (OS) in IDH1 mutated and nonmutated patients: 75% and 86% for IDH 1 mutated patients and 34.12% and 47.1% for IDH1 unmutated patients.*



Disease-free survival (DFS) was unreached for IDH 2 mutated patients and 20.7 months for IDH2 unmutated patients. Overall Survival (OS) was 26.1 months for IDH 2 mutated patients

and 21.75 months for IDH 2 unmutated patients. Two-year DFS was 56% for IDH 2 mutated patients, and 28.8% for IDH2 unmutated patients, and 2-years OS was 83% for IDH 2 mutated and 40.9% for IDH2 unmutated patients. Log-rank (Mantel-Cox) test of comparison of survival was non-significant (p=0.1574) **(Figure4)**.

Figure 4. *Two-years Disease-Free Survival (DFS) and Overall Survival (OS) in IDH2 mutated and nonmutated patients: 56% and 83% for IDH 2 mutated patients and 28.8% and 40.9% for IDH2 unmutated patients.*



Discussion

Malignant gliomas are tumors with one of the worst scenarios, and standard treatment hardly changed overall survival in the past three decades (20).

The median survival of patients with glioma is around 12-15 months for glioblastoma and up to 5 years for grade 3 tumors. However, reclassification within the novel WHO classification will not increase survival, but will be more important for predicting outcome and prognosis. In our small series of patient treatments, we noticed that IDH mutation and MGMT methylation are shown as favorable prognostic factors. Also, there is a trend of separation of survival curves, both for DFS and OS. Unfortunately, our series of patients was small, so we did not show a statistically significant difference. The prognostic difference has been shown between methylated/ mutated patients and nonmethylated/ unmutated in various patients and multicentric studies (8,10,20 – 23).

Conclusion

We are planning to further enlarge our series of patients with a continuously increasing number of included patients. Still, it is challenging to confirm this difference in a real-world setting. With longer follow up we think that we will be able to reproduce the result from large data series and maybe in the future to re-shape treatment with the introduction of new agents and procedures in the treatment of patients with high-grade glioma.

Authors' Contribution

All authors contributed equally to this manuscript.

List of abbreviations used in the manuscript

IDH – Isocitrate dehydrogenase
MGMT – O6-methylguanine DNA methyltransferase
3D-CRT – Three-dimensional conformal radiotherapy
IMRT – Intensity Modulated Radiotherapy
RT – Radiotherapy
DFS – Disease-Free Survival
OS – Overall Survival
WHO – World Health Organization
CNS – Central Nervous System
ECOG – Eastern Cooperative Oncology Group
CT – Computed Tomography
MRI – Magnetic Resonance Imaging
QUANTEC – Quantitative Analyses of Normal Tissue Effects in the Clinic
RANO – Response assessment in neuro-oncology criteria
EANO – European Association of Neuro-Oncology
GTV – Gross tumor volume
CTV – Clinical target volume
PTV – Planning target volume

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ORIGINAL RESEARCH UDK: 616-036.88-053.31(497.711)"2013/2017"

NEONATAL MORTALITY RATE AT GYNECOLOGY AND OBSTETRICS CLINIC IN SKOPJE IN THE PERIOD OF FIVE YEARS IN NEWBORNS TREATED AT NEONATAL INTENSIVE CARE UNIT

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ABSTRACT

Introduction: Neonatal mortality is a number of neonatal deaths per 1,000 live births in a given year or period. Neonatal mortality is defined as a death in the first 28 days of life or a neonatal period after delivery. It includes all life born neonates after 22 gestational week of pregnancy and with birth weight over 500 g. Neonatal mortality is divided into early neonatal mortality which count deaths in 0-7 days after delivery, and late neonatal mortality 8-28 days after delivery.

AIM: The aim of the study is to present hospital neonatal mortality rate at the GOC-Skopje, among newborns treated at NICU in the neonatal period of 0-28 days after births, in the period of five years 2013-2017 and to determinate the leading causes of neonatal deaths at NICU.

Material and Methods: Retrospective study counts neonatal mortality rate in the early and late neonatal period, as well as the leading causes for neonatal deaths in neonatal period of 0-28 days after delivery at the GOC-Skopje, in the period of 5 years. The data is collected from the Data basis of NICU at GOC-Skopje.

Results: Hospital neonatal mortality rate in the 5 years period was 25.6‰, or 25.6 neonatal deaths in the neonatal period. There were 688 neonatal deaths on 26,891 live-born neonates. Neonatal mortality rate in early neonatal period (0-7 days) is – 547 or 20.34‰ of all neonatal deaths in the five years period. Late neonatal mortality (8-28 days) after delivery was in 141 casesor 5.24‰. The leading causes for neonatal death in newborns treated at NICU were complications due to prematurity, respiratory distress syndrome and neonatal sepsis.

Conclusion: The hospital neonatal mortality rate at GOC-Skopje in five years period is high, and requires more prospective studies and strategies to reduce neonatal mortality in the future.

Keywords*: early neonatal mortality, late neonatal mortality, neonatal mortality, NICU, GOC – Skopje*.

Introduction

Neonatal mortality is a number of neonatal deaths per 1,000 live births in a given year or period. Neonatal mortality is defined as a death in the first 28 days of life, known as a neonatal period in newborns after delivery. It includes neonatal deaths between all life-born newborns, born after 22 gestational week of pregnancy and with birth weight over 500 g. (1). Neonatal mortality is divided into early neonatal mortality which counts deaths in 0-7 days after delivery, and late neonatal mortality in the period from 8 to 28 days after the delivery (2). Early neonatal mortality in the first week after delivery is higher than the late neonatal deaths and participates with three-quarters in total neonatal mortality of 0-28 days after delivery. Early neonatal period is the most vulnerable period of live and the mortality is highest in this period of live. Especially survival of newborns in the first 24 hours after delivery is important and almost 50% of neonatal deaths in early neonatal period happened in the first day after delivery (1,2,3). Neonatal mortality rate decreased globally in the last 30 years for more than 50%, from 37neonatal deaths per 1,000 live births in 1990 to 18 in 2017. Almost 4.9 million babies died in neonatal period in the first month after delivery in 1990 globally and number of neonatal deaths was reduced to 2.5 million in 2017 (4). Neonatal mortality rate is still the highest in sub-Saharan Africa and South Asia with 30 and 27 deaths per 100 live-births in 2017 (5). Neonatal mortality in these regions is 9 times higher than the neonatal mortality in high-income countries (5). The highest neonatal mortality rates are recorded in some African countries like Angola, Sudan, Central African Republic and Asian countries like Pakistan, Bangladesh, with more than 40 neonatal deaths per 1,000 live-births. The lowest neonatal mortality is recorded in Slovenia, Iceland, Japan, Baltic countries and Scandinavia with 1 neonatal death on 1,000 live-births (6).

