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Betimi i Hipokratit

Në çastin kur po hy në radhët e anëtarëve të profesionit mjekësor premtoj solemnisht se jetën time do ta vë në shërbim të humanitetit. Ndaj mësuesve do ta ruaj mirënjohjen dhe respektin e duhur. Profesionin tim do ta ushtroj me ndërgjegje e me dinjitet. Shëndeti i pacientit tim do të jetë brenga ime më e madhe. Do t'i respektoj e do t'i ruaj fshehtësitë e atij që do të më rrëfehet. Do ta ruaj me të gjitha forcat e mia nderin e traditës fisnike të profesionit të mjekësisë.

Kolegët e mi do t'i konsideroj si vëllezër të mi.

Në ushtrimin e profesionit ndaj të sëmurit tek unë nuk do të ndikojë përkatësia e besimit, e nacionalitetit, e racës, e politikës, apo përkatësia klasore. Që nga fillimi do ta ruaj jetën e njeriut në mënyrë apsolute. As në kushtet e kërcënimit nuk do të lejoj të keqpërdoren njohuritë e mia mjekësore që do të ishin në kundërshtim me ligjet e humanitetit. Këtë premtim po e jap në mënyrë solemne e të lirë, duke u mbështetur në nderin tim personal.

The Oath of Hippocrates

Upon having conferred on me the high calling of physician and entering medical practice, I do solemnly pledge myself to consecrate my life to the service of humanity. I will give my teachers the respect and gratitude which is their due. I will practice my profession with conscience and dignity. The health of my patient will be my first consideration. I will respect the secrets which are confided in me, even after the patient has died. I will maintain by all the means in my power, the honor and the noble traditions of the medical profession.

My colleagues will be my brothers.

I will not permit considerations of religion, nationality, race, party politics or social standing to intervene between my duty and my patient. I will maintain the utmost respect for human life from its beginning even under threat and I will not use my medical knowledge contrary to the laws of humanity. I make these promises solemnly, freely and upon my honor

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Beyond the Paris climate agreement: Health central to climate change action

Кон договорот од Париз за климата: здравјето средиште за акција кон климатските промени

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ABSTRACT

The changing global climate affects human health, well-being, and life on earth. Evidence of the health effects of climate change and future health risks for the WHO European Region is emerging. The new Paris climate agreement is essential forsafeguarding public health as it will help bring about healthier people:through cleaner air, safer freshwater and food and more effective and fairer health and social protection systems.The health sector can also improve its own practices and simultaneously minimise its carbon emissions. The World Health Organization (WHO) works to identify policies that could prevent, prepare for, and respond to the health effects of climate change. This could be the greatest global health opportunity of this century. Health professionals, health ministries, and WHO have a vital role to play in ensuring progress on climate changemitigation and health adaptation action; we need to protect and promote health worldwide.

Keywords: Climate change, health, health policy, public health, World Health Organization

INTRODUCTION

Climate change differs from traditional European local and regional environment and health issues, in that it requires local, regional, and global solutions. It acts over long periods of time; is subject to multiple uncertainties; is strongly influenced by social, economic and environment determinants; causes diverse and interacting health impacts;andposes new threats, challenges, and opportunities at all levels of society.Our health and well-beingare affected by climate change both directly due to amplified extreme weather eventsand indirectlythrough its effects on economic conditions and social determinants (1). Climate change presents multiple hazards which interact with pre-existing vulnerabilities causing substantially worse health outcomes. Health impacts are moderated by the strength of the health system and its capacity to manage and adapt to climate sensitive health risks. Well-designed mitigation climate change policies result in health co-benefits (2, 3, 4).

Worldwide, climate change is expected to cause approximately 241 000 additional deaths per year between

2030 and 2050: 38 000 by heat exposure in elderly people, 48 000 by diarrhoea, 60 000 by malaria, and 95 000 by childhood undernutrition (5,6). The estimated economic damage costs are huge, ranging between 5% and 10% of gross domestic product (7).

The main risks to health from climate change are more intense heatwaves and fires,increased prevalence of food-, water- and vector-borne diseases, increased likelihood of undernutrition resulting from diminished food production in poor regions, and lost work capacity in vulnerable populations. Uncertain but potentially more serious risks include breakdowns in food systems, conflict and population movement due to resource scarcity, and exacerbation of poverty, undermining the health and other objectives of the post-2015 sustainable development agenda.Globally in 2012, 3.7 million deaths (482 000 in the WHO European Region) were attributed to ambient air pollution (8).

Poorer populations and children are more at risk from climate change, with impacts differing between men and women. Overall climate change is expected to widen existing health inequalities, both between and within populations. Evidence of the direct and indirect health effects of climate change and future health risks for the WHO European Region is well established. Robust policy is now required to push for effective mitigation and adaptation in all sectors (2, 5, 9).

In 2009, The Lancet Commission on Managing the Health Effects of Climate Change called climate change "the biggest global health threat of the 21st century" (10). Six years on, the new Commission has reached the same conclusion, adding that responding to climate change could be the greatest global health opportunity of the 21st century (5).

The United Nations Framework Convention on Climate Change (UNFCCC) is the primary international and intergovernmental forum for negotiating the global response to climate change. The ultimate objective of UNFCCCis to stabilize greenhouse gas concentrations in the atmosphere at a level that will prevent dangerous human interference with the climate system (1). The main goal of the annual Conference of the Parties (COP) is to review UNFCCC's implementation.

The ParisCOP21agreement acknowledges that climate change is a common concern of humankind and thus countries should, when taking action to address climate change, respect, promote and consider their respective obligations on right to health(12).

AGREEMENT CAPTURES ESSENTIAL ELEMENTS TO DRIVE HEALTH ACTION FORWARD

The first COP took place in Berlin in 1995 and significant meetings since then have included COP3 where the Kyoto Protocol was adopted, COP11 where the Montreal Action Plan was produced, and COP17 in Durban where the Green Climate Fund was created (13, 14, 15, 16).

COP21 in Paris marks a key juncture in the work of the UNFCCC. The Paris Agreement and the outcomes of COP21 were agreed by 195 nations on 12 December 2015 (12). Theagreement's main aim is to keep a global temperature rise well below 2^0C this century and drive efforts to limit the temperature increase even further to 1.5^0C above pre-industrial levels. The 1.5^0C limit is a significantly safer defence line against the worst impacts of a changing climate.

The agreement will be held at the United Nations in New York and opened on 22 April 2016 for signatures for one year. The agreement will enter into force after 55 countries that account for at least 55% of global emissions have signed.

The agreement recognizes the social, economic, and environmental value of voluntary mitigation actions and their co-benefits for adaptation, health, and sustainable development (12).

It recognizes that climate change represents an urgent andpotentially irreversible threat to human society and thus requires the widest possible cooperation byallcountries, and their participation in an effective and appropriate international response, with a view to accelerate the reduction of global greenhouse gas emissions (12).

Additionally, the agreement aims to strengthen the ability to deal with the impacts of climate change, to combat climate change, and unleash actions and investment towards a low carbon, resilient, and sustainable future.

The agreement covers both crucial areas identified as essential for a landmark conclusion:mitigation (reducing emissions fast enough to achieve the temperature goal) and adaptation (increasingcountries' ability to deal with climate impacts). Furthermore, it intendsto strengthen the ability to recover from climate impacts and financial support for nations to build clean, resilient futures.

For WHO a strong climate agreement is also is a vital global health agreement, as health acts as a trigger for actions to combat climate change. The primary role of WHO is to direct and coordinate international health within the United Nations system. This is an historic opportunity for WHO and the entire health community (18). For COP21, WHO developed a fact sheet "Did you know: by taking action on climate change you can strengthen public health?", designed for specific audiences from health ministers, health professionals, finance ministries, local authorities and the general public (19). The climate and health country profiles project was also introduced (20).

CLIMATE CHANGE AND HEALTH – THE WHO ROAD

In 2008, health ministers passed a World Health Assembly resolution on climate change, with two action plans of implementation (2009 and 2014) committing countries to take action to protect human health from climate change (21, 22, 23). The first WHO conference on health and climate was held in August 2014. The assembled high-level government representatives, development partners, and technical experts explored ways of building health resilience to climate risks and deliberated how best to ensure that more sustainable and low-carbon development choices result in improved environments and health-care provision (24).

The WHO European Region has taken action since 1989: at the first ministerial conference on environment and health, climate change was flagged as a growing problem. At the 1999 ministerial conference in London, a call for action on increasing research, monitoring, and identification of adaptation measures as well as healthy mitigation measures was endorsed. In 2004, after the 2003 heat-wave, countries called for increased action on disaster management and prevention (25). At the2010 conference in Parma, European countries formally confirmed their commitment to act on climate change and health (26).The European environment and health process provides an ideal platform for continuation of the process. It brings together the ministries of health and environment of the 53 European Member States. A working group on health in climate change was created. As a result, 32 countries examined their vulnerability to climate-change-related health threats; 24 prepared adaptation plans including health. While most countries in the Region have taken action to reduce greenhouse gas emissions, more needs to be done to capitalize on the health co-benefits of energy, transport, building and agriculture (27). Much is already happening to adapt to climate change health impacts and to reduce emissions, hence protecting health at local, national, and regional levels in the Region. For example, WHO has already supported countries in establishing heat-health warning systems to save lives during heat-waves and in piloting climate-resilient water-safety plans. Health 2020, the European policy for health and well-being, providescontextual analysis, strategies, and interventions for various policy challenges affecting public health, including climate change (28).

In 2015, the World Health Assembly passed a resolution to address the health impacts of air pollution. In line with this agreement, the WHO secretariat is scaling up its capacity to help countries implement WHO's guidelines for outdoor and indoor air quality (29).

A public health perspective on the benefits of climate solutions has a key role to play in engaging people in issues related to climate change and in driving more ambitious climate policy. There remains a long way to go to ensure that all countries in the Region have adequately integrated health into their national climate change plans. Thus, countries must work or continue to build capacity to address the local health risks posed by climate change; assess health benefits of mitigation options; and develop, implement, and evaluate health-focused interventions through an integrated, multisectoral approach.

INVESTING IN BETTER HEALTH

To protect health from risks derived from climate change, decision-makers, from national leaders to individual citizens, need access to the best information possible on the risks and any opportunities for action. In preparation for COP21, countries made important commitments to cut greenhouse gas emissions and scale up adaptation to climate change, but more needs to be done.Implementing and enforcing higher standards for vehicle emissions and engine efficiency can reduce emissions of short-lived climate pollutants, such as black carbon and methane. Doing so could save at least 2.4 million lives a year by 2030 and reduce global warming by about 0.5 °C by 2050. New estimates could raise that to 3.5 million lives saved annually by 2030, and 3–5 million lives per year by 2050. There are direct health benefits from reduced air pollution, since nearly all non-carbon dioxideair pollutants that alter climate (e.g. black carbon and ozone-producing gases) have direct adverse effects on health. Policies that promote walking and cycling bring

added dividends for health. Placing a price on polluting fuels to compensate their negative health impacts would be expected to cut outdoor air pollution deaths by half, reduce carbon dioxide emissions by more than 20%, and raise approximately US$ 3 trillion per year in revenue – over half the total value of health spending by all of the world's governments (30, 31).

The new Paris funding mechanism must be used to protect health by providing financing explicitly for strengthening health systems, and targeting the social determinants of health in order to strengthen community resilience. Investments in low-carbon development, clean renewable energy, and greater climate resilience are also investments in better health.

The health sector can also improve its own practices and simultaneously minimise its carbon emissions. Health services in some developed countries are responsible for between 5-15% of carbon emissions. Reducing the 4.2% of annual CO_2 emissions of European health care could eliminate 15 000–30 000 cases of illness. Energy efficiency, shifting to renewables, and greener procurement and delivery chains can all improve services and cut carbon emissions (31).

In order to address the challenges posed by climate change and to create climate-resilient communities, the health sector will probably have to undertake measures such as:

- enhancing disease surveillance, especially for climate-sensitive vector-borne diseases;
- monitoring changing environmental exposures;
- ensuring essential medical supplies and health services during disasters;
- improving preparedness, planning, and response for heat-waves and other extreme events; and
- facilitating coordination between health and other sectors to deal with changes in the incidence and geographical range of diseases (31).

WHO is developing the operational framework for building climate resilient health systems which aim to respond to policy mandates at global, regional and, increasingly, national levels(32). It includes resolutions of the World Health Assembly and WHO Regional Committee for Europe on health protection from climate change, strengthening national health emergency and disaster management capacities for managing the risks of weather extreme events, health system strengthening, and implementation of International Health Regulations (33). It responds to requests by UNFCCC Partiesfor support in planning adaptation to climate change in key sectors,including health. It responds to the post-2015 development agenda and associated Sustainable Development Goals and the Sendai framework for disaster risk reduction (34, 35).

CONCLUSION

This Paris climate agreement is essential for public health:it reinforces the original UNFCCC principle of health as a motivation for action; identifies health as an adaptation priority; and promotes climate change mitigation policies that also bring health benefits, would be even more beneficial. It will help bring about cleaner air, safer freshwater and food, more effective health and social protection systems – and as a result, healthier people. Puttingthe Paris agreement into practice will need to happen primarily at the national level. Health professionals, and WHO more broadly, have a vital role to play in ensuring the progress on climate change we need to protect and promote health worldwide.

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Кон договорот од Париз за климата: здравјето средиште за акција кон климатските промени

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ИЗВАДОК

Промената на глобалната клима влијае врз здравјето на луѓето, благосостојбата и животот на Земјата. Доказите за здравствените ефекти од климатските промени и за идните ризици по здравјето на Европскиот регион на СЗО се јасни. Новиот Договор од Париз за климата има суштинско значење за заштита на јавното здравје, затоа што ќе придонесе за подобро здравје, почист воздух, побезбедна вода за пиење и храна, како и кон поефикасни и пофер системи на здравствена и социјална заштита. Здравствениот сектор, исто така, може да ја подобри својата функционалност и истовремено да ги смали емисиите на јаглерод. Светската здравствена организација (СЗО) работи на идентификување на политиките со кои би можеле да се превенирааттздравствените ефекти од климатските промени, но и на практиките за подготвеност и одговор на тие ризици. Тоа може да биде една од најголемите глобални можностиза здравството во овој Век. Здравствените работници, министерствата за здравство и СЗО имаат витална улога во обезбедувањето на напредокот во однос на акциите за митигација и здравствена адаптација кон климатските промени; сите ние треба да го заштитиме и промовираме здравјето во целиот свет.

Клучни зборови: климатски промени, здравје, здравствена политика, јавно здравје, Светска здравствена организација.

Original scientific paper

INITIAL ALBANIAN EXPERIENCE IN MINIMALLY INVASIVE CARDIAC SURGERY

EKSPERIENCA FILLESTARE NË KIRURGJINË MINI INVASIVE KARDIAKE NË SHQIPERI

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ABSTRACT

Introduction and Objectives: The minimally invasive surgical approach (MISA) consisting in various techniques such as right-anterior mini-thoracotomy (MT) or mini-sternotomy (MS) are the techniques of choice, especially in female patients requiring cardiac surgery. We are presenting our experience with MISA in terms of hospital outcome and patient's satisfaction.

Materials and methods: Between February 2010 and February 2015, 60 patients (Group I) with simple congenital heart defects (sCHD) and 13 patients (Group II) with mitral valve (MV) disease underwent MISA. In Group I, 30 patients had atrial septal defect (ASD) secundum type, 12 had subaortic ventricular septal defect, 10 ASD sinus venosus type, 6 posterior extension ventricular septal defect, 2 muscular ventricular septal defect. In Group II, 6 patients had (MV) regurgitation and 7 MV stenosis. All patients were followed with a physical examination 1-month, 1-year and 3-years after surgery to assess the quality of the cosmetic result.

Results: None of the patients required to be converted to a classic full sternotomy or a larger thoracotomy. All patients survived and were discharged home on the 5th postoperative day. Only one patient developed femoral thromboembolism and later cholecystectomy.

Conclusions: Such operations, rarely employed even in Europian countries, now are feasible with excellent outcome even in Albania.

Keywords: MISA, MT, MS, sCHD, valvular heart diseases.

INTRODUCTION

What can cardiac robotics offer that other simpler and less expensive techniques cannot? Improved surgical results in patients with simple congenital heart disease (sCHD) and valvular heart diseases have stimulated the surgeons to adopt minimally invasive techniques, with the aim of combining a good functional outcome with a better cosmetic result. The aim of this study is presenting our experience with minimally invasive surgical approach (MISA), since 2010 in terms of hospital outcome and patient's satisfaction.

METHODS

In this study the data were collected retrospectively, from clinical charts of the Biostatistical Department between February 2010 and February 2015. We included 73 patients, 60 patients (Group I) with congenital heart defect and 13 patients (Group II) with mitral valve (MV) disease. All patients underwent MISA. Patients were all managed under the same postoperative practice guidelines: 1-Early extubation (less than 6 hours after surgery) 2 - Early discharge (less than 24 hours) from the intensive care unit (ICU). In Group I, 30 patients had ASD

secundum type (fig.2), 12 had subaortic ventricular septal defect, 10 ASD sinus venosus type, 6 posterior extension ventricular septal defect, 2 muscular ventricular septal defect. In Group II, 6 MV regurgitation and 7 MV stenosis. All patients were followed with a physical examination 1-month, 1-year and 3-years after surgery to assess the quality of the cosmetic result. Late results of surgical repair and patient's satisfaction were also evaluated by means of direct contact with a patient or a phone interview.

Tab.1 Diagnosis leading to surgery in Group I (n=60 patients) and Group 2 (n=13 patients)

Diagnosis	MT (n=53pt)	MS (n=20 pt)	Total (n =73pt)
ASD secundum type	30	0	30
Subaortic Ventricular Septal Defect	0	12	12
ASD sinus venosus type	10	0	10
Posterior Extension Ventricular Septal Defect	0	6	6
Muscular Ventricular Septal Defect	0	2	2
Mitral valve regurgitation	6	0	6
Mitral valve stenosis	7	0	7

Tab.2 Variables

Follow-up variables
■ Self health assessment (described as excellent, good, medium, fair)
■ Exercise tolerance, compared to peers (described as equal to peers or 100%, 50%, 25%, or < 25%)
■ Personal satisfaction for the cosmetic result (satisfied or unsatisfied)
Additional variables for female patients who underwent mini-thoracotomy
■ Occurrence of scoliosis
■ Breast asymmetry
■ Restriction of shoulder motility
■ Sensibility deficit presence or persistence at the mammary area.
■ Eventual onset of lactation disturbances after pregnancy.

RESULTS

In Group I all patients were discharged home in good clinical conditions, without residual intracardiac shunts at the pre-discharge echocardiography and none required a re-operation. 40 patients underwent MT in the 4th intercostals space (fig. 1), 20 upper MS (fig.3). During the operation, induced ventricular fibrillation (IVF) was employed in 40 patients, while the aorta was cross-clamped in the remaining patients. None of the patients required to be converted to a classic full sternotomy or a larger thoracotomy. Median follow-up time was 24 months (range 4-84 months).There were no cardiac-related deaths. In Group II, all patients underwent MT on the 3rd or 4th intercostals space through subclavian vein and femoral vein and artery cannulation. With arrested heart the MV was replaced in 7 patients and repaired in 6 of them. In Group II, the youngest patient was a 17 years old female and the oldest 62 years. All patients survived and were discharged on the 5th postoperative day. Only one patient developed femoral thromboembolism and later cholecystectomy. 7 of 40 (17%) MT patients complained temporary (<6 months after surgery) mild sensitive skin deficits in the mammary area at the physical examination. None of the 13 pre-puberal patients who underwent MT had asymmetric breast development, shoulder movement deficit, scoliosis and no lactation problems were reported in those 2 patients who had pregnancy. The vast majority of patients in both groups were satisfied with the cosmetic result of surgery and the satisfaction rate was greater in MT patients. The reason of non satisfaction was represented by the presence of a "too long/visible scar" or for a cheloid at the incision level.

DISCUSSION

Are we doing this, "just because it could be done" or is it really advantageous for our patients? Since 1998 in the study made by Chang [2], their results suggested that minimally invasive surgical approach (MISA) is a good option for surgical closure of ASD (Atrial septal defect) and the study by Lin [3] showed that minimally invasive cardiac surgical techniques were technically feasible and an alternative option for the repair of a ventricular septal defect. The minimal access via lower partial sternotomy for congenital heart defects , operated by surgeon staff and residents, showed no difference in results and clinical course, in the study made by Nigishaki K, in 2005 [4].

Thoracic scoliosis should, however, be remembered as a possible complication after lateral thoracotomy in childhood [5]. In the study of Bleiziffer S, in 2004, according to the orthopedic investigation, this surgical approach does not cause a higher rate of scoliosis. A long-term follow-up in prepubescent female patients after

right anterolateral thoracotomy revealed significantly impaired unilateral breast development, so was proposed to abandon right anterolateral thoracotomy in this subgroup of patients, although the subjective satisfaction with the cosmetic result was high. To avoid potential damage of future breast tissue, other surgical approaches, such as right posterior thoracotomy, should be considered[6].

In the study of Padova in 2009, routinely used a minimally invasive sex-differentiated surgical approach for surgical repair of various simple congenital heart diseases, mostly including a right anterior minithoracotomy in female subjects and a midline ministernotomy in male subjects. The sex-differentiated surgical approach for simple congenital heart disease resulted a safe procedure, providing both excellent functional and cosmetic results. Anterolateral minithoracotomy is a valid and highly appreciated procedure in female patients [7].

It can be performed with the same degree of ease and speed as a conventional operation, with no difference in mortality. It provides access to the relevant parts of the heart and reduces dissection of other areas. It greatly facilitates a reoperation at a later date, as the lower part of the pericardium remains closed [1].

There are also objective elements to this field which have concluded that current clinical data suggest that minimally invasive mitral valve surgery is a safe and a durable alternative to a conventional approach and is associated with less morbidity [8]. There were no complications, only one of the patients developed femoral thromboembolism and later cholecystectomy, but a meta-analysis and systematic review comparing minimally invasive versus conventional open mitral valve surgery,shows that the risk of stroke is higher, but they have not come up with the results of what is causing it[9]. Also, the recent meta-analysis examining the difference of minimally invasive versus conventional mitral valve repair for patients with degenerative mitral disease, shows that is not worse, it may be equivalent, but the duration of stay in the ICU was significantly shorter than conventional mitral valve repair [10].

As for the subjective elements there are cosmetic ones, especially in female patients requiring cardiac surgery and also those who underwent MT. None of the 13 pre-puberal patients who underwent MT had asymmetric breast development, shoulder movement deficit, scoliosis and no lactation problems were reported in those 2 patients who had pregnancy. It shows to have quicker recovery, since the patients were discharged at the 5 postoperative day. Only 17% of MT patients complained temporary (<6 months after surgery) mild sensitive skin deficits in the mammary area at the physical examination, so it also has pain related advantages. It is also cost effective and there is no apparent detriment.

Such operations are now feasible with excellent outcome even in Albania, they are safe and effective alternative to the conventional approach and are associated with better short-term outcomes and a trend towards longer survival. It seems that the future of cardiac surgery is going to be minimally invasive surgical approach.

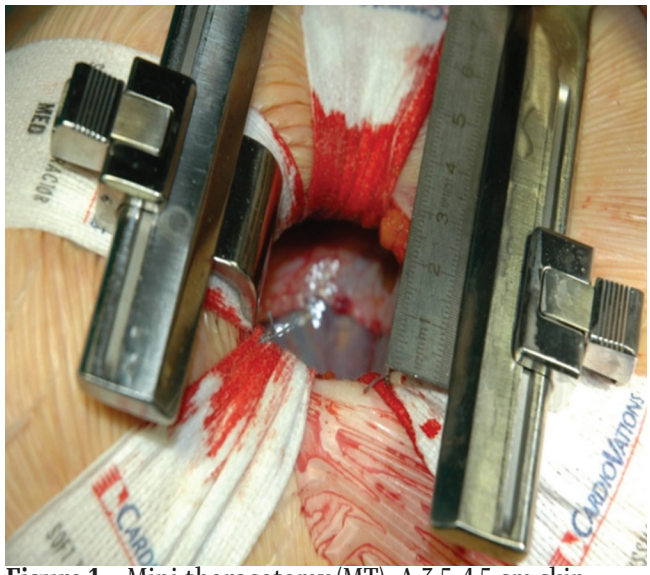

Figure 1. Mini-thoracotomy (MT)- A 3.5-4.5 cm skin incision in the 4th inter-costal space

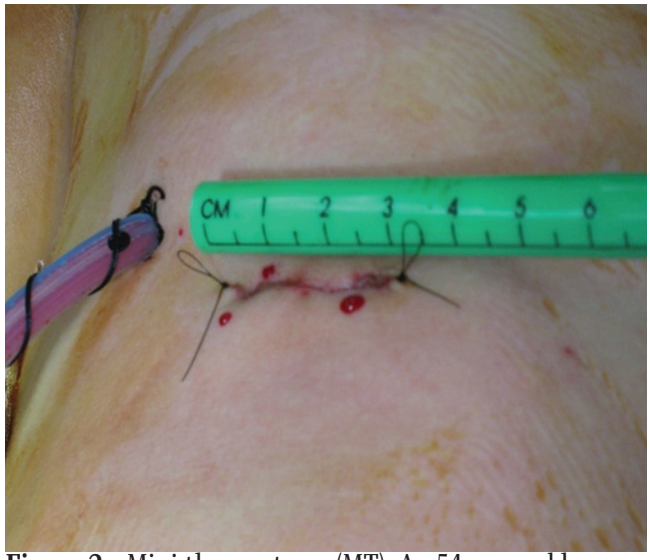

Figure 2. Mini-thoracotomy (MT)- An 54 years old woman after atrial septal defect (ASD) closure, type II

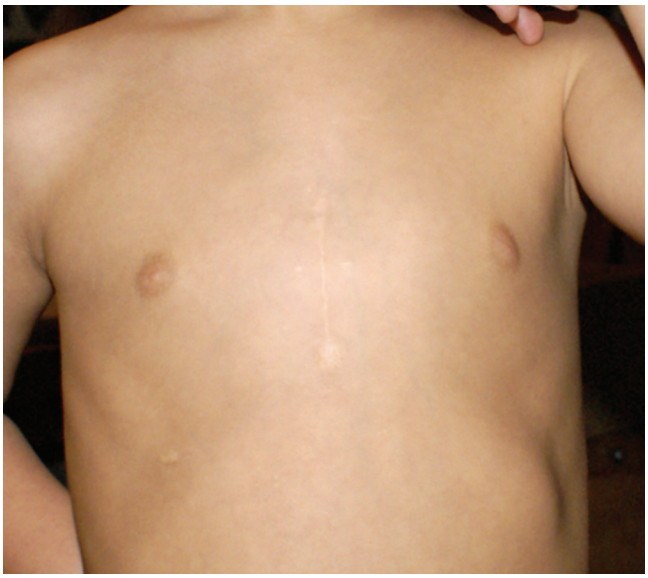

Figure 3. Mini- sternotomy (MS)- A 5 years old child after ventricular septal defect (VSD) closure

P.s. All the photos were taken in the University Hospital Centre " Mother Theresa" 's operation theatre, Department of Cardiac Surgery.