Neonatal mortality is much higher in low-income counties than in developing countries. High developed countries have low neonatal mortality rates 1-2.5‰. Macedonia is considered a middle-income country, with high neonatal mortality rate, ranked as second in Europe in 2017 (6). Neonatal mortality in the Balkan countries in year 2017 was: Turkey – 6.5; Albania – 6.2; Bosnia and Herzegovina – 4.7; Bulgaria – 4; Serbia – 3; Montenegro-2; Croatia – 2 neonatal deaths on 1,000 live-born newborns (7). Macedonia is a European country with the highest neonatal mortality rate, after Moldavia in year 2017 (8). The leading causes of neonatal death globally are preterm birth complications, intra-partum related complications from birth asphyxia, respiratory distress syndrome, neonatal sepsis and other infections and birth defects (9). A respiratory distress syndrome in newborns is usually developed in premature infants with insufficient pulmonary surfactants and formation of a hyaline-membrane disease. Neonatal sepsis and infections during the neonatal period in the first four weeks of birth can be with trans-placental transfer to the newborns, during delivery or can be developed after delivery due to intra-hospital infections and are also result from prematurity and lack of immunity in these newborns. Especially in the extremely preterm newborns, born before 28th gestational week of pregnancy and in very preterm newborns, delivered before 32ndg.w. (9-11). More neonatal deaths in low-income countries and developing countries are caused by complications of preterm births and infectious diseases while in the developed countries the leading causes were congenital malformations and prematurity (5). The aim of the study is to present hospital neonatal mortality rate in newborns in the first four weeks of live (early and late neonatal mortality rates), among newborns treated at NICU in the neonatal period, in the period of five years 2013-2017 and to determine the leading causes of neonatal deaths at NICU like prematurity, RDS, neonatal sepsis and infections.GOC-Skopje is the largest perinatal and neonatal center in the country and participates with 70% in the total neonatal mortality in Macedonia, where complicated pregnancies and newborns with complications are treated. Newborns are treated at the Neonatal Intensive Care Unit.

Material and Methods

The retrospective study shows neonatal mortality rate and leading causes for neonatal deaths in neonatal period from 0 to 28 days after deliveryat the GOC-Skopje, in the period of 5 years. The data is collected from the Data basis of NICUat GOC-Skopje.

All live-born neonates who died in the period of 0-28 days after delivery were included in the study-688 of them were treated at NICU, or those born after 22 g.w. of pregnancy, with birth weight over 500 g. The total number of live-newborns in the period of five years, 2013-2017, on GOC-Skopje was 26,891. Neonatal mortality is being calculated as percent of neonatal deaths of the live-born neonates per 1,000 live births and is displayed in per mile, for early, late and total neonatal mortality. Neonatal deaths are divided into early neonatal mortality 0-7 days after delivery and late neonatal mortality 8-28 days after delivery. Neonatal deaths in the first 24 hours of life as a specific part of early neonatal mortality is also processed. The neonatal mortality was processed for each year separately and in total for the whole period of 5 years.

Inclusion criteria was all live-born neonates admitted at NICU who died in the neonatal period 0-28 days after delivery, born at GOC-Skopje, in the period 2013-2017.

Exclusion criteria was neonatal deaths after 28 days of delivery or in post-neonatal period. Study also determines the most common causes for neonatal deaths at NICU, like prematurity, RDS and neonatal sepsis. Results for the neonatal mortality rate at GOC-Skopje, during these years will be shown as a total neonatal mortality rate and the early and late neonatal mortality in the same period.

Results

Table 1.In the period of 5 years at GOC-Skopje, there were 26,891 live-born newborns. In this period 3,601 newborns were admitted and treated at NICU after delivery, or 13.5% from all live-newborns at Gynecology and Obstetrics Clinic in Skopje. The most of them – 17.1% were admitted at NICU in 2017 and the lowest percentage was in 2014 or 11.8%. Hospital neonatal mortality from 0-28 days after delivery among newborns delivered at GOC-Skopje and admitted at NICU, in the five years period was 688 newborns or 25.6‰. The highest neonatal mortality

rate of 34‰ is present in 2017. From all 3,601 newborns who were transferred and treated at NICU on GOC-Skopje in five years period, 688 or 19.1% died in the neonatal period from 0-28 days after delivery.

Table 1. *Live born newborns at GOC-Skopje, newborns admitted at NICU and neonatal mortality rate, GOC – Skopje, 2013-2017*

Year	2013	2014	2015	2016	2017	Total
Live born newborns	5613	5632	5644	5445	4557	26891
Hospitalized at NICU	744	665	669	742	781	3601
Hospitalized at NICU(%)	13.25%	11.8%	11., 85%	13.6%	17.1%	13.5%
NNM-0-28 days	123	135	97	178	155	688
NNM rate (‰)	21.91‰	23.97‰	17.2‰	32.7‰	34‰	25.6‰

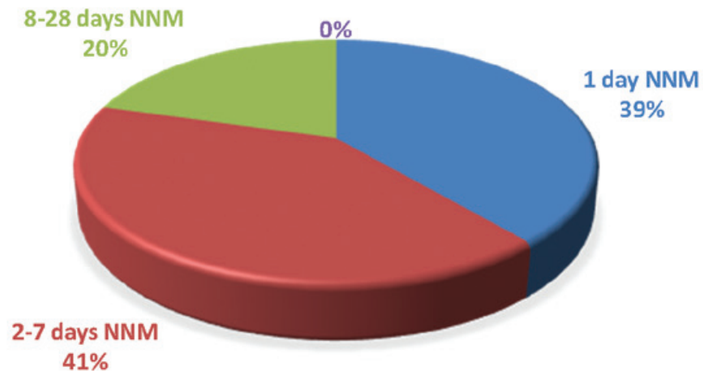
The results show that hospital early neonatal mortality rate 0-7 days after delivery, in five years period-2013-2017 is 20.34‰. Neonatal mortality rate in the first 24 hours after delivery, as part of early neonatal mortality is 9.93‰ and in 2-7 days is 10.41‰. Late neonatal mortality rate 8-28 days after delivery is 5.24‰. The total neonatal mortality at GOC-Skopje in the 5 years period is 25.6‰ or 25.6 neonatal deaths per 1000 live-births in the neonatal period of 0-28 days after delivery. Neonatal mortality rate at GOC-Skopje was the highest in year 2017 with 34‰.

Table 2. *Neonatal mortality rate divided in tree groups, GOC – Skopje, 2013-2017.*

Year	1 day	2-7 days	8-28 days	Total
2013	53 9.44‰	41 7.3‰	29 5.17‰	123 21.91‰
2014	50 8.88‰	55 9.76‰	30 5.33‰	135 23.97‰
2015	38 6.73‰	37 6.56‰	22 3.90‰	97 17.2‰
2016	65 11.94‰	78 14.33‰	35 6.43‰	178 32.7‰
2017	61 13.39‰	69 15.14‰	25 5.48‰	155 34.01‰
Total	267 9.93‰	280 10.41‰	141 5.24‰	688 25.6‰

Neonatal deaths in the first day or first 24 hours after delivery in this period of five years (2013-2017), is 267 newborns or 9.93‰ from all neonatal deaths. Neonatal deaths from 2-7 days after delivery is 280 neonatal deaths or 10.41‰. Neonatal deaths in early neonatal period in total was 20.34‰. Early neonatal mortality participates with almost 80% in the total neonatal mortality rate at GOC-Skopje. Late neonatal mortality in the period 8-28 days after delivery or mortality of the live-born neonates in late neonatal period was 141 or 5.24‰ (Figure 1).

Figure 1. *Presentation of neonatal mortality 1 day, 2-7 days, 8-28 days at GOC – Skopje, 2013-2017*



The most common causes for neonatal mortality of newborns admitted to NICU were complications due to preterm births, before 37 gestational week, respiratory distress syndrome and neonatal infections and sepsis. 94.7% of neonatal deaths were from the preterm births.

Congenital malformations were not subject of this study, because the most of the newborns with complex congenital malformations were admitted to Pediatric surgery and Cardiac surgery immediately after delivery and were not treated at NICU.