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EKSPERIENCA FILLESTARE NË KIRURGJINË MINI INVASIVE KARDIAKE NË SHQIPERI

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ABSTRAKTI

Hyrje dhe Objektivat: Kirurgjia mini-invazive kardiake (MISA- minimal invasive surgical approach) konsiston në teknikat e ndryshme të tilla si mini-torakotomia (MT) anteriore e djathtë, ose mini-sternotomi (MS), janë teknikat e zgjedhjes veçanërisht në pacientët femra që kërkojnë kirurgji kardiake. Ne po paraqesim eksperiencen tonë me MISA në aspektin e rezultateve spitalore dhe sa kanë mbetur të kënaqur pacientët me rezultatin kozmetik.

Materialet dhe metodat: Midis Shkurtit 2010 dhe Shkurtit 2015, 60 pacientë (grupi I) me defekte të thjeshta lindura të zemrës (sCHD) dhe 13 pacientë (Grupi II) me sëmundje të valvulës mitrale (MV) ju nënshtruan MISA. Në Grupin I, 30 pacientë kishin defekt të septumit atrial (ASD) tip ostium secundum, 12 kishin defekt septal ventrikular subaortal, 10 ASD tip sinus venosus, 6 defekt septal ventrikular me zgjerim posterior, 2 defekt septal ventrikular muskulor. Në grupin II, 6 pacientë kishin regurgitacion të valvulës mitrale (MV) dhe 7 stenozë të saj. Të gjithë pacientët janë ndjekur me një ekzaminim fizik në 1-muaj, 1-vit dhe 3-vjet pas operacionit për të vlerësuar cilësinë e rezultatit kozmetik.

Rezultatet: Asnjë nga operacionet nuk u konvertua në një sternotomi mediane klasike të apo një torakotomi të zgjeruar. Të gjithë pacientët mbijetuan dhe shkuan në shtëpi në ditën e 5-postoperative. Vetëm një pacient zhvilloi trombemboli femorale dhe më vonë kolecistektomi.

Konkluzione: Operacione të tilla, rrallë të kryera edhe në vende europiane, tashmë janë të realizueshme me rezultate të shkëlqyera edhe në Shqipëri.

Fjalët kyçe: MISA, MT, MS, sCHD, sëmundjet valvulare të zemrës.

Original scientific paper

BIOETHICS EDUCATION IN MEDICAL SCHOOLS IN REPUBLIC OF MACEDONIA

EDUKIMI I BIOETIKËS TE STUDENTËT E MJEKSISË NË REPUBLIKËN E MAQEDONISË

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ABSTRACT

Background: The basis for the design ofcurricula in bioethics education for medical student should be the level of knowledge which the students have from their pre-university education.

The aim of this paper is to compare the knowledge and understanding of first-year medical students with those of students who are in their last year of studies (V-VI) in order to observe the influence of medical education during the university years with the purpose of evaluating the current situation upon which proposals could be made over ways in which to improve medical education containing bioethical studies.

Material and methods: We have conducted a survey based on standardized questionnaire with questions that reflect frequent ethical dilemmas in every day medical practice. Total number of 120 first year studentsand 80 last year students of the Medical Faculty of the University of Tetovo and the Medical Faculty of the University of Skopje have completed the questionnaires. The obtained answers were entered into the software program SPSS 16.0.

Results: show that first year students have a low level of knowledge on bioethical issues and a burden of worldviews which are carried largely from their family tradition. The results of the answers by last year students show an unsatisfactory improvement of knowledge and very small change of worldviews.

Discussion: medical studies must strengthen the curricula to increase knowledge of bioethics. Our findings are in accordance with many other studies which have been made in other countries.

Key words: bioethics education, medical students, Republic of Macedonia.

INTRODUCTION

Ethics is a philosophical discipline pertaining to notions of good and bad, right and wrong, our moral life in community, *as a such, it was subject of interest since* Socrates, understanding ethics as a name given to our concerns with good behavior [1], Plato, Aristotle, Epicurus in antic period,being followed in the middle age by Saint Augustine, rehabilitating the platonic philosophy; and Saint ThomasAquinas, reaffirming approach based in the reinterpretation of Aristotelic philosophy [2].

Ethics has become main topic in modern age as well, being in the center of observations of the philosophers (the rationalist, with Descartes as major exponent), and the empiricist, (with a participation of Thomas Hobbes, John Locke and David Hume). Immanuel Kant, in his Critics of Reason, will refuse the supremacy of any of these theories, basing his moral in the autonomy of reason. Kant sustained that moral standards should emerge from human reason, with man acting in accordance to duty [3].

According to this current conception, the concepts of value, moral, and ethics are introjected from life experience. Thus, morality would be a system of values, from which results norms considered as correct by certain social or professional group [4].

The discussion about human nature and the possibility of teaching ethics falls back to Ancient Times. Plato, who dedicate excessively to this topic, questioning if virtue can be taught [5]. It is necessary that degrees attest not only knowledge of intellectual order but also from the psychological and moral outcomes [6]. This warning, important for any area of formation, is essential for medicine, whose graduates, as seen, need to be gifted fully both technically and ethically.

One of the major questioning coming from such requirements, nowadays, regards to if it is possible to teach medical ethics and bioethics to medical students during the formal and regular course, that is, if it is possible to teach attitudes and skills by means of theoretical classes with slides and pictures [2].

Ethics, taught at schools, should be a transversal topic in the curricula, in general. However, the majority of medical schools just do not do it, as it is not thought that this is how it should be.

Bioethics is the application of ethics to the field of medicine and healthcare. The term "bioethics" was first coined in 1971 (by University of Wisconsin-Kennedy Institute in Washington) as a part of ethics, bioethics is multidisciplinary. It blends philosophy, theology, history, and law with medicine, nursing, health policy, and the medical humanities. Insights from various disciplines are brought to bear on the complex interaction of human life, science, and technology.

Bioethicists explore even deeper issues such as the meaning of life and death, pain and suffering, and rights and responsibilities. During the past decade, biomedical ethics (commonly called bioethics) has become a popular topic. This is largely due to increased complexity of caring for patients and the difficult decisions that new technologies demand.

The concept of integrative bioethics as an interdisciplinary scholarly and pluriperspectivistic area goes beyond such one-sided determinations, both philosophical and scientific, and intends to integrate the philosophical approach to bioethics with its particular scientific contents, as well as different cultural dimensions and perspectives [7].

Bioethics education for medical practice is essential in today's complex world because: Practicing medicine today often involves decisions about ethical and other patient issues, medical policies and patient rights legislation are ever-changing, health care systems function differently than before, clinical practice now involves decision-making about many new issueslike: the human genome project, cloning, patenting of human tissue products, and transplants, other issues such as ensuring patient self-determination and proper informed consent for medical procedures, end-of-life decision making, research ethics, reproductive medicine, and managed care and related economic issues.

In the early seventies medical colleges introduce formal teaching of bioethics. In Medical schools in Republic of Macedonia, bioethics as e subjects was introduced 2005/2006. Based on this fact, it is understandable that bioethics could not be consolidated as efficiently complete subject; therefore the specific interest represents the evaluation of knowledge on ethical values and attitudes of the students of medicine towards those values.

The aimof this paper is to compare the knowledge and understanding of first-year medical students with those of students who are in their last year of studies (V-VI) in order to observe the influence of medical education during the university years with the purpose of evaluating the current situation upon which proposals could be made over ways in which to improve medical education containing bioethical studies.

MATERIAL AND METHOD

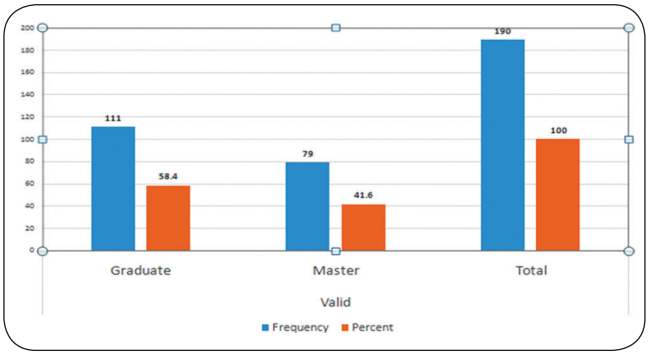
Total number of 120 first year students and 80 last year students in the Medical Faculty of the State University of Tetovo and the Medical Faculty of the University of Skopje have completed the questionnaires. We have conducted a survey based on standardized Likert-type and frequency scales with a five-choice format. Questionnaire with questions that reflect frequent ethical dilemmas in every day medical practice.

The questionnaire consisted of 12 questions, but we will present here, in addition to those regarding demographic data, only the four that are related to the aim of this paper:

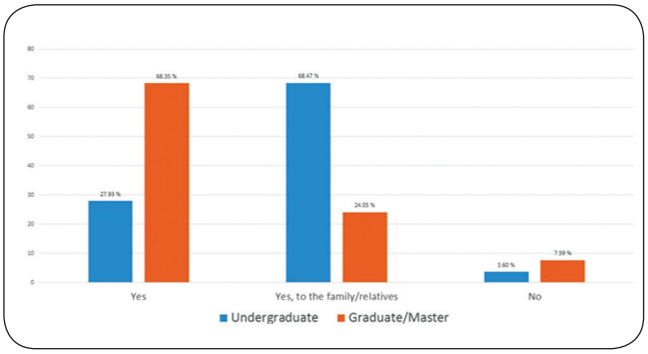
The obtained answers were entered into the software program SPSS 16.0.

RESULTS

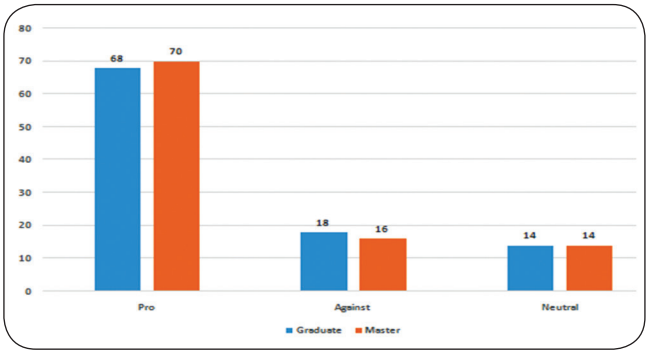
Frequency of population was representatively distributed, abaut 60% represents undergraduatesand about 40% graduated students.



Graphic 1. Frequency of the population - student participants: 111 undergraduates (or 58.4 %) and 79 graduate/master (or 41.6 %)

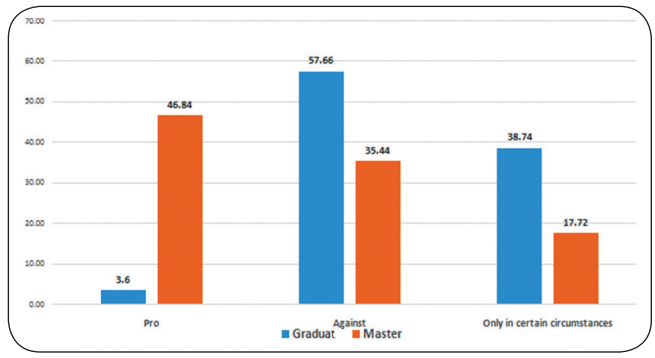


Graphic 2. The patient's right to know the truth about theirs health condition



Graphic 3. Student'sview on organ donation

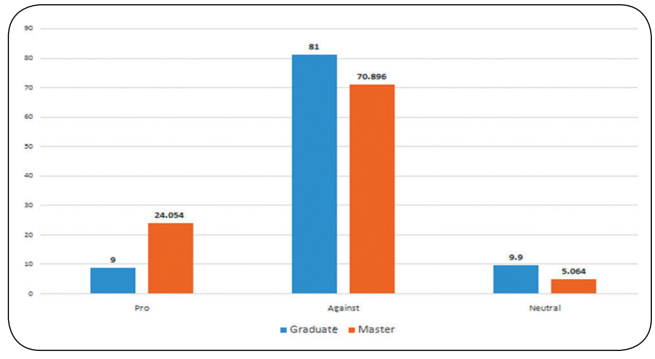
Both, undergraduate and graduate/master students had a similar opinion on organ donation. Namely, they were pro 68 and 70 %, respectively, 18 and 16 %, and a neutral were 14 % on both sides.



Graphic 4. Student's views on abortion

Justifications for abortion were as follow: undergraduates– 34% to keep mothers health, 32% to prevent birth with defects, graduates – 25% for mother's health, 57% to prevent defective births)

Students' attitude towards abortion significantly changes according to the level of studies. For example, while only 3.6% of the graduate level students are pro abortion, there is a huge difference at the graduate/master level with 46.84 %.



Graphic 5. Student's views on euthanasia

When asked about euthanasia, the students responded mostly against (81 % at undergraduate level, 71% at graduate/master level) – pro were more from the graduate level (24 %) and only 9% from the undergraduates.

DISCUSSION

As we mentioned in themethodology, to assess influence of education in student's attitude for ethical values respectively evaluating the development of ethical attitudes during the process of education, we drafted only a few questions in order to giveus thesome basic information. These questions have also practical importance because they are more frequently encountered in clinical practice as a dilemma requiring appropriate answers from the medical personnel.

First question, regarding, personal attitude to the right of the patient to be informed about his health? From the results we can see that students in last years of education mostly approve the patient's right to know the truth about their health condition, in a comparison with students of first year.

To the second question regarding their moral attitude to organ transplantation. Both, undergraduate and graduate/master students had a similar opinion on organ transplantation. Namely, they were pro 68 and 70 %, respectively, 18 and 16 %, and a neutral were 14 % on both sides.

Personal moral stance on abortion (artificial termination of pregnancy).The circumstances that justify abortion are:

Justifications for abortion were as follow: undergraduates – 34% to keep mothers health, 32% to prevent birth with defects, graduates – 25% for mothers health, 57% to prevent defective births).Students' attitude towards abortion significantly changes according to the level of studies. For example, while only 3.6% of the graduate level students are pro-abortion, there is a huge difference at the graduate/master level with 46.84 %. Do you consider abortion as an acceptable method of family planning?

Last question was related to their attitude towards euthanasia. To the question "do you approve the right of doctors to end the life of the patient if he is in the terminal stage of the disease?". The students responded mostly against (81 % at undergraduate level, 71% at graduate/master level) – pro were more from the graduate level (24 %) and only 9% from the undergraduates.

The results show that first year students have a low level of knowledge on bioethical issues and a burden of worldviews which are carried largely from their family cultivated by tradition, religious and other principles.

The results of the answers by last year students show an unsatisfactory improvement of knowledge and very small change of worldviews. Even thou we can see slight changes of views in the last years of studies.

Facing similarities in a different studies in the different parts of the word, ethical education has become important topic in clinical practice and research with the aim to find the ways to strengthen and to consolidate ethics education as an integral part of medical education. There are different approaches and experiences.

All proponents and opponents agree that the values of respect for human life and for individuals' autonomy are relevant to the debate [8].

In recent years, medical practice has followed two different paradigms: evidence-based medicine (EBM) and values-based medicine (VBM). There is an urgent need to promote medical education that strengthens the relationship between these two paradigms [9].

Physicians are trained, since their university formation (and this has been a vicious cycle), to decide based just in facts. In the past century, the great physiologist Claude Bernard definitively introduced medicine into the realm of science, taking it from the governing empiricism at the time. Since then, physicians began to turn into objective everything that was subjective by quantifying and measuring. Decisions were taken based in facts and the clinic, example of working area with strict observation and interpretation of phenomena from sensitive reality, it became sovereign [10].

Currently, medical ethics is studied formally, either through vertical transmission of contents related to deontological and bioethics principles or by the analysis of ethical and moral problems met in clinical practice. These attempts to incorporate ethical and moral values in the teaching-learning process derive from the understanding that a medical ethics code is not enough to guide professionals' behavior; to speak in medical ethics is to speak on moral and on decision-making that transcend purely cognitive features currently so valuated in medical ambience [11,12].

In face of the credibility crisis that affects professional practice, it became primary to give particular attention to medical students who, during their academic formation, should acquire not just a range of technical knowledge, but, equally, ethical knowledge and values that will guide them throughout their professional life, according to contemporary medical morality concepts.

Bioethics education has not cumulative impact in knowledge, rather it should be consider as an integral part of all education and professional period [13].

Any medical school that intends to establish a better ethical humanist formation of the future physician needs to be aware that a program targeted to student's ethical development needs to interact will all discipline, from the first until the sixth year of schooling. In order to awaken

and stimulate ethical stands in students, professors should receive specific formation and training.

Routine bioethics education for medical students and resident physicians, and continuing medical education for practicing doctors, are the best ways to accomplish this goal. Over the past few years bioethics has become an integral component of medical education worldwide. In the early seventies, only 4% of American medical colleges taught bioethics as a formal course. By 1994, all medical colleges in the United States had bioethics as a required part of the medical curriculum. In the United Kingdom (UK) formal teaching of bioethics was also introduced around same time. The General Medical Council code of ethics stipulates that medical ethics should be taught in every medical school in the UK, Ireland and fortunately bioethics has found its way into formal medical curricula [13].

Authors have begun to discuss professional identity formation (PIF), distinguishing it as the foundational process one experiences during the transformation from lay person to physician. This integrative developmental process involves the establishment of core values, moral principles, and self-awareness [14].

Healthcare education is a process of socialization, of moral enculturation, transmitting a distinctive morality [15]. Clinical bioethics employs clinical cases and situations as an instrument for discussion. These discussions entail analysis of not only the facts and circumstances surrounding each case, but also the values which lead to patients, health teams and institutions opting to recommend, accept or refuse a given conduct [16].

The most critical barrier to achieving uniform bioethics education in the medical curriculum is financial constraints. Most bioethics programs in medical schools are not funded in a way that ensures their continuation.

A review of the literature reveals that studies consistently have failed to uncover any significant effect of ethics education on the moral reasoning, moral competency, and/or moral development of medical professionals. Further, in the absence of any firm empirical basis, calls for ethics education for medical professionals and ethics committee members should be rethought [18].

The objective of teaching bioethics is not to create bioethicists but to equip the graduate with adequate reasoning skills to be able to identify ethical dilemmas as they occur in his practice and to attempt judicious resolution using the knowledge and experience imparted during training.

If having an excellent bioethics program in a medical school and affiliated teaching hospitals can reduce exposure to legal risks. It is vital that physicians understand basic aspects of law and the legal system in order to practice good medicine. Improving doctor's knowledge of medical law can help them better understand and estimate risks.

As a firs survey conducted recently in Republic of Macedonia. Weconsider this animportant work because it deals with sensitive questions such bioethics. Level of knowledge basic understanding of medical student for bioethical values. Those basic information's can help in a process of evaluation, development and consolidation of curriculum for medical students. In addition we have got some basic but very important information regarding the impact of biomedical studies on their bioethical views.

Having in mind that Macedonia is characterized with a diversified cultural heritage, where traditional values still have impact on peoples' views, this study needs to be expanded to see the traditional cultural impact on these views upon the medical students.

CONCLUSIONS

Students have a low level of knowledge on bioethical issues and a burden of worldviews which are carried largely from their family cultivated by tradition, religious and other principles.

The results of the answers by last year students show an unsatisfactory improvement of knowledge and very small change of worldviews. Even thou we can see slight changes of views in the last years of studies.

Therefore it can be concluded that medical studies must strengthen the curricula and teaching methods to improve knowledge of bioethics.

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EDUKIMI MBI BIOETIKËN TE STUDENTËT E MJEKSISË NË REPUBLIKËN E MAQEDONISË

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ABSTARKTI

Hyrja Baza për hartimin e kurrikulave të bioetikës për student e mjekësisë duhet të jetë niveli i njohurive të tyre për këto vlera nga edukimi i tyre parauniversitar.

Qëllimi i këtij punimi është që të krahasojnë njohuritë dhe të kuptuarit e studentëve të mjekësisë të vitit të parë me ato të studentëve të cilët janë në vitin e fundit të studimeve (V-VI), për të parë shkallën e ndikimit të edukimit të bioetikës gjatë viteve të studimit në universitetit me qëllim të vlerësimit të gjendjes për ta patur si bazë për

propozimin e mënyrave për të përmirësuar studimet për njohuritë bioetike.

Materiali dhe metoda. Është kryer një studim bazuar mbi pyetësorë të standardizuar me pyetje që reflektojnë dilemat etike më tështpeshta në praktikën mjekësore. Pyetësorëi kanë mbushurr 120 studentë të vitit të pare dhe 80 studentët e viteve të fundit të Fakultetit të Mjekësisë të Universitetit të Tetovës dhe Fakultetit të Mjekësisë të Universitetit të Shkupit. Përgjigjet e marra ishin të përpunuar në program softwerik SPSS 16.0.

Rezultatet tregojnë se studentët e vitit të parë kanë nivel të ulët të njohurive mbi çështjet bioetike dhe një barrë të botëkuptimeve me prejardhje nga tradita e tyre familjare. Rezultatet e përgjigjeve nga studentët e vitit të fundit tregojnë një përmirësim të pakënaqshëm të dijes dhe ndryshim të vogël të botëkuptimeve për këto vlera..

Discusion: Nëstudimet e mjeksisë duhet forcuar korikula me qëllim të rritjes së njohurive mbi bioetikën. Të dhënat e konstatuara janë në përputhje me tëdhënat e shumë studime që janë bërë në vende tëtjera.

Fjalët kyç: edukimi bioetik, studentët e mjekësisë, Republika e Maqedonisë.

Original scientific paper

IMPACT OF CONCURRENT CHEMORADIOTHERAPY ON OVERALL SURVIVAL AS COMPARED TO RADIOTHERAPY ALONE IN UTERINE CERVICAL CANCER PATIENTS AT ONCOLOGY HOSPITAL OF ALBANIA

EFEKTI I KIMIORADIOTERAPISË NË MBIJETESËN E PËRGJITHSHME I KRAHASUAR ME EFEKTIN E RADIOTERAPISË NË PACIENTË TË KANCERIT TË CERVIKSIT TË UTERUSIT NË SPITALIN ONKOLOGJIK TË SHQIPËRISË

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ABSTRACT

Objective of study: The study's objective is to compare five-year overall survival among patients treated with concurrent chemoradiotherapy and those treated with radiotherapy alone in Albania's Oncology Hospital at 'Mother Theresa' University Hospital Center.

Methods: Patients with uterine cervical cancer diagnosis, treated with either radiation or concurrent chemoradiation who completed full treatment were selected for the study. Kaplan-Meier 5-year survival analysis and multivariate Cox regression were conducted to determine the effect of treatment on survival.

Results: Number of patients that fulfilled study's selection criteria was 379. Kaplan-Meier analysis revealed a survival probability of 60% (95% CI: 45-71) vs. 76% (95% CI: 64-85) in the radiotherapy and chemoradiotherapy groups, respectively (p=0.06). While, in advanced-stage patients, survival probability was 25% (95% CI: 19-33) and 54% (95% CI: 43-64) in radiotherapy and chemoradiotherapy groups, respectively (p<0.05). Patients in the chemoradiotherapy group had a hazard ratio of death of 0.50 (95% CI: 0.36-0.69) compared to radiotherapy (reference category). Stage and treatment group were the only statistically significant factors in predicting survival, while age and histopathology were not.

Conclusion: This study concludes that in the Oncology Hospital of Albania, concurrent chemoradiotherapy improved overall survival more than radiotherapy alone in uterine cervical cancer patients.

Key-words: Concurrent chemoradiotherapy, radiotherapy, uterine cervical cancer, overall survival.

INTRODUCTION

According to the World Health Organization's report of cancer in the world, uterine cervical cancer (cervical cancer) is one of the five most common cancer worldwide. [1]. According to the International Agency for Research on Cancer, uterine cervical cancer in Albania is among the ten most frequent cancers in women, and among top ten cancers with the highest mortality [2].

Most cervical carcinomas originate at the columnar – squamous epithelial junction and may involve the outer squamous cells as well as inner glandular cells [3]. The major risk factor for this disease is the human papilloma virus infection [4].

Depending on the degree of cancer invasion, clinical stages of uterine cervical cancer have been defined [4]. Thus, if carcinoma is confined strictly to the cervix, it

is defined as stage I. Stage I can further be classified as stage IA, if invasive carcinoma can be diagnosed only by microscopy and as stage IB when there are clinically visible lesions. Stage II carcinomas are defined as carcinomas that extend beyond cervix, but have not reached to the pelvic wall or to the lower one third of the vagina. Stage IIA is defined as stage II carcinoma without parametrial invasion. If parametrial invasion is present, then it is called stage IIB. If tumor extends to the pelvic wall and/or involves lower one third of the vagina and/or causes hydronephrosis or nonfunctioning kidney, then it is defined as stage III cervical cancer. If a stage III tumor involves lower third of the vagina with no extension to the pelvic wall, then it is defined as stage IIIA tumor. If there is extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney, then it is defined as stage IIIB cancer. If carcinoma has extended beyond true pelvis to the adjacent organs then it is defined as stage IVA. If spread of carcinoma is extended to distant organs, then it is defined as stage IVB [4].

Stages with no parametrial invasion such as IA, IB and IIA, are considered as early stages of disease, while stages IIB, III and IV are advanced stages of cervical cancer [5].

Early stages of cervical cancer have traditionally been treated with radiation and/or surgery. Meanwhile, treatment of advanced stage cervical cancer has been subject to changes due to challenges encountered in defeating the disease. So, until the end of '90s, radiation therapy (radiotherapy) was the standard of care for advanced-stage cervical cancer. In 1999, the National Cancer Institute (NCI) (USA), after reviewing data from five ongoing clinical trials, announced that survival of advanced-stage cervical cancer patients might improve if in addition to radiotherapy, they are treated with chemotherapy concurrently [6]. Nowadays, the National Comprehensive Cancer Network, a network of most developed cancer treatment centers in the USA, recommends that concurrent treatment of radiation and chemotherapy should begin at stage IB [6].

In this study, concurrent radiation and chemotherapy treatment will be referred to as 'concurrent chemoradiotherapy' or simply 'chemoradiatiotherapy'.

Concurrent chemoradiotherapy is thought to be more successful than radiotherapy alone, because it combines benefits of radiation with those of chemotherapy which also acts as a sensitizer of cells to radiation [7].

As with any type of cancer, cervical cancer treatment effectiveness may be measured by evaluating patient's survival time after treatment. It has been found from studies that beside type of treatment, factors such as cancer stage, histopathology, age, tumor size, positive periaortic nodes and bilateral disease influence survival of patients [4].