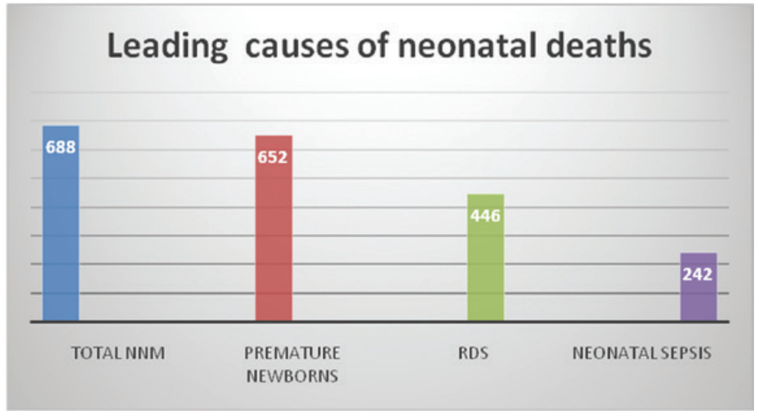
Table 3. *Causes of neonatal deaths at NICU, GOC – Skopje, 2013-2017*

Year	2013	2014	2015	2016	2017	Total
Neonatal mortality	123	135	97	178	155	688
Premature newborns	117 95%	128 94%	90 92.7%	170 95.5%	147 94.8%	652 94.7
RDS	83 67.5%	87 64.44%	63 64.94%	114 64.04%	99 63.9%	446 64.82%
Neonatal sepsis	40 32.52%	48 35.5%	34 35.05%	64 35.6%	56 36.12%	242 35.17%

652 newborns or 94.7% of neonatal deaths were from preterm births or live-newborns delivered before 37 weeks of pregnancy. Complications from preterm births like RDS and sepsis were the leading causes for neonatal deaths at NICU. RDS as a leading cause of neonatal mortality was recorded in 446 newborns or 64.82% of all neonatal deaths and the most of them were in early neonatal period. Sepsis and infections as leading causes of neonatal mortality were

recorded in 242 or 35.17% of newborns and the most of them in the late neonatal period from 8-28 days after delivery (Figure 2).

Figure 2. *Leading causes for neonatal deaths at NICU, GOC – Skopje, 2013-2017*



In this period of 5 years in Macedonia, there were 114,538 live-born newborns, out of which 986 newborns died in the neonatal period 0-28 days after delivery with 8.62‰ neonatal mortality rate. The highest neonatal mortality rate in the country was recorded in 2015 with 9.1‰, while the lowest rate was 7.9‰, recorded in 2013. At the same time there were 688 neonatal deaths on 26,891 deliveries at GOC-Skopje, with neonatal mortality rate of 25.6‰. The highest neonatal mortality rate at GOC-Skopje was recorded in 2017 with 34‰, while the lowest was in 2015 with 17.2‰. GOC-Skopje participates with 23.5% in the total number of births in Macedonia, but at the same time GOC-Skopje participates with 70% in the total neonatal mortality of the country.

Table 4. *Birth rate and neonatal mortality at GOC-Skopje versus Macedonia, 2013-2017*

Year	2013	2014	2015	2016	2017	Total
Birth-rate GOC-Skopje	5613	5632	5644	5445	4557	26891
NNM GOC-Skopje	123 21.91‰	135 2397‰	97 17.2‰	178 32.7‰	155 34.01‰	688 25.9‰
Birth-rate Macedonia	23138	23569	23075	23002	21754	114538
NNM Macedonia	182 7.9‰	200 8.5‰	210 9.1‰	206 9‰	188 8.6‰	986 8.62‰

Discusion

The study shows that there is a high hospital neonatal mortality at GOC-Skopje in this period of five years (2013-2017) of 25.6‰ in the neonatal period from 0-28 days after delivery. Early neonatal mortality rate (0-7 days) after delivery was 20.34‰, while the late neonatal mortality rate (8-28 days) was 5.24‰. Neonatal deaths in newborns admitted and treated at NICU was 19.1%. Other studies from the low-income countries and developing countries show the same or higher neonatal mortality rate (12,13). Studies from developed and from more developing countries show low neonatal mortality rates from 1-4‰ and low hospital neonatal mortality rate (14,15). The leading causes for neonatal mortality at NICU on GOC-Skopje, were complications due to premature deliveries, RDS and sepsis and infections in neonatal period. More neonatal deaths in low-income countries and developing countries are caused by complications of preterm birthsand infectious diseases, while in developed countries congenital malformations and prematurity are the leading causes (12-15). For reducing the hospital neonatal mortality rate at GOC-Skopje in the future, it is necessary to improve prospective studies, which will follow in a long period of time in order to discover some causes and predictors for neonatal mortality. Such a predictors could be some socio-demographics and reproductive variables, maternal conditions and co-morbidities during the pregnancy and some neonatal conditions during pregnancy, on birth and after delivery. All these causes, together or separately, could rise the rate of neonatal mortality. GOC-Skopje participates with 70% in the neonatal mortality in Macedonia and is the biggest tertiary perinatal and neonatal center in Macedonia. GOC-Skopje needs to implement prospective studies for long-term follow-up of neonatal mortality in the future. Such studies on GOC-Skopje and in Macedonia have not been done yet. Also, continuously improving the new standards of professional and technological management as the biggest perinatal and neonatal center in Macedonia, will decrease the neonatal mortality rate in the future.

Conclusion

Hospital neonatal mortality rate at GOC-Skopje and in Macedonia is higher than in a mid-developed countries and developed ones. Strengthening of the complete health care system from primary to tertiary level, with efficient antenatal care for pregnant women, programs for protection of mothers and children, professional and modern technological management with hospitals and neonatal and perinatal centers, will decrease the neonatal mortality rate. Macedonia needs to implement all these facts, for lower neonatal mortality in the future. Also prospective studies for long-term follow-up of neonatal mortality must be done.

Abbreviations: GOC – Skopje – Gynecology and Obstetrics Clinic-Skopje; NICU – Neonatal Intensive Care Unit; G.W. – gestational week; WHO: World Health Organization.

Acknowledgements: We would like to thank to all participants in this study and specially to Prof. Nikola Orovchanec for his support and data collection.

Authors' Contribution: All authors participated in the conception of this manuscript and approved publication.

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CASE REPORT UDK: 616.152.33:616.441-002.951.21-089.87

IATROGENIC HYPERNATREMIA AFTER HYPERTONIC SALINE IRRIGATION OF SPLENIC HYDATID CYST –

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ABSTRACT

Pediatric hypernatremia is a rare electrolyte abnormality. However, it can be a complication of hypertonic saline irrigation in hydatid disease. In our case report, we present a ten-year-old boy with splenic hydatid cyst who received operation treatment and developed electrolyte disturbances. Our aim is to emphasize the potential dangers of the use of hypertonic saline and the appropriate management of hypernatremia.

Key Words: *Hydatid cyst, hypernatremia, hypertonic saline, pediatric patient.*

Introduction

Hypernatremia is typically defined as a serum or plasma sodium greater than 145 mmol/L. It can be graded from mild (146 – 149 mmol/L), moderate (150 – 169 mmol/L) to severe (>170mmol/L) (1). Although pediatric hypernatremia is rare electrolyte abnormality, there can be significant neurologic injury in patients with acute and rapid changes in serum sodium, especially those with severe hypernatremia.

Here we report a case with severe hypernatremia after splenic hydatid cyst surgery.