In Albania's Oncology Hospital at 'Mother Theresa 'University Hospital Center', chemotherapy was added to the cervical cancer treatment protocol in 2004 [8]. Before 2004, cervical cancer patients in this center were treated by radiation and/or surgery. Concurrent chemoradiotherapy, also known as combined treatment, was begun in several patients in 2004, and by 2006 it was used almost in all advanced cervical cancer patients. According to treatment protocol, all advanced-stage cancer patients should be treated with concurrent chemoradiotherapy. Although controlled clinical studies suggest an increased survival of concurrent chemoradiotherapy compared to radiotherapy alone, until today no study has compared these two treatments' effectiveness in terms of overall survival in patients of Oncology Hospital at 'Mother Theresa' University Hospital Center.

This study aims at identifying any difference in overall survival among patients treated with concurrent chemoradiotherapy and those treated with radiotherapy alone.

MATERIAL AND METHODS

Patient selection

This is a retrospective cohort study based on patient charts' data at the Oncology Hospital, 'Mother Theresa' University Hospital Center. Records of patients registered at the Gynecology Unit during 2002-2010 were reviewed. Patients were included in the study if they fulfilled the following criteria: 1) uterine cervical cancer diagnosis; 2) treatment with radiation or concurrent chemoradiation, 3) patients should have started and completed treatment in the Oncology Hospital. Patients that, for any reason, did not complete either treatment were not included in this study.

Treatment

Cervical cancer treatments were radiation and concurrent chemoradiation (w/o surgery). Radiotherapy consisted of 1.8 Gy daily for 5 days a week for 28 days on the pelvic region by four-field box technique, totaling 50.4 Gy of radiation for the whole treatment.

Concurrent chemoradiotherapy consists of concomitant chemotherapy and radiation. Chemotherapy is administered as a single dose 50 mg of cisplatin once a week for 5 weeks. In addition to treatments mentioned above, hysterectomy is performed in the early stages of the disease, by protocol.

Patient characteristics

The following data were selected for each patient in the study: age, number of pregnancies, living area, histopathology (squamous or other carcinomas), FIGO stage of cancer, year of diagnosis, treatment group, and whether patient has undergone hysterectomy (yes/no).

Definition of the treatment outcome

The selected treatment outcome was overall patient survival within five years after treatment. Patients were followed up for a five-year period, during which time patient's condition is assessed periodically (every three months for the first two years, and every 4-6 months for the next three years). Five-year overall patient survival was defined as patients's survival status (alive/deceased) within five years from completion of treatment. If patient survives disease is confirmed within follow-up time period, then five-year survival is noted as yes. Otherwise, if patient did not survive then five-year survival is noted as 'no' along with the time patient survived since completion of treatment. If patient who has received treatment, leaves the study, i.e., does not show in routine follow-up visits (lost to follow-up), then patient's follow-up time is noted.

Statistical Analysis

Data from patients records were electronically listed in excel worksheet and analyzed statistically by SAS University Edition Virtual Application (Release 3.1 basic) (SAS Institute Inc.Cary, NC, USA). Descriptive analysis of patients' characteristics were performed to analyze patients' characteristics as well as distribution of these characteristics across treatment groups. Chisquared test of association [9] and T tests [100 were performed to compare distribution of patients characteristics across treatment groups.

Kaplan-Meier analysis [11] was performed to calculate the probability of overall survival of patients in the two treatment groups and these probabilities were compared using log-rank test. Then survival probabilities were separately estimated and compared across treatment groups for patients with early-stage and those with advanced-stage disease. Kaplan-Meier analysis calculates the probability of survival by taking into consideration the time to death. In addition, data of patients that leave the study early (lost to follow-up) are taken into consideration for the time period they participated in the study.

Power analyses were conducted to test whether there was enough power to detect a difference across treatment groups for the early- and advanced-stage patients, separately. Results showed that our data was adequate to perform Kaplan Meier analysis in early and advanced-stage patients, separately (power =99.9%).

Cox-regression [11, 12] analysis of proportional hazards was conducted to identify any difference in overall survival across treatment groups after controlling for other factors. Cox regression analysis predicts hazards of death based on a model of variables, i.e. treatment group and other co-factors selected by the researcher as influencing factors on treatment failure. Other factors, except treatment group, thought to be related to treatment failure and included in the study were: stage, histopathology and age. Co-factor selection was based on previous literature [4, 5] and our data availability. Based on clinical significance of each cancer stage, stage variable was divided in the following categories: early-stage cancer, stage IIB (majority of patients) and stage III or higher. In our overall survival predicting regression model, the hysterectomy variable (yes/no) was not included in the regression model, as hysterectomy's role in predicting overall survival is heavily confounded by its association to early stages (IA, IB, IIA) of disease where survival probability is higher than in the advanced stages. Hysterectomy is not a treatment option in advanced-stage cervical cancer patients as it is not beneficial to the patient.

Statistical significance was set at p=0.05 and 95% confidence intervals (CI) were reported for the estimated survival probabilities or hazard ratios (HR).

This study does not involve human subjects directly; data collected on individuals are used. No attempts are made by the authors to identify any participants in the study. Patient data are kept in strict confidence in a password-protected file.

RESULTS

During 2002-2010, 379 uterine cervical cancer patients of the Oncology Hospital fulfilled the study's selection criteria. Median follow-up time was 24 (0-60) months.

Number of patients selected each year varied from 31 to 55. Patients' average age was 49.9 years (median: 49.0 years). Average number of pregnancies was 4.3 (median: 4). Most patients (82.7%) live in urban areas, while 64 patients (17.3%) live in rural areas. Histopathology data revealed that 351 patients (92.6%) had squamous carcinoma and 28 patients (7.4%) have carcinomas of other types (adenocarcinoma or clear cell carcinoma).

Of 379 patients, 1 (0.26%) was diagnosed with stage IA cancer, 39 (10.3%) with stage IB cancer, 83 (21.8%) with stage IIA, 159 (41.8%) with stage IIB, 5 (1.3%) with stage IIIA and 92 (24.2%) with stage IIIB. Hysterectomy was performed in 156 (58.8%) patients (Table 1).

Chi-squared tests of association (table 1) between treatment group and characteristics such as histopathology, age and number of pregnancies resulted not statistically significant ($p>0.05$). Meanwhile, chi-squared tests revealed significant associations between treatment group and stage, living area and hysterectomy ($p<0.05$). Accordingly, there were more advanced stage patients in radiotherapy group than in the concurrent chemoradiotherapy group. Fewer patients in the radiotherapy group had received hysterectomy than patients in the concurrent chemoradiotherapy group. Fewer patients in rural areas received chemoradiotherapy than patients in urban areas. No test of association was performed between treatment group and year of patient diagnosis, as it is a fact that concurrent chemoradiotherapy started on a few patients in 2004 and 2005 and was fully implemented the subsequent years.

Table 1. Characteristics of uterine cervical cancer patients

Patient characteristics			**Treatment group**		**p value**
	Characteristic categories*		**Radiation (n=226) (%)**	**Chemoradiation (n=153) (%)**	**Test of association $\chi 2$**
Cervical cancer stage (according to FIGO)	Early-stage	I	19 (8.4)	21 (13.7)	0.02
		IIA	40 (17.4)	43 (28.1)	
	Advanced-stage	IIB	105 (46.5)	54 (35.3)	
		III	62 (27.4)	35 (22.9)	
Living area	Rural area		47 (21.7)	17 (11.1)	0.01
	Urban area		170 (78.3)	136 (88.9)	
Histopathology	Squamous carcinoma		207 (91.6)	144 (94.1)	0.36
	Other carcinomas		19 (8.4)	9 (5.9)	
Surgical intervention	Hysterectomy		80 (35.4)	76 (49.7)	0.01
	No hysterectomy		146 (64.6)	77 (50.3)	
Year of diagnosis	2002		31 (13.7)	0 (0.0)	See note below**
	2003		40 (17.7)	0 (0.0)	
	2004		41 (18.1)	3 (2.0)	
	2005		30 (13.3)	4 (2.6)	
	2006		29 (12.8)	16 (10.5)	
	2007		11 (4.9)	36 (23.5)	
	2008		14 (6.2)	32 (20.9)	
	2009		9 (4.0)	28 (18.3)	
	2010		21 (9.3)	34 (22.2)	
					p value (T test)
Age (years) Interval			50.5 (±10.8) 25-79	48.9 (±9.4) 28-77	0.13
Number of pregnancies			4.5 (±2.9) 0-13	4.1 (±2.4) 0-13	0.07

* Note: Overall number of patients accross categories of a variable might not total 379 due to missing values in our data.

** Note: No test of association performed.

Number of patients who survived during the five-year follow-up period was 185 (49%). Of 226 patients who were treated with radiotherapy, 38% (87 patients) survived within 5 years. Of 153 patients who were treated with concurrent chemoradiotherapy 64% (98 patients) survived within 5 years.

Kaplan Meier analysis was performed to detect any difference in five-year overall survival across treatment groups. A Kaplan Meier analysis was conducted for the two treatment groups. Five-year survival probabilities were 64 % (95% CI 55 – 71) for chemoradiotherapy group and 34% (95% CI 28 - 41) for the radiotherapy group

(p< 0.0001). This analysis was separately conducted across stage strata, i.e. early-stage and advanced-stage disease. Overall survival probability in early-stage cancer patients was 60% (95% CI: 45-71) and 76% (95% CI: 64-85) in radiotherapy and chemoradiotherapy groups, respectively (p=0.0371). While, in advanced-stage patients, overall survival probability was 25% (95% CI: 19-33) and 54% (95% CI: 43-64) in radiotherapy and chemoradiotherapy groups, respectively (p=0.0002) (Table 2).

Table 2. Five-year survival probabilities (percentage)*

Stage	Radiation		Chemoradiation		p value
	N	(%)	N	(%)	
Early stage	59	60% (45-71)	64	76% (64-85)	0.0371
Advanced stage	167	25% (19-33)	89	54% (43-64)	0.0002

Graph outputs were produced where probability of survival versus time graphs are shown across treatment groups for the early-stage (figure 1) and advanced-stage cancer patients (figure 2), separately.

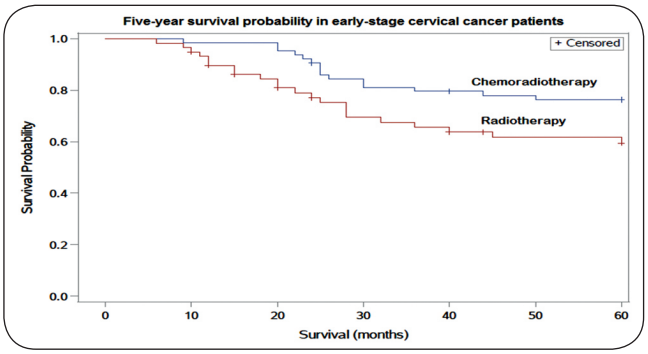

Figure 1. Survival probability of early-stage disease patients versus time (months).

'+' means censored observations, which are patients who have survived during the follow-up time.

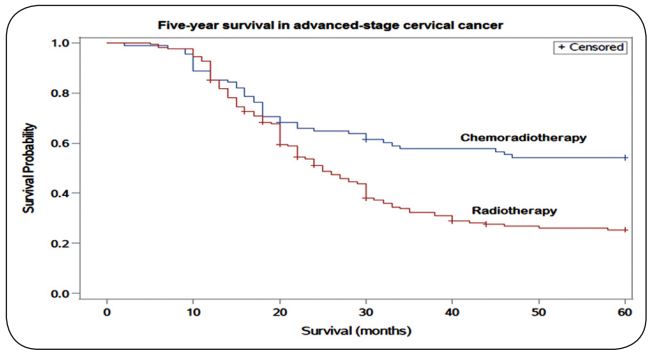

Figure 2. Survival probability of advanced-stage disease patients versus time (months).

'+' means censored observations, which are patients who have survived during the follow-up time.

Cox regression analysis of proportional hazards is a multivariate analysis that predicts death hazards by controlling for treatment group and other patient variables that affect survival. The Likelihood Ratio test resulted in p<0.05, showing that overall model significantly predicts survival. Patients in the chemoradiotherapy group had a hazard ratio of death of 0.50 (95% CI: 0.36-0.69) compared to radiotherapy (reference category).

Among the other predicting factors, cancer stage, treatment group were significant factors (p<0.05). Thus, keeping early-stage cancer as reference category, hazard ratio of death for stage IIB patients was 1.90 (95% CI: 1.30-2.85). Stage III patients had a hazard ratio of 4.12 (95% CI: 2.77-6.25) as compared to the early stage cancer patients (reference category).

Other variables in the model such as age (p=0.57) and histopathology (p=0.56) were not found statistically significant in our analysis (table 3).

Table 3. Cox regression analysis of proportional hazards for five-year survival.

Cox regression analysis of proportional hazards (N=379)				
Patient characteristics	Charcteristic categories	Parameter estimate	Hazard ratio (95% confidence interval)	p value
Ca cervix uteri stage (FIGO)	I and IIA	Reference category	1.00	
	IIB	0.64	1.90 (1.30-2.85)	0.0013
	III	1.42	4.12 (2.77-6.25)	<0.0001
Treatment group	Radiation	Reference category	1.00	
	Chemoradiation	-0.69	0.50 (0.36-0.69)	<0.0001
Age		-0.004	0.996 (0.98-1.01)	0.57
Histopathology	Other carcinomas	Reference category	1.00	
	Squamous carcinoma	-0.17	0.85 (0.53-1.54)	0.56
Likelihood ratio test: Chi-Square= 79.3511, p<0.0001.				