Case Report

A 10 year old boy was admitted to the University Clinic for Pediatric Surgery complaining of left upper quadrant abdominal pain for over 2 months. Ultrasound of the abdomen was done and a low density image was detected of about 47 mm × 33 mm in size in the spleen, with sharp rims (Figure 1) and also free intraperitoneal fluid in retrovesical pouch around 93 cm^3 (Figure 2). The computed tomography findings were hepatosplenomegaly, with double enlarged spleen by intraparenchymal hypodense tumor formation with irregular shape suspected of hydatid cyst (Figure 3). Residual cavity from previous surgery of hydatid cyst was seen in the left lung parahilar with dimension 32 mm x 25 mm. Laparotomy was done. After aspiration of the cyst content in the spleen, the fluid and cyst content were carefully removed, followed by irrigation

of 10% hypertonic saline and normal saline into the cyst cavity and abdominal cavity for 5 minutes. Total amount of 1250 ml 10% hypertonic saline was used. 10 minutes later, during the intervention, the blood pressure (BP) decreased and blood examination showed abnormalities (sodium: 181 mmol/L, potassium: 2.8 mmol/L, glucose: 7.1 mmol/L). During the intraoperative period potassium chloride, dextrose 5%, and ringer infusion were intravenously infused and the sodium decreased to 178 mmol/L. The patient postoperatively was transferred to the intensive care unit, was sedated with fentanyl (4μg/kg/h) and midazolam (4μg/kg/min) and placed on mechanical ventilation (VC mode).

Figure 1. *Ultrasound of the spleen*

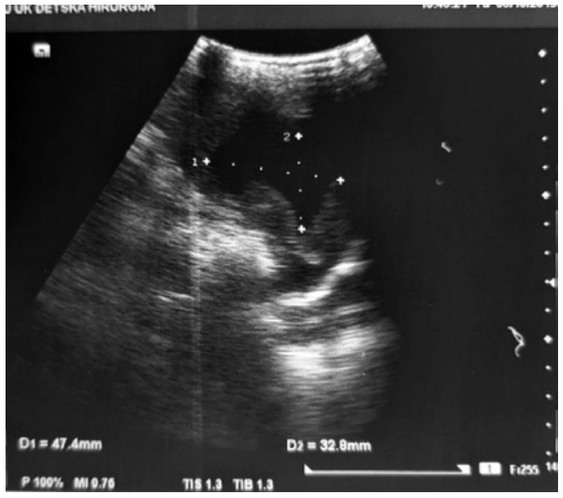


Figure 2. *Ultrasound findings of free intrapertitoneal fluid in retrovesical pouch.*

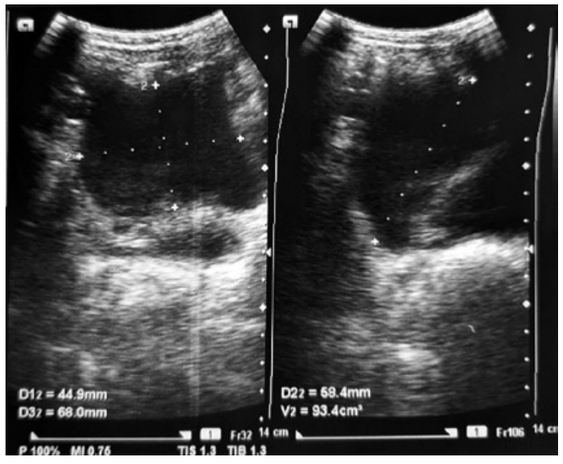
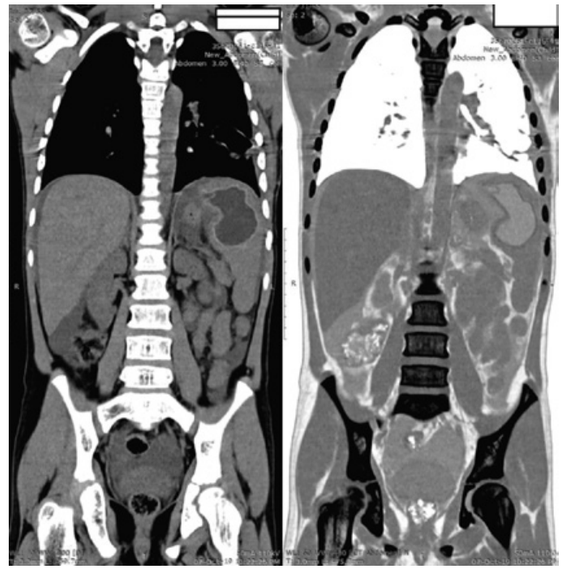


Figure 3. *CT scan of thorax and abdomen*



The next day, the patient was hemodynamically stabile. Moreover, CT scan of the brain was done and there were no abnormalities diagnosed. The patient was sedated all the time until the electrolytes were stabilized (Figure 4, 5). Ringer infusion and 5% dextrose were administered intravenously without affecting hematological abnormalities.

Figure 4. *Time course of sodium concentration pre and postoperation*

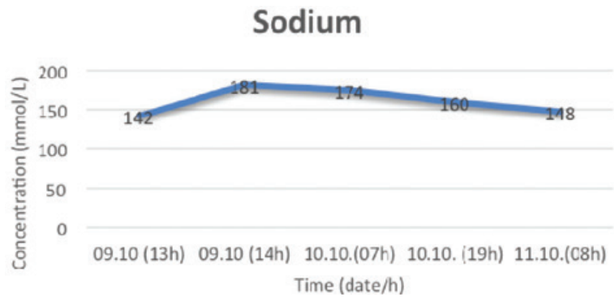
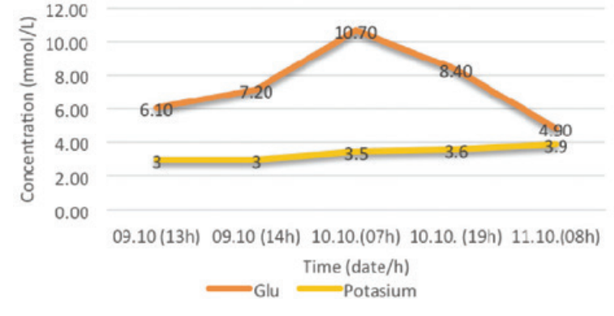


Figure 5. *Time course of potasium and glucose concentration pre and postoperation*



On the second day after surgery, sedation was turned off and the patient was extubated. There were no neurological abnormalities. The patient was discharged from ICU on the 6th day postoperatively and left home 10 days after the admission.

Discussion

The incidence of pediatric hypernatremia is unknown. Gastroenteritis was the main reason for hypernatremia in pediatric population. However, the latest studies show that it is hospital-acquired disease (2).

There are two mechanisms that can cause hypernatremia. The first one occurs when excessive water loss will result in an increase in sodium concentration because water losses are not replaced (for e.g. diarrhea, diabetes insipidus, sweating, skin burns). The second one, when there is excessive salt intake. Iatrogenic administration of excess sodium is the main reason of excessive salt intake in children.

There are several options for treating patients with hydatid cyst (antiparasitic treatment, percutaneous treatment, or surgery), however standard first line procedure is surgery. For preventing recurrence, hypertonic saline (3-30%) is used for irrigation of the hydatid cysts. Hypernatremia is the major complication in these patients (3). Formalin and silver nitrate were used in the past, but there was a risk of obliterative cholangitis, biliary epithelium injury and death due to acidosis (4). Hypertonic saline is absorbed through peritoneal membrane and extracellular compartment results with higher osmolarity. Moreover, fluid from intracellular transfer to extracellular compartment which leads to pulmonary edema and brain dehydration. Hence, clinical manifestation of acute pediatric hypernatremia (acute rise of sodium for less than 24 hours) can include irritability, weakness, vomiting, altered mental status, muscular twitching, seizures, lethargy and coma. In the most severe cases, brain dehydration can lead to vascular rupture, cerebral hemorrhage, irreversible brain damage and can end fatal (5).

We need to take into consideration two things when we correct hypernatremia: the free water deficit and a rate of correction. We can calculate the free water deficit by using these equation:

Free water deficit (ml) = current total body water (TBW) × ([current plasma Na/140] – 1) or
Free water deficit (ml) = (4 ml/kg) × (weight in kg) × (desired change in plasma Na)

TBW is 60% of the child's weight in kilograms (0.6L/kg)

In our case, in a 28 kg boy with plasma sodium of 181 mmol/L, free water deficit was: 0.6 L/kg x 28 kg x ([181/140] – 1) = 4900 ml or 4 ml/kg x 28 kg x 41 = 4600 ml

Also, we always need to account maintenance fluids (in this case 70 ml/h).

Two-thirds of the free water deficit should be replaced over the first 24 hours and the last third in the next 12 or more hours with rate of correction 0.5 mmol/L per hour (10-12 mmol/L for 24 hours) (6, 7).

In our case, in the first 24 h postoperatively the patient received 2000 ml 5% dextrose with 1000 ml ringer infusion and 500 ml normal saline. The next 24 h he received 2000 ml 5% dextrose and 1000 ml normal saline. We decreased sodium level from 181 mmol/L to 148 mmol/L for fifty hours. We should always take in consideration the rate of correction because if correction is applied too fast extrapontine myelinolysis can occur (8).

Conclusion

Hypertonic saline should be used with caution for irrigation since it can develop severe hypernatremia. It's necessary to keep close monitoring of the electrolytes perioperative. If hypernatremia occurs calculation of free water deficit and the rate of correction should be taken into the consideration.

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INTRAVAGINAL BRACHYTHERAPY SUPPORTED BY LOCAL ANAESTHESIA IN THE TREATMENT OF ENDOMETRIAL CANCER – SINGLE INSTITUTIONAL EXPERIENCE

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ABSTRACT

Intravaginal brachytherapy in endometrial cancer is an inevitable part of the treatment. In the early stages of the disease, it significantly reduces the risk of local recurrence in the vaginal cuff with low rates of late toxicity. In the advanced stages, it provides palliative control usually with a hemostyptic effect. Brachytherapy may be the only postoperative treatment – monotherapy, or as a boost following the external beam radiotherapy, depending on many prognostic factors. Placing the vaginal applicator deep into the vagina is certainly an uncomfortable feeling, combined with pain, anxiety and discomfort. Local anaesthesia helps in reducing the painful sensations, gives adequate relaxation, but more importantly provides a quality insight into the condition of the vagina, and thus a successful application. Through our experience with the local vaginal anaesthesia with lidocaine 2% gel, we want to emphasize that intravaginal brachytherapy, supported by local anaesthesia, regardless of the degree of pain relief is directly related to successful treatment.

Key Words: *anaesthesia, analgesia, endometrial cancer, intravaginal brachytherapy.*

Brachytherapy role

Endometrial cancer is one of the most common type of malignancy in women around the word. Bourdais of the GLOBOCAN cancer statistics, estimated that 382,069 new cases and 89,929 deaths worldwide in 2018 are attributed to endometrial cancer. Futhermore, this type of cancer was reported as the the second most common and the fourth leading cause of death in respect to the gynecological cancer types in 2018 (1). In North Macedonia, the number of newly diagnosed women with uterine cancer is 192 cases per 100,000 population and mortality is 37 deaths per 100,000 population.

Primary management of endometrial cancer is consisted in surgical removal of the uterus (total abdominal hysterectomy) and bilateral salpingo-oophorectomy. Adjuvant radiation therapy may be recommended when higher stage of the disease is present, with proved increased depth of myometrial invasion, concomitant lymphovascular space invasion, increased age, increased tumor size, histology, lymph node positivity and other adverse risk factors (2-6). Recurrence rate of the tumors is 10-20% and out of these rates (80-90%) will recur within three years (7). Treatment of recurrences may be a real challenge. If local vaginal recurrences are diagnosed early are curable while pelvic and distant recurrences have a poor prognosis and outcome. Furthermore, in these patient's chemotherapy and/or external beam radiotherapy (EBRT) may decreases the risk of locoregional failure. However, the toxicity over all will be increased.

Local recurrences are most often present in the vagina so vaginal brachytherapy (VBT) rather than EBRT is a good choice for patients since it decreases this risk of recurrence rate with minimal toxicity present (6). VBT treatment for early stage endometrial cancer should provide sterilization of the vaginal incision from possible postoperative microscopic spread of the disease (8,9). In patients who have not had surgery (usually due to internal comorbidity) or in patients who cannot have EBRT (usually due to obesity), VBT plays a key role in treatment. Therefore, VBT has become an inevitable part nowadays in the treatment of endometrial cancer.

Brachytherapy presents a form of internal radiation treatment. In this type of treatment radioactive sources are placed direct on or into cancer tissues, or on tumor bed. It this way extremely high dose of radiation are allowed to be received by the tumor and the sparing of the organs at risk is relative. VBT compared to EBRT, delivers a conformal dose to the vagina and small spread to the surrounding tissues. This is certainly allowed by its anatomy and placement.

The vagina is a **fibromuscular tube** with anterior and posterior walls. These walls are collapsed in contact with one another. At the upper end vagina is surrounding the cervix where it creates two domes, the an anterior and a posterior one. The length of the vagina is different from woman to woman. Due to the presence of the cervix in the front wall of the vagina and there is difference in length between the front wall (7.5 cm long) and the back wall (approximately 9 cm long).

Intravaginal brachytherapy is usually adjuvant after a hysterectomy. It is realized with a vaginal applicator, through which the required irradiation dose will be realized in the region of the vaginal cuff on the upper vaginal area, an area at high risk for recurrence (10). Therefore, VBT is an important part of the treatment of endometrial cancer, either as a single treatment, or in combination with EBRT and/or chemotherapy in advanced stages of disease (11, 12). Apart from the benefit, it must be emphasized that its side effects are insignificant and easy to manage, due to the specific possibility of brachytherapy for high dose loading of the target volume, and almost complete protection of healthy structures. It has been proven toxicity rates shown by the bladder, rectum, bowel, bone, or bone marrow are quite low. However primary risk of toxicity with VBT is forwarded to the proximal vagina which may result in vaginal atrophy, stenosis, and/or shorten vaginal length.

Intravaginal brachytherapy modalities

VBT technique can be realized with many different applicators. A vaginal mold applicator has been studied with the potential benefit of customization of the applicator to the patient's vaginal anatomy with decreased air pockets and potentially improved dosimetry (13) (Image 1). There is also a set of vaginal cylinders that contain applicators with equal length of 14 cm, but with different diameter in the range of 2 to 3.5 cm (Image 2). Another set is the set of segmented

vaginal applicators that allow a difference in lengths (Image 3). However, the vaginal cylinder is a smooth, plastic cylinder, with one central channel or more channels distributed across the diameter of the applicator, through which the radioactive source can move and create the radiation dose shaping around the target volume.

Most commonly used applicator is a single channel vaginal cylinder. This applicator is the simplest to plan. It treats the vagina circumferentially and equally to the depth of dose specification. Single channel vaginal cylinder delivers decreased dose at depth superior to the vaginal apex as a result of anisotropy. Multi-channel vaginal cylinders show advantage of customizing dose to either deliver asymmetric doses or avoid adjacent normal structures. The multi-channel cylinder has been shown to decrease dose to the bladder and rectum, but at the expense of increased vaginal mucosa dose. Patients with large lesions or those that are >5mm thick may benefit from a multi-channel cylinder, but they may still be difficult to be adequately treated without delivering excess dose to the vaginal surface (6,8).