DISCUSSION

This study's objective was to detect any difference in overall survival among patients receiving two different treatments: radiation and concurrent chemoradiation. This is the first time that a survival analysis is being conducted on cervical cancer patients of Oncology Hospital in 'Mother Theresa' University Hospital Center in Tirana, Albania. The outcome of study was five-year overall survival of patients after treatment.

Analysis of association between each patient characteristic and treatment groups showed that there is an association between treatment group and cancer stage. In the radiotherapy group there are more patients with advanced-stage disease than in the chemoradiotherapy group. This may be explained from the fact that before 2004, all patients were treated with radiation, and even after 2004, the year when concurrent chemoradiation entered standard treatment protocol, there were still several advanced-stage disease patients who received only radiation as treatment. The reason that advanced-stage cancer patients did not receive chemotherapy may be the inability of the patient to tolerate chemotherapy (side effects) or to purchase high - cost chemotherapy agents when the chemotherapy drugs were unavailable by patient's health care insurance.

There were fewer patients in the radiotherapy group undergoing hysterectomy than in the chemoradiotherapy group ($p<0.05$). The reason might be the fact that in the radiotherapy group there are more patients with advanced-stage cancer, where hysterectomy is not a treatment option.

Fewer patients living in the rural areas received chemoradiotherapy than those living in the urban areas. Further analysis to identify any connection between cancer stage and living area revealed non-significant results (patients in rural areas were not sicker than those in urban areas). This could be explained with the inability of patients of rural areas to purchase the high-cost chemotherapy drugs when chemotherapy agents were unavailable by patient's health care insurance.

Kaplan-Meier analysis in early-stage cancer patients revealed that probability of overall survival was higher in the chemoradiotherapy group than in radiotherapy group (73% vs. 57%). However, the result was not statistically significant ($p=0.06$). While, in the advanced-stage cancer patients, -overall survival probability was significantly higher in the chemoradiotherapy group as compared to the radiation group, 54% vs. 26%.

Studies analyzing survival probabilities in cervical cancer patients are many; however treatment regimens, as well as follow-up periods are different among these studies. Below we discuss our results with those of several clinical studies with similar treatment and follow-up times.

The RTOG trial of 403 patients with disease stage IB to IVA compared treatment of cisplatin and fluoruracil plus radiotherapy with extended field radiotherapy [13]. Patients in the chemoradiotherapy and radiotherapy group had 73% vs 52% 5-year survival probability, respectively. Among patients with tumor stage of IB and II, those in the chemoradiotherapy group had higher five-year overall survival probability than patients in the radiotherapy group (79% vs. 55%). Among patients of stages III and IVA, those in the chemoradiotherapy group had also better survival than patients in the radiotherapy group (59 % vs. 45 %).

Another clinical trial study by Peters et al. compared the effect of the two treatments (radiotherapy vs radiotherapy plus chemotherapy with cisplatin and fluorouracil) on 243 early-stage cancer patients [14]. Four-year overall survival was similar to our results, 81% vs. 71%. All patients had undergone a radical hysterectomy and pelvic lymphadenctomy before treatment, and chemotherapy agents used were cisplatin and 5-fluorouracil.

In their randomized clinical trial, Stehman et al. examined the six-year survival in stage IB cervical cancer patients [15]. A 0.63 hazard ratio was reported in favor of concurrent chemoradiation or 78% vs. 64% survival probability in chemoradiation and radiation treatment groups, respectively.

Cox regression analysis revealed that stage and treatment group were the only significant factors in survival analysis. Hazards of death decreased by 50% when patients were treated by concurrent chemoradiotherapy as compared to radiaotherapy alone (HR=0.50, 95% CI: 0.36-0.69).

Our Cox regression analysis results agree with the studies mentioned above, in that concurrent chemoradiotherapy increases survival more than radiotherapy. Clinical trials have shown a similar result of a reduction in relative risk of death or recurrence of by 30%-50% [16]. Other predicting factors of survival such as stage and treatment were significant predictors, while histopathology and age resulted non-significant. However, in literature

histopathology is mentioned as an influencing factor on survival [17]. In our study, majority of patients had squamous carcinoma, and only few of them (28 patients) had adenosquamous or clear cell carcinoma. This might have contributed in non-significant result for histopathology.

In literature, other factors such as tumor grade, enlarged paraaortic and pelvic lymph nodes are reported as predicting factors of survival [17, 18]. It was not possible to collect all these data in our study and this might have affected accurate estimation of survival hazard ratio across treatment groups.

One of the strengths of our study is the sufficient number of patients to conduct survival analysis. This number of patients was achieved by reviewing patient records registered in 13 years, including two years of patients' data before implementation of concurrent chemoradiotherapy protocol.

It was noticed that not all eligible patients benefited from concurrent chemoradiotherapy due to unavailability of chemotherapy agents provided by the health care insurance fund; further attempts by the healthcare policymakers are necessary to acquire the necessary quantities of chemotherapy agents for cancer patients.

More than half of patients had advanced-stage disease; more work should be done for prevention and early diagnosis of this disease, as probability of survival is greater at these stages.

CONCLUSIONS

This study aimed at comparing overall survival across radiotherapy and chemoradiotherapy treatment groups of uterine cervical cancer patients. In early-stage cancer patients, overall survival probability was higher in the chemoradiotherapy group, although it was statistically non-significant. In advanced-stage cancer patients, survival probability was significantly higher in the chemoradiotherapy group.

After controlling for other factors, Cox regression analysis revealed that the only significant predicting factors for overall survival were stage and treatment group. This study concludes that concurrent chemoradiotherapy treatment at the Oncology Hospital improved overall survival as compared to radiotherapy alone in uterine cervical cancer patients. Our study results match the results of previously conducted clinical trials.

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EFEKTI I KIMIORADIOTERAPISË NË MBIJETESËN E PËRGJITHSHME I KRAHASUAR ME EFEKTIN E RADIOTERAPISË NË PACIENTË TË KANCERIT TË CERVIKSIT TË UTERUSIT NË SPITALIN ONKOLOGJIK TË SHQIPËRISË

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ABSTRAKTI:

Qëllimi i studimit: Qëllimi i këtij studimi është krahasimi i efektit të kimioradioterapisë në mbijetesën e përgjithshme 5-vjeçare me efektin e radioterapisë në pacientë të kancerit të cerviksit të uterusit të trajtuar në Spitalin Onkologjik në Qendrën Spitalore Universitare "Nënë Tereza", Shqipëri.

Metoda dhe materiali: Në studim u përzgjodhën pacientët me diagnozë kanceri të cerviksit të trajtuar me rrezatim ose me kimioradioterapi konkomitante të cilët përfunduan trajtimin. Analiza Kaplan-Meier dhe regressioni multivariat Cox i të dhënave u kryen për të përcaktuar efektin e trajtimit në mbijetesën e përgjithshme 5 – vjeçare të pacienteve.

Rezultatet: Numri i pacienteve që u përfshinë në studim ishte 379. Sipas analizës Kaplan-Meier probabiliteti i mbijetesës ishte 60% (95% intervali i konfidencës: 45-71) përkundrejt. 76% (95% intervali i konfidencës: 64-85) përkatësisht në grupet e trajtimit me radioterapi dhe kimioradioterapi në pacientët në fazë të hershme të sëmundjes (p=0.06). Ndërsa, në pacientë në fazë të avancuar të sëmundjes, probabiliteti i mbijetesës ishte 25% (95% intervali i konfidencës: 19-33) dhe 54% (95% intervali i konfidencës: 43-64), përkatësisht në grupet e radioterapisë dhe kimoradioterapisë (p<0.05). Pasi u mor parasysh stadi i sëmundjes, pacientët në grupin e kimioradioterapisë kishin 50% (intervali i konfidencës: 31% - 64%) më shumë mundësi mbijetese se pacientët në grupin e radiotherapisë..

Përfundime: Në Spitalin Onkologjik të Shqipërisë, kimioradioterapia konkomitante përmirëson mbijetësën më shumë se radioterapia në paciente me kancer të cerviksit të uterusit.

Fjalët kyç: Kimioradioterapi konkomitante, radioterapi, kancer i cerviksit të uterusit, mbijetesë e përgjithshme.

Original scientific paper

EVALUATION OF THE HOSPITAL PREPAREDNESS FOR RESPONSE TO MAJOR MEDICAL INCIDENTS WITH CHEMICAL, BIOLOGICAL AND RADIOLOGICAL AGENTS IN THE REPUBLIC OF MACEDONIA

ЕВАЛУАЦИЈА НА ХОСПИТАЛНАТА ПОДГОТВЕНОСТ ЗА ОДГОВОР ПРИ МАСОВНИ МЕДИЦИНСКИ ИНЦИДЕНТИ СО ХЕМИСКИ, БИОЛОШКИ И РАДИОЛОШКИ АГЕНСИ ВО РЕПУБЛИКА МАКЕДОНИЈА

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ABSTRACT

Introduction: Chemical, biological and radiological agents (CBR) are constantly significant threat to public health. An adequate hospital preparedness is an essential condition for reducing the impact of this kind of major medical incidents.

Aim: Evaluation of the hospital preparedness of the Health System of the Republic of Macedonia for response to major medical incidents with CBR agents.

Material and methods: The evaluation is performed based on a survey conducted on twenty four major medical institutions in the Republic of Macedonia.

Conclusion: Health institutions in the country are not fully prepared for an adequate response in the event of a major incident with CBR agents.

The fact that 77.8% of hospitals do not provide annual fund for possible major medical incidents with CBR agents is warning information for timely provision of financial and medical resources.

The implementation of continual education and training of the hospital staff to work in conditions during incidents with CBR agents, and the introduction of specialization of disaster medicine are necessary to ensure a higher level of hospital preparedness of the health system of the Republic Macedonia.

Keywords: CBR agents, hospital preparedness, disaster medicine, hospital preparedness plan, continuing medical education.

INTRODUCTION

The chemical, biological and radiological agents represent more common threat to public health. They can be released and cause significant human and material losses in case of: technological and industrial accidents, natural disasters, acts of war, terrorism and occupational exposure [1,2,3].

The first use of biological agents as a weapon is recorded in 600 BC when the Athenian statesman Solon used the purgative herb Helebora, during the siege of the city Cristo. With the further development of the science and technology the production of biological agents becomes simpler, and thus the possibility of their use as special weapons becoming more common. So the bacterium Yersinia pestis was used as a biological weapon by Japan during the 1932-1945 war with China, causing 260 000 deaths [4,5]. However biological agents throughout

history caused the most disastrous effect during various epidemics. Among the most significant pandemics of the 21st century include: pandemic of SARS-severe acute respiratory syndrome 2002-2004, with 8273 cases and 775 deaths, the pandemic of "swine flu" virus H1N1 with 89 million cases and 18,200 deaths and Ebola virus pandemic in 2014 which took over 4,500 lives [6.7].

The rapid development of the chemical industry in the 19th century was accompanied by numerous crashes and poisoning with toxic substances. The chemical agent chlorine gas was used for the first time as a weapon of mass destruction in World War I, in the region Ipres (Belgium) [8,9,10]. Today the use of the chemical agents in military and terrorist purpose is more current. During the terrorist attack with the gas poison Sarin in Tokyo subway on 20th of March 1995, 12 people lost their lives, 50 were injured and more than 1000 received visual impairment.

The use of nuclear bombs on Hiroshima and Nagasaki in August 1945 by the United States remains a unique historical event of the use of radiological agents for military purposes. Today medical accidents with radiological agents commonly occur in crashes nuclear reactors. The first disaster was recorded in 1957 at the plant for atomic bomb Kumberlend-UK, which were cast by 20000q (Curie) of radioactive material.

The explosion of the nuclear reactor in 1986 in Chernobyl, Ukraine, is the largest medical incident with radiological agent in the postwar period. During this event over 300 000 inhabitants were evacuated and irradiation caused several thousand cases of cancer.

The latest disaster in 2011 in Fukushima, Japan, is a combination of natural disasters and medical incident with radiological agent. Thus it caused the death of several workers, outage, evacuation of thousands of people and huge material damage [11,12,13,14,15].

In today's world more than 3.38 billion dollars are spent for production of equipment for protection against CBR agents. While in the last 50 years over 60 different protective products against this kind of incidents were invented [16].

AIM

Purpose of the evaluation is to determine the readiness of hospital health system of the Republic of Macedonia for medical response to major incidents involving chemical, biological and radiological agents.

MATERIAL AND METHODS

The evaluation system for preparedness and response to threats caused by CBR agents or the hospital readiness of the Republic of Macedonia, is based on data obtained from a questionnaire specially designed for this purpose. The questionnaire was developed at the Institute of Public Health of the Republic of Macedonia in 2013. It contains 14 questions divided into two groups:

a) questions about the existence of specialized medical staff, number of hospital beds allocated in case of major medical incident, existence of spare medicines, medical equipment, antidotes, personal and collective protection in the event of a major incident with CBR agents and
b) questions about the existence of a hospital plan stratification (increase of hospital capacity in the event of a major medical incident), perform of continuous medical education, participation in local and regional medical exercises and the existence of annual budget allocated to the response to an incident with CBR agents.

The questionnaire surveyed 24 health institutions in Macedonia, which would be the main carriers of response during possible major incident with CBR agents.

RESULTS

Completed answers by the hospitals were applied generally to all kinds of agents (chemical, biological and radiological), without specifically differentiating readiness in relation to specific agents listed in the questionnaire. The completed questionnaires showed the following information about the current readiness of the hospitals in the Republic Macedonia, regarding the adequate medical response to major incidents with CBR agents:

In terms of whether hospitals have a sufficient number of qualified personnel for the treatment and detection of injured and sick in major incidents with CBR agents, 55% said they do not have and do not intend in the next 6 months to obtain such staff, while 45% reported sufficient number of suitable qualified staff for such conditions.