Image 1. *Vaginal mold applicators*

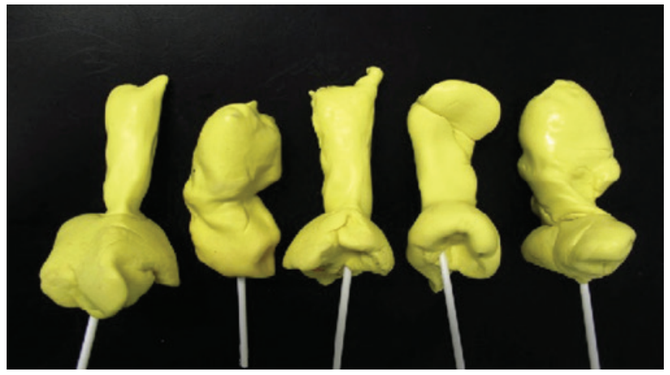


Image 2. *Vaginal cylinder applicator set*

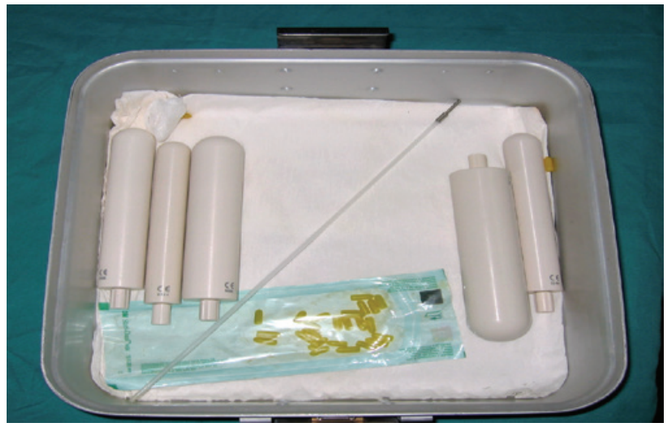
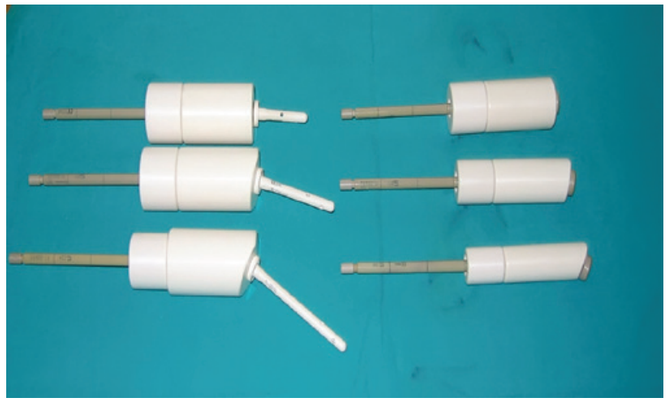


Image 3. *Segmented vaginal applicator set*



VBT procedure usually requires patient's cooperation and immobilization which can only be achieved when the patient is comfortable and relatively free from pain. On the contrary, insertion may not be properly done and this may result in poor distribution of dose and complications arising from giving too much radiation dose to the organ at risk (rectum and bladder) and inadequate dose to the tumor itself.

Type of vaginal pain

Vagina is innervated predominantly from the autonomic nervous system. Parasympathetic and sympathetic nerves arise from the **uterovaginal nerve plexus** (in turn a subsidiary of the inferior hypogastric plexus). Inferior 1/5 of the vagina receives somatic innervation. This is throught the pudendal nerve, the **deep perineal nerve**. Because the pudendal nerve carries motor and sensory fibers that innervate the pelvic muscles, a pudendal nerve block relieves pain.

The presence of a vaginal applicator deep in the vagina triggers different sensations in patients, depending on their sensitivity – pain threshold. That stimulates sympathetic autonomic afferents which enter the spinal cord at the T10-L1 level. This produces poorly localized, central, lower abdominal pain, sometimes associated to nausea and vomiting. Distension of the upper vagina stimulates parasympathetic autonomic afferents from the pelvic splanchnic nerves of S2-4 to cause lower back pain. Distension of the lower parts of vagina through the labia stimulates somatic afferents via the pudendal nerves of S2-4 (14).

The optimal anaesthetic technique has not been recognized by published data. In practice, local anaesthesia is preferred. Lidocaine is a commonly used local anesthetic for vaginal procedures. The aim is to provide good analgesia (painlessness) and muscle relaxation. More importantly, it allows better placement of the applicators. Topical or local anaesthesia is used by radiotherapists.

Anaestesia modalities

Anaesthesia in brachytherapy does not have a single prescribed recommendation, it varies from one center to another, depending on the technique of application. Almost all anaesthesia procedures are used. Uterovaginal applications are invasive, so they usually use general, epidural, or spinal anaesthesia. In intravaginal applications, as less invasive, local anaesthesia is an excellent choice and is increasingly being implemented.

Lim et al, showed the complications related to different methods of anaesthesia (general anaesthesia, topical anaesthesia and sedation, paracervical nerve block and conscious sedation) using the Common Toxicity Criteria (15). General anaesthesia has significantly more complications than other methods, spinal or topical anaesthesia (16).

According to Elumelu et al (17) local vaginal anaesthesia with 10% xylocaine spray can decrease the degree of pain during HDR intracavitary brachytherapy with no expected major side effects.

Some centers use a vaginal pack with lidocaine 2% gel, which is placed about 15 minutes before starting the procedure. Significant pain control is achieved during the procedure, but an additional comfort period is also noted after the procedure (18).

Generally, local lidocaine anaesthesia is considered easy to administer, comfortable, and low-priced which makes it affordable.

Single institutional experience

The Brachytherapy Department within the University Clinic of Radiotherapy and Oncology, Skopje, the only one of its kind in our country, is also a regional center, because in addition to domestic, also treats patients from neighboring countries, thanks to the technical and staff support. Starting from 2005 until today, an average of 250 intravaginal applications are realized per year, the most of which (about 75%) are postoperative, and the remaining 25% are part of the definitive treatment of endometrial carcinoma. Through our clinical experience, including excellent response and patient monitoring, we want to highlight the importance of intravaginal brachytherapy in the treatment of endometrial cancer.

The aim is to point up that VBT supported by local anaesthesia, regardless of the degree of pain relief, even with minimal pain relief, is directly related to successful application and an optimum brachytherapy treatment effect.

Selecting patients

All patients requiring intravaginal brachytherapy are candidates for application under local anaesthetic. These are patients in postoperative setting (because of shortened vagina), non-operative patients (because of local active disease, vaginal stenosis) or patients after EBRT (because of radiation fibrosis).

Intravaginal application technique

The treatment is carried out in a dedicated brachytherapy room (Image 4). The procedure is an aseptic one. It begins with catheterization of the bladder, Foley's catheter is inserted, filled with 7 ccm contrast and fixed against the bladder neck, necessary for visualization of the organ at risk. An examination under the speculum makes an assessment of the local finding in the vagina, its length and the possibility of stretching. The choice of vaginal applicator depends on it. We use a single channel vaginal applicator. After the betadine wash, lidocaine 2% gel is smeared in the vagina, which after about 5 minutes provides easy pain relief in the vagina and easier sliding of the vaginal cylinder deep into the vagina. The position of the applicator is fixed with a *universal Varian applicator clamping device (Image 5)*. The vaginal applicator is CT/MRI compatible. Only for 2D planning rectal marker is placed deeply in the rectum to visualize it (Image 6). In patients with active hemorrhoidal problems, local anaesthesia is also used for a more comfortable placement of the rectal marker (by applying a gel on the tip of the marker). After that, all patients undergo 2D or 3D – CT simulation and return to the operating room – brachytherapy bunker, without fear of applicator displacement, because of special transport tabletop.

Image 4. *Brachytherapy treatment room*

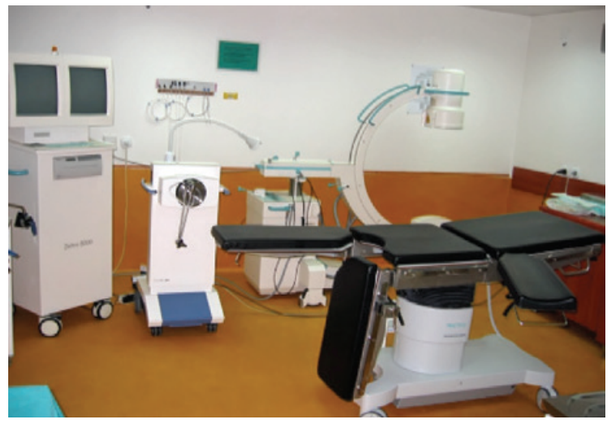
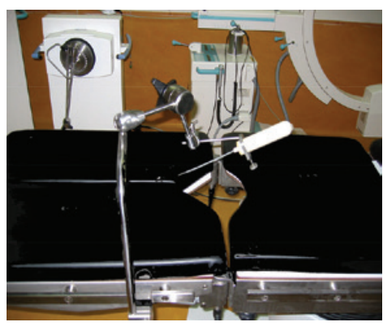


Image 5. *Fixed position of the applicator with a universal Varian applicator clamping device*



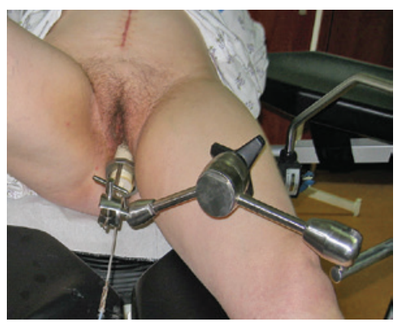
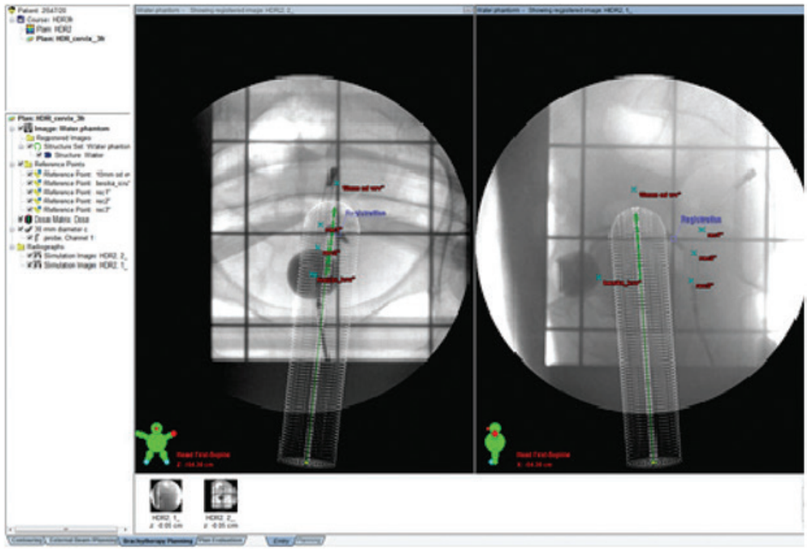


Image 6. *Orthographic images with vaginal applicator*



Adjuvant intravaginal brachytherapy (postoperatively or after EBRT) is administered via 1 fraction, with a prescribed dose of 7 Gy, at 5 mm from the tip of the applicator. As part of the definitive treatment (non-operative patients or inoperable active disease) 3 fractions are realized, once a week, with a prescribed daily dose of 7 Gy, at 10 mm from the tip of the applicator, until realization of a total tumor dose of 21 Gy.

When dosimetric planning is completed, we deliver HDR brachytherapy using a remote after loader device (Varian, GammaMedPlus) with Iridium 192. Once the prescribed dose is delivered, we remove the applicator and the Foley catheter. The entire procedure is usually in the outpatient setting.

Depending on the local finding (shortened vagina, presence of surgical incision, pain threshold), patients may be prepared intravenously before treatment with analgesics and muscle relaxants.

Our experience with VBT supported by local anesthesia has so far shown no impairment of patient's safety, no adverse effects during the procedure or any periprocedural morbidities or complications. Acute side effects are very rare. If they occur, first-degree cystitis and proctitis (according to Common Terminology Criteria for Adverse Events), are the most common and are easily managed and completely acquired. Late side effects include vaginal dryness and stenosis, which are solved by vaginal dilators. We haven't registered mortality as a result of this treatment. The follow-up of patients is always adjusted according to the overall treatment, not specifically for brachytherapy.

It must be noted that this report has few limitations. Our experience is associated exclusively to the use of lidocaine 2% gel, therefore without the possibility of comparison with other anaesthetics. We don't evaluate the patient's emotions, such as fear, anxiety, pain and distress. The reduction of pain clearly provides better relaxation of the patient, which in the quality intravaginal application is the most important segment. Our future plans are to prove the above objectively by scoring the pain, through the appropriate pain relief scales.

Conclusion

Intravaginal brachytherapy in endometrial cancer is an inevitable part of treatment. In the early stages of the disease, it has a curative effect that provides long and quality life and in the advanced stages, it provides palliative control usually with a hemostyptic effect. The maximum benefit is directly dependent on the proper placement of the vaginal cylinder, where the local anaesthesia has the significant role. Lidocaine gel alleviates patient discomfort, thus providing clear insight into the local status and proper placement of the vaginal applicator, with a fully regulated safety profile, without any side effects.

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COVID-19: CHALLENGES AND OPPORTUNITIES FOR NURSING CARE IN NON-COVID, INTENSIVE CARE UNIT (ICU)

What is it like being an intensive care nurse on the front lines during the COVID-19 pandemic?

The Covid-19 pandemic is placing an unprecedented strain on the nation's health care facilities and revealing many underlining weaknesses that exist in the health care system. The policies, processes and capacities of individual health units for safe and timely patient care, emergency preparedness, resources allocation and intra and inter-sectional collaboration, are the key determinants for a successful response to the pandemic. Preparing the ICU is an integral part of any pandemic response.

The University Clinic for Surgical Diseases "St. Naum Ohridski" is an established healthcare facility in our country's health system. Intensive Care Unit (ICU) in the clinic of surgery is the multispecialty medical care center for critically ill patients who require surgery, such as a motor vehicle accident or other trauma, accident victims. It provides care to patients suffering from brain injuries and to patients recovering from complex surgeries that need frequently nursing care. In this letter, I would like to discuss some of the key principles and strategies for ICU preparedness, and our experiences in such conditions.

Since the beginning of the pandemic until now (end of August 2020), the ICU at the University clinic for surgical diseases "St. Naum Ohridski", Skopje, has been following all the protocols and guidelines according to world standards and WHO recommendations.