The majority of hospitals (55%) reported that they have provided a sufficient number of hospital beds in case of need stratification in major medical incident with CBR agents and 45% of them said they do not have such conditions and do not intend to provide for the next 6 months.

Asked whether the hospital has sufficient stocks of medicines, equipment and antidotes for 3 days in case of major incidents with CBR agents, 66.7% said they do not have and do not plan to fill in the future, 11.1% said no, but they plan to fill and 22.2% that have provided enough medicines and supplies for three days.

The lack of personal and collective protection in case of major injuries and suffering from CBR agents is evident in most of the hospitals in Macedonia (77.8% said they do not have and do not plan to provide in due time, 11.1% do not have but plan to provide and only 11.1% have such assets).

In terms of existing laboratory facilities and experts for detection and treatment of designated biological agents: 44.5% said they do not have such opportunities and 55.5% that have a sufficient number of experts and laboratory facilities for such cases.

Regarding the personal and collective protection from biological agents in particular, currently available only in 22.2% of the hospitals in Macedonia, while the remaining 66.7% said that they did not have and 11.1% do not have but plan to buy in the next 6 months.

Currently 55.5% of the hospitals do not have a plan for isolation (quarantine) for larger number of patients in case of mass disorders with biological agents (isolation rooms, disinfectants, clothes etc.), 11.1% said no, but work on preparing such plan and only 33.3% have developed an appropriate plan.

Overall, in terms of all designated CBR agents in the questionnaire, 55.5% of the hospitals said they do not have and do not intend in the next 6 months to draw up a plan for responding to major medical incidents and 45% reported having such a plan and it is continually updated.

In 66.7% of the hospitals there is no any continuing education and training related to work during major medical incidents with CBR agents, 22.2% of the hospitals have performed the same but not in the last 2 years and 11.1 % said that it is regularly performed and evaluated.

The majority (66.7%) of the surveyed hospitals provided evidence that their medical personnel have not participated in local or regional medical exercises as preparation for medical response to major injuries from CBR agents, unlike other 33.3% where they have participated.

So far 88.9% of the hospitals have not been assessed for the level of preparedness for response to major medical incidents from CBR agents. Only 11.1% were evaluated in various medical exercises, but not specifically for response to major incidents combined with chemical, biological or radiological contamination.

All of the hospitals showed lack of fund that would cover financial losses in event of a major incident with CBR agents. Most of the large hospitals (77.8%) reported no such budget and no plan for the next year and 22.2% do not, but plan to provide finance for such purposes in the coming year. Data from the survey findings are presented in Table 1.

Table 1 Level of preparedness of the hospitals in the Republic of Macedonia for response to major incidents involving chemical, biological and radiological agents

Level of preparedness	Chemical agents	Biological agents	Radiological agents
Sufficient professional staff for response	45%	55%	45%
Sufficient number of hospital beds	55%	55%	55%
Reserve medications, equipment and antidotes for 3 days	22,2%	33,3%	22,2%
Personal and collective protection	22,2%	22,2%	22,2%
Developed a work plan for major incidents with CBR agents	33,3%	33,3%	33,3%
Continuing education	11,1%	11,1%	11,1%
Annual budget for medical incidents with CBR agents	10%	10%	10%

DISCUSSION

The hospital preparedness to major medical incidents with CBR agents recently has tremendous importance, especially because of the fact that in the event of such major incidents, over 80% of the victims, would seek urgent medical aid directly into one of the closest hospitals without prior medical assistance from the emergency medical aid or the local health stations [22]. Such a situation would be expected also in the Republic of Macedonia considering its demographic and topographic distribution of the population and the fact that every

major township has a general hospital or medical health center.

The analysis of the survey showed lack of sufficient supplies of materials, technical facilities, laboratories for identification of agents, equipment for communication and personal and collective protection for working during CBR contamination. Also it showed an evident lack of a sufficient number of specialized, educated and trained medical staff, and a system for continuous education, practicing and checking the knowledge of all the structures that would be involved in this type of medical incidents.

An important segment in the planning of the preparation for response to CBR agents, is the planning and training of the medical staff ("staffing"). Introducing programs of Medicine disasters and incidents is the most productive way to educate physicians about the basics of planning and response in times of crisis. In the so-called "Code of Medical Ethics" of the American Medical Association under number 9067 described the requirement of physician preparedness for response in case of disasters, which contains an obligation for providing emergency care during accidents and major disasters including acquisition and maintenance of the relevant knowledge [17,18,19,20,21].

The necessity of specific education and training of the medical staff for an adequate response to incidents with CBR agents in the health system of the R. of Macedonia initiates need not only for continuing education but also for development of national consensus on ethical behavior of doctors during disasters and formulation of a professional practicum for handling in extreme situations.

Given the fact that definitive care of injured and sick patients in case of major incidents with CBR agents should take place in hospitals, the existence of a plan for working during this type of emergencies, is an essential prerequisite for adequate response.

According to our survey only 33% of the hospitals have prepared hospital plan for response to major medical incident with CBR agents. These hospital plans also have not been updated and standardized according the national plan for response to such medical incidents.

An example of a well developed plan for hospital preparedness response to major medical incidents is the "Hospital Preparedness Plan"(HPP) of the US health care system. Within this plan there is also a special plan for hospital preparedness called "Hospital Surge Model" which was prepared with an intention to assess the resources required for the treatment of injured and sick during attacks with biological (anthrax, measles and flu), chemical (chlorine, mustard gas and Sarin), nuclear (blasts from 1 to 10KT) and radiological agents (means for dispersion and radiation sources) [22].

The preparedness of the health institutions of the R. of Macedonia (hospitals, health centers, medical centers and clinics), for quick and efficient response to major incidents with large number of injured and suffering from CBR agents directly would depend on two factors:

1. existence of adequate well trained and specialized medical personnel who continuously go through regular medical training and exercises associated with this kind of specific situations, and
2. equipping health facilities with adequate and sufficient amount of: personal and collective protection, medicines, vaccines and other medical supplies for at least 3 days in case of a massive number of injured and diseased, sufficient number of beds and adequate space for isolation , decontamination and treatment of contaminated or irradiated patients.

In April 2009 the European Commission adopted a three-year programme (2009–2011) to fight terrorism, trafficking and proliferation of chemical, biological, radiological and nuclear (CBRN) materials and weapons of mass destruction with a budget of €225 million.

The newly created "Health Security" EU Programme for Research, FP7, has an overall budget of €1.3 billion for 2007–2013. This budget is entirely dedicated to develop civil security research activities in support of EU policies and industry, aiming at developing the new knowledge and technologies needed to ensure security of citizens against threats such as CBRN agents, natural disasters and industrial accidents, while respecting fundamental human rights [23].

The fact that only 10% of the surveyed hospitals in the R. of Macedonia have annual budget for response to major incidents with CBR agents, indicates need for an urgent financial intervention in this sector of the health system.

The major medical incidents with CBR agents are commonly combined with traumatic injuries of the population, the law enforcement and military personnel,

because it usually occur as a result of various industrial accidents, explosions, acts of war, natural disasters or terrorist attacks. When it incurs the contaminated injuries or wounds require adequate decontamination or neutralization of the chemical, biological or radioactive agent prior to the surgical treatment of the injury. Inadequate access to this type of patients can easily jeopardize not only theirs but also the lives of medical personnel due to insufficient knowledge of the principles in treating contaminated patients or due to lack or non-use of appropriate personal and collective protection [23,24,25]. Surgical interventions in terms of chemical or radiological contamination of the environment or the hospital, according to some research conducted having a significant reduction in the speed of execution of around 30%, due to the need to use personal protective equipment in the operating room [26,27,28].

Therefore organizing continuing education of hospital staff on proper, timely and effective care of the wounded and suffering from CBR agents is one of the basic prerequisites for reducing the impact of this kind of major medical incidents [29,30,31,32,33,34].

CONCLUSION

From the survey findings it can be concluded that the health institutions in the country are not fully prepared for a timely and adequate response in the event of possible major incidents with CBR agents.

The fact that 77.8% of the hospital's annual budget does not provide fund for massive injuries and sufferings from CBR agents is warning information for timely provision of necessary funds for equipment, medicines, protective equipment, sanitary materials and etc., so as to enable quick and appropriate medical response throughout the country.

The evident lack of specialists in emergency medicine in 55.5% of the surveyed hospitals, indicate need for regular organization of continuing education for working during medical incidents with CBR agents and introducing specialization of Disaster Medicine, as is the practice in developed health and educational systems in the world.

The specific surgical principles, methods and means of taking care of injured and sick in major medical incidents with CBR agents determined in this study, as sublimation of the latest world standards and practices, can serve as a basis for drawing up a protocol for surgical treatment of injured and suffering from CBR agents for the health system of the Republic of Macedonia.

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ЕВАЛУАЦИЈА НА ХОСПИТАЛНАТА ПОДГОТВЕНОСТ ЗА ОДГОВОР ПРИ МАСОВНИ МЕДИЦИНСКИ ИНЦИДЕНТИ СО ХЕМИСКИ, БИОЛОШКИ И РАДИОЛОШКИ АГЕНСИ ВО РЕПУБЛИКА МАКЕДОНИЈА

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РЕЗИМЕ

Вовед: Хемиските, биолошки и радиолошки агенси (ХБиР) претставуваат се почеста закана по здравјето на населението. Адекватна хоспитална подготвеност претставува основен предуслов за намалување на последиците од овој вид на масовни медицински инциденти.

Цел: Евалуација на хоспиталната подготвеност на здравствениот систем на Република Македонија за одговор при масовни медицински инциденти со ХБиР агенси.

Материјал и методи: Евалуацијата е извршена врз основа на спроведена анкета на 24 најголеми медицински установи во Република Македонија, за што е изготвен посебен прашалник.

Заклучок: Здравствените установи во Република Македонија не се целосно подготвени за адекватен одговор при евентуален масовен инцидент со ХБиР агенси.

Фактот дека 77,8% од болниците не предвидуваат годишен фонд за масовни повреди и заболени од ХБиР агенси претставува предупредувачки податок за навремено обезбедување на потребните финансиски и медицински средства.

Воведувањето на континуирана едукација и обука на болничкиот персонал, за работа во услови за време на инциденти со ХБиР агенси, како и воведувањето на специјализација по медицина на катастрофи се неопходни за обезбедување на повисоко ниво на болничка подготвеност на здравствениот систем на Република Македонија.

Клучни зборови: ХБиР агенси, хоспитална подготвеност, медицина на катастрофи, плана за хоспитална подготвеност, континуирана медицинска едукација.

Original scientific paper

MANAGEMENT OF ACUTE RENAL COLIC ACCORDING GUIDELINES IN GENERAL HOSPITALSAND UNIVERSITY HOSPITALS

ТРЕТМАН НА АКУТНА РЕНАЛНА КОЛИКА ВО ОПШТИТЕ И УНИВЕРЗИТЕТСКИ БОЛНИЦИ ВО Р.МАКЕДОНИЈА СПОРЕД ПРЕПОРАКИТЕ СОДРЖАНИ ВО ВОДИЧОТ

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ABSTRACT

Background: Renal colic is a frequent disorder with incidence of less than 1%. Guidelines are recommended as the best clinical practice , they facilitate decision-making in clinical diagnostic and therapeutic process, improve clinical practice, minimize the potential harms and reduce variations in the delivery of health care in the state.

Aim is to evaluate implementation of current guidelines for renal colic in general hospitals and university hospitals

Material and Methods: thirty-five urologists from eight general hospitals (GH) and sixteen urologists from two university hospitals (UH) were invited to participate in the survey.

Results: Application of renal colic guidelines in (GH) was 3/21 versus 5/9 in UH. Urinalysis was performed almost equally in both GH and UH.Regarding the imaging methods, majority performX-ray urography and ultrasound in both hospitals and CT is only used in UH. According to the therapy of acute renal colic in GH as first line treatment is trospium chloride unlike in UH, where NSAIDs are prescribed in 65%.

Conclusion: Administration of medicament therapy presents differences between GH and UH. Physicians in both type of hospitals need better implementation of guidelines.

Key words: renal colic, guidelines, general hospital, university hospital

INTRODUCTION

Approximately one in ten people will be affected by renal colic at some stage in their life.It is estimated that 12% of males and 6% of females will experience an episode of renal colic at some stage in their life, with incidence peaking between age 40 and 60 years for males, and in the late 20's for females [2]. Renal colic is caused by stones in the urinary tract (urolithiasis) predominantly upper tract calculi that obstruct the flow of urine [1]. The blockage in the ureter causes an increase in tension in the urinary tract wall, stimulating the synthesis of prostaglandins, causing vasodilatation and muscle spasm of the ureter resulting in the waves of pain (colic). Individual urinary stones are aggregations of crystals in a noncrystalline protein matrix [2]. The pain of renal colic develops suddenly and is often described by patients as "the worst pain they have ever felt" [3] many patients with renal colic can be managed in primary care with a watchful waiting approach where their pain can be controlled. Referring to an urologist is advisable in order to confirm the diagnosis [2]. If CT urogram is not available then a kidney-bladder ultrasound in combination with an x-ray can achieve detection rates for urinary stones that approach those

of CT urogram [2,4]. Ultrasound is the preferred imaging technique for patients who are unable to be x-rayed, e.g. a female who is pregnant, and is also useful for identifying urate stones which cannot be detected with standard x-ray [3,4]. NSAIDs are the first-line treatment for renal colic pain because they have been shown to achieve greater reductions in pain scores, have a longer duration of action and result in a reduced need for additional analgesia in the short-term, compared with patients treated with opioid analgesics [5]. Opioid analgesics can be prescribed in addition to, or as an alternative, to NSAIDs for patients with renal colic who are at risk of NSAID-induced adverse effects, e.g. in patients with chronic renal impairment, who are dehydrated or have a history of peptic ulcers. Paracetamol and a weak opioid, e.g. codeine or tramadol, can be prescribed for ongoing pain management if NSAIDs are not appropriate once any nausea and vomiting has passed [6]. Alpha-receptor blockers, e.g. doxazosin and terazosin can accelerate the passage of urinary stones by relaxing smooth muscle without preventing peristalsis [7,8]

All of the above is a content of our guidelines recommendations for the treatment of renal colic since 2014. In clinical practice it has proved to be the simplest and most effective type of treatment.

According to the use of renal colic guidelines we were interested if there are any differences in diagnosis, treatment and recommendations given to patients with renal colic in emergency departments (ED) in general hospitals (GH) and university hospitals (UH). Since 2014, the use of updated guidelines for renal colic is an obligation for all family doctors and urologists in the country. Previously there were wide differences in the treatment of this condition.

MATERIAL AND METHODS

In our study we used open format questionnaire. The methodology used is key informant approach, where the target group consists of urologists from different parts of the country. Statistical analysis is made by presenting results for each question in percents in tables.

Thirty-five (35) physicians from ED in eight general hospitals (GH) and sixteen (16) physicians from ED in two university hospitals (UH) were invited to participate in survey about their practice regarding Cochran's guidelines of the diagnosis, treating and counseling patients with renal/ureteral colic in September 2015. Twenty-one doctors from GH and nine from UH responded on a survey.

RESULTS

Table 1. Investigations performed in GH(General Hospital) and UH(University Hospital)

Hospital type	Number of responders	Urinalysis	Blood analysis	Urine culture	X-ray	NCT	IVU	Ultrasound	Guidelines
GH	60%	95%	20%	15%	87%	23%	5%	9%	14%
UH	56%	100%	55%	45%	90%	55%	66%	88%	55%

As shown in Table 1, implementation of urolithiasis guidelines in GH was 3/21 versus 5/9 in UH. In GH ninety-five percent (95%) urinalysis was performed, in 15% urine culture, blood analysis (number of leukocytes, serum creatinine and urea) was performed in 20%. Regarding imaging methods, eighty-seven percent (87%) of urologists prefer X-ray urography, twenty three percent (23%) use noncontrast CT, IVU in 35% and ultrasonography is performed in fifty-nine percent (59%).Physicians in UH performed in 100% urinalysis, laboratory analysis(blood analysis for leucocytes number, creatinine, uric acid, serum calcium)- 55%. 45% use urine culture test. From imaging procedures 55% of urologist use non contrast CT, X-ray urography in 90%, IVU in 60%, ultrasonography-95%.

Table 2. Medicament therapy in different hospitals

Hospital type	NSAIDs	opoides	trospium chloride 0.2 mg iv	tamsulosin	infusion therapy	NSAID+ Opoides
GH	30%	20%	90%	5%	71%	24%
UH	65%	45%	55%	10%	77%	44%

The first line therapy of acute renal colic in GH is trospium chloride-antimuscarins-90%, NSAID-30% and opioids in 20%, combination of NSAID and opioids in 25%, tamsulosin-5%. Physicians from UH prescribe NSAID in 65%, trospium chloride in 55%, opioids in 45%,combination of NSAID and opioids in 45% and tamsulosin-10%., as shown in Table 2. Patients with septic signs and obstructive finding were treated in UH.

DISCUSSION

According to the Guidelines,patients with an uncomplicated presentation of renal colic can often be managed in primary care, following prompt referral for imaging to confirm the diagnosis (same-day if possible). Non-steroidal anti-inflammatory drugs (NSAIDs) are generally preferred over morphine for pain management in patients with renal colic. Most urinary stones will pass spontaneously, however, alpha-blockers are now recommended to accelerate their passage.

There are a few studies that evaluate current practice patterns in different types of hospitals for the diagnosis, treatment, and counseling of patients with ureteral calculi. In an American study of current practices in an emergency department (ED) it is established a need for educational opportunities for ED physicians in the management of renal colic and establishing collaborative practice guidelines between urology and emergency medicine associations [9]

In the survey we performed during September 2015, we found out that urologists in GH are less likely to implement guidelines regarding the diagnostic and treatment options for renal/ureteral colic i.e. 15% in GH versus 60% in UH.

The rate of urinalysis performed in GH isclose to UH, urine culture was three times less investigated in GH 15% than in UH, where 45% of renal colic patients needed it. Blood analysis in GH revealedonly urea and creatinine measurement in 20% of the patients compared to UH where in 55% of patientscalcium and uric acidwere analyzed as well. There is great difference in implementation of imaging investigation especially ultrasonography, IVU and non-contrast CT; in GH in smaller percent then UH. Only X-ray urography is in a close percent.The difference in the diagnostic approaches might relay on the equipment which is poor in the regions where general hospitals are located.

Administration of medicament therapy presents differences between GH and UH. In GH Trospium chloride is the first line drug administrated in renal colic patients, after that follows NSAID, opioids,combination of NSAID and opioids and only 5% use expulsive therapy. On the other side in UH the first line of treatment are NSAIDs, after that follows trospium chloride and opioids and the combination of NSAIDs and opioids in similar percentage.

Hyperhidratation with intravenous fluids is dominant in both type of hospitals which is in contrast with recommendations from guidelines

It is a fact that both GH and UH have all kinds of pharmaceutical medicaments needed for renal colic treatment. It is only the familiarity and up to date with the guidelines instructions that is individual and varies in different types of hospitals. This is probably because of the fact is that University hospital`s urologists are more likely to follow up to dates either by online advanced learning or intensively taking part of congresses and other teaching activities.

Physicians in both types of hospitals need better implementation of guidelines.

The development of collaborative practice guidelines between urologists in general hospitals and university hospitals may be warranted in order to establish unique approach in diagnosis and treatment of renal/ureteral colic.

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ТРЕТМАН НА АКУТНА РЕНАЛНА КОЛИКА ВО ОПШТИТЕ И УНИВЕРЗИТЕТСКИ БОЛНИЦИ ВО Р.МАКЕДОНИЈА СПОРЕД ПРЕПОРАКИТЕ СОДРЖАНИ ВО ВОДИЧОТ

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АБСТРАКТ

Вовед: ренална колика е често нарушување со инциденца помалку од 1%. Водичот содржи препораки за најдобра клиничка пракса, кои го олеснуваат процесот на дијагностицирање , донесување одлуки, подобрување на клиничката пракса, минимизирање на потенцијалните штети и намалување на варијациите во испорака на здравствената заштита во државата.

Целта е да се оцени спроведувањето на тековните насоки за ренална колика во општите болници и универзитетските болници содржани во водичот.

Материјал и методи: триесет и пет уролози од осум општи болници и шеснаесет уролози од две универзитетски болници беа поканети да учествуваат во истражувањето.

Резултати: Примената на водичот за ренална колика во општите болници беше 3/21 наспроти 5/9 во универзитетските. Анализа на уринатa е извршена речиси подеднакво и во ОБ и УБ. Што се однесува до методот на дијагносика, мнозинството индицираат РТГ урографија и ултразвук во двата типа болници, а КТ се користи само во Уб. Во однос на терапија на акутна ренална колика во ОБ како прва линија на третман е троспиум хлорид за разлика од УБ, каде НСАИЛ се пропишани со 65%.

Заклучок: Администрацијата на медикаментозна терапијата е различна во ОБ и УБ. Лекарите во двата типа на болниците треба подобро да ги спроведуваат упатствата.

Клучни зборови: ренална колика, водич,општа болница, универзитетска болница

Original scientific paper

HEALTH CHALLENGES FOR ALBANIAN CHILDREN DURING THE 20 YEARS OF DEMOGRAPHIC, EPIDEMIOLOGICAL AND NUTRITIONAL TRANSITION

SFIDAT SHËNDETËSORE PËR FËMIJËT SHQIPTARË GJATË TRANZICIONIT DEMOGRAFIK DHE EPIDEMIOLOGJIK TË PERIUDHËS 20 VJEÇARE (1994 – 2014)

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ABSTRACT

Albania has witnessed during the last twenty years great transformations in demographic, political, economic, health and social fields. This period in Albania can be defined as years of demographic, epidemiological and nutritional transition. According to current infant mortality rate, reduction of fertile population, lengthening life expectancy and population aging it seems Albania has entered into last phase of demographic transition. Infant Mortality Rate (IMR) shows a dramatic and constant reduction during this period, which relates to improved health, sanitary and economic conditions of Albanian population. The Neonatal Mortality Rate (NMR) reduction, on the other side, doesn't follow the overall improvement of IMR, which represent the next coming pitfall for the paediatric health system to tackle. Despite the significant control of infectious diseases in the country, still these diseases are responsible for a great number of deaths amongst paediatric population. Nutritional status follows pretty well the IMR as a trend during the last 20 years, as well as in its distribution amongst urban and rural areas. On the other side, the increasing overweight and obesity frequency amongst children in Albania is increasing steadily although still far behind neighbouring Italian children. Health protection of every child in Albania represents a big challenge for health system, which need to provide high quality services and equally distributed for all social categories.

Key words: demographic transition, infant mortality, malnutrition paediatric care, obesity

BACKGROUND

During the last twenty years in Albania have occurred great transformations in political, economical, cultural and social arena. The change from dictatorship to free market democracy has requested a difficult transformation, not only for the Albanian society and economy of the country but also a hard transition, which takes place every day in the household level [1,2].

During this period this process has gone through different stages, some were fairly dramatic and destabilizing other instead have brought to marked economic recovery, an improvement change of social and cultural structure of the Albanian society.

The most significant example of the painful part of this process is related to the mass migrations to foreign countries, especially in the neighbouring ones such as Greece and Italy. Instead in the last 10 years we have seen a peacefully economic transformation happening in galloping rhythms through the improvements of micro and macro economic indicators linked to families and individuals welfare as well [3,4].

The objectives of this work are multiple a) to draw some of the most important changes that occurred in relation to the health and nutritional status of the Albanian paediatric population since the early nineties to the present time (1994 to 2014); b) to describe, according to this data analyses the development of the country in general, and specific health programs; and at the end c) to conclude on the paediatric health needs and recommend health priorities based on the Italian experience.

MATERIALS AND METHODS

This work represents a literature review on publications in scientific journals in Albania and abroad in the field of paediatrics. Periodic reports issued from INSTAT, Ministry of Health, UNICEF and WHO have been reviewed as well. An important reference to be mentioned is the data coming from programs implemented from Sant'Egidio Community targeting the malnutrition in paediatric age-groups in north and north-east areas of Albania and health promotion and education campaigns affecting both health personnel and community in those regions.

RESULTS AND DISCUSSIONS

These twenty years has lead to a demographic, epidemiological and nutritional transition. [6]. According to the current demographic scenario Albania seems to have entered into the final stage of demographic transition according to the reduction of paediatric population (0-14 years old), an equally decrease of population in the child-bearing age (between 30 and 40 years old), lengthening life expectancy, an aging population, reduction of mortality and birth rates. Figures 1 and 2 express the reduction of the Albanian population in general as well as the paediatric age-group, and the figure 3 shows the modification of population age pyramid of Albanian population in only 10 years time space [7,8].

Figure 1

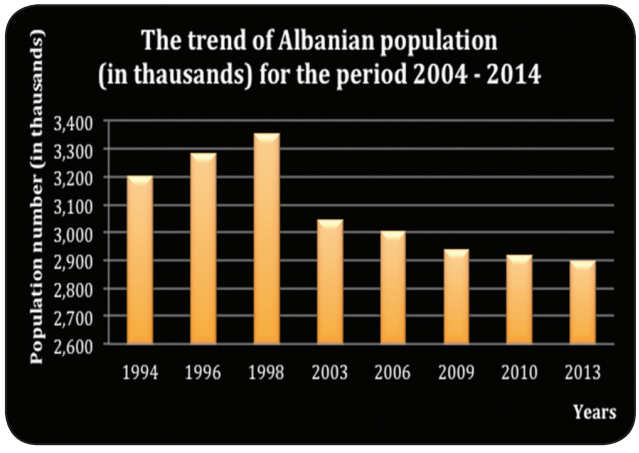


Figure 2

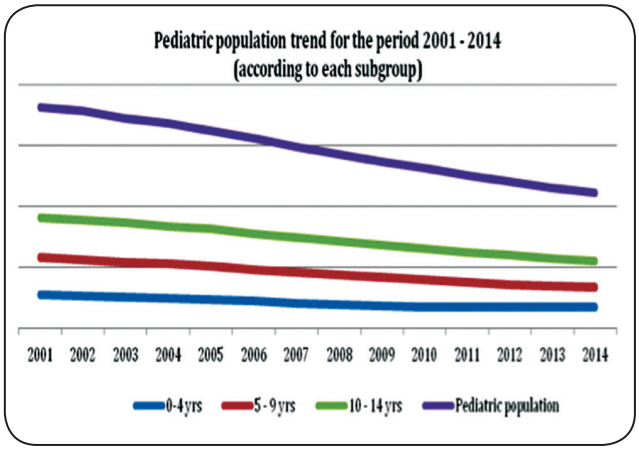