Firstly, the clinic has set up a Coordinating Commission to deal with global coronavirus conditions. Generally, ICU nurses provide the most of the direct care to the critically ill patients with life threatening conditions, they develop and implement nursing care plans, and maintain medical records. They use their advanced skills to care for patients who are critically ill and at high risk with life-threatening health problems. ICU nurses must be physically, mentally, and emotionally strong in order to be able to work with seriously ill patients. Wearing protective equipment, visors, masks (surgical and N95), surgical hats, disposable gowns, tins, as well as continuously care for hand disinfection, have been mandatory for all medical staff, especially nurses.

According to the protocols, the first action was based on measuring body temperature at the entrance of the hospital, where triage is performed for the degree of urgency. Any patient who had a fever (above 37 C degrees) was considered suspicious and was referred to the Covid Center for further treatment. An area is defined in which an individual is evaluated and screened using the case definition; if the person becomes a suspected case, the nurse should refer to COVID-19 protocol. Isolation: If the case definition is met, the patient should immediately be given a mask and directed to a separate area (an isolation room, if available). At least 1 meter distance should be kept between suspected patients and other patients. Acuity-based triage is the standard method of sorting patients in the medical setting. This is used as the basis for identifying patients who require immediate medical intervention, patients who can safely wait, or patients who may need

to be transported to a specific facility based upon their condition. A standard, validated tool should be used to assess for severity of patients and designation to the appropriate part of the facility or the health care system. Patients, who came for regular surgical treatment, additionally filled in questionnaires where they had to answer several questions, such as whether they were in one of the crisis Covid regions, whether last days have had any of the specific Covid symptoms and the like. But all life-threatening situations, urgently, resulted in admission to the ICU. At the ICU admission, those who do not have a mask are immediately given one, body temperature is measured, staff approaches with complete protective equipment and exposure is reduced during each intervention around the patient, of course if possible. It is the most difficult to maintain a distance of at least 1 m in a patient who needs continuous care and management of all its symptoms, and thus not to reduce the quality of health care provided. During the shift, we tried to minimize all possible contacts between the other departments, moving only where we had to. Each nurse drank their coffee on her own and kept an eye on the clock when her shift was over. The most of us probably were not as much afraid of ourselves as we were of transmitting the virus to our loved ones at home. And of course, then came the first major shortcomings of nurses.

Nurses were missing for various reasons. The most often not due to illness, but self-isolation after contact with a suspicious or confirmed case of "covidium". Some of them were exempted by the newly enacted Government Law (a State of emergency was also declared) and stayed at home due to pregnancy, chronically illness or the care of children as kindergartens and schools were closed. In fact, only 10 nurses went to work, 10 of them stayed at home. It was necessary to keep everyone in the workplace, where there was large number of patients, as well as very serious cases, including 2 of them in coma and the same after three months of treatment were discharged from the hospital in good general condition without contractures or decubitus. At the same time swabs were taken on all suspected cases of Covid, fortunately all being negative at that time. All this speaks about the experience of the nurses, their professionalism and achieving positive results in some exceedingly difficult working conditions.

As the head nurse in the ICU, I had the most difficult task in this world (or so at least I thought to myself), how, with 10 nurses, in conditions of comfort, to provide continuous care and attention to all patients in the Intensive Care Unit and recovery room? … these included the first, second, and third shifts, weekends, holidays … And at the same time it was ideal to have a "clean team" of at least 2 nurses in stock at all times, who had no contact with the sick for several days, in case they had to replace one of the nurses that went into self-isolation. Then, I made a schedule by rotating 2 nurses who came on 24 hours duty, with the same ones being free 5 or 6 days after duty. For them, that meant 5 or 6 days without contact with a high-risk patient. In fact, it was the ideal setup. I was also involved in the duty scheduling, and the social worker of the department was immensely helpful. Under normal circumstances, nurses take a third shift every fourth or fifth night and one shift consists of a total of 3 nurses, who as everywhere in the world are also insufficient in the process of providing health care.

Not only myself, but all of the nurses who have gone through this period, will always remember those exhausting shifts, where you withstand superhuman strength on duty. But only through teamwork and complementarity, results have been achieved. There were nurses who had to be in self-isolation for a second time due to risky contact. In May, almost all nurses have returned, except mothers of children (up to 10 years) and pregnant women. Fortunately, so far, only 1 nurse has tested positive for the virus and she later returned to work in good general condition. At the beginning of June, Covid 19 antibody test was performed on all staff at the hospital level. The results obtained for the staff in the intensive care unit were good, in fact all of them were negative. As the coronavirus progressed in the world, so did the number of infected people in Macedonia. To achieve sustainable ICU services, we needed to 1) prepare and implement rapid identification and isolation protocols, and a surge in ICU bed capacity; (2) provide a sustainable workforce with a focus on infection control; (3) ensure adequate supplies to equip ICUs and protect healthcare workers, nurses and (4) maintain quality clinical management, as well as effective communication.

Since June, all patients admitted to the hospital are required to have a Covid-swab, after which the patients are placed in solitary confinement, the Covid-test is waited for, and later they are admitted to the operating room. If there is an emergency (perforated appendix or incarcerated hernia, illeus, etc.) the patient is taken to intensive care, where all protection measures are observed again with proper use of protective equipment. However, in the case of a life-threatening condition, the patient is admitted to ICU, where in addition to the regular protocols for admission of a patient in coronary conditions, the nurse in the ward receives a throat and nose swab. Proper preparation when taking a nurse swab is extremely important when it comes to Covid-19. The nurse must in every case conduct as that they are positive, until the opposite is confirmed.

Since March until September, the number of patients who passed through our emergency intensive care room was 755 patients, 705 of whom have been operated on.

The number of patients in the ICU from March to September was 513 patients, 389 of whom were operated on. The total number of tests for Covid-19, at the level of the entire hospital was 424, of whom 22 have been tested positive and were later referred to the Covid Center.

ICU nurses need to be specialized in evaluating intensive care patients, recognizing complications, administering care, and coordinating with other members of the critical care team. Successful critical care nurses also excel at interpersonal communication, leadership, strategic planning, and a variety of high-level nursing skills, critical thinking, as well as rock-solid decision-making.

Head Nurse, ICU
Daliborka Dushanovska
Specialized Intensive Care Nurse
September, 2020

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

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

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

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Review articles, case reports, therapeutic and technological innovation, discussions, critics, impressions from meetings, information for international conferences and reviews of new books or variate may be written in different sequences and manners.

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The title of the manuscript written in CAPITAL LETTERS.

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Abstract in English. Abstract should include up to 250 words and should contain goals of the paper, important elements from the methodology, concisely displayed results and conclusion. Each abstract at the end must have **Key words:** in alphabetical order.

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Results are displayed in simple manner with text, images, tables and charts that are submitted in the text where author wants to stand, titled and numbered appropriately. Additionally, on separate document all carts images and tables are send together with the manuscript.

Title and the number of the charts and tables are placed above them while the explanations, abbreviations and comments are placed below. Images title and number is placed below and the image should include proper explanation.

Discussion section emphasize the key finding of the actual research and compares these result to other relevant literature data.

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

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

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

Examples:

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2. Journal supplements:

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

3. Books

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

4. Doctoral or master thesis

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5. Electronic reference

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

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

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

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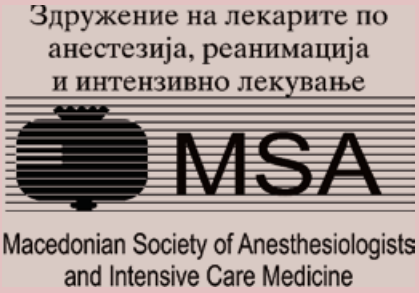
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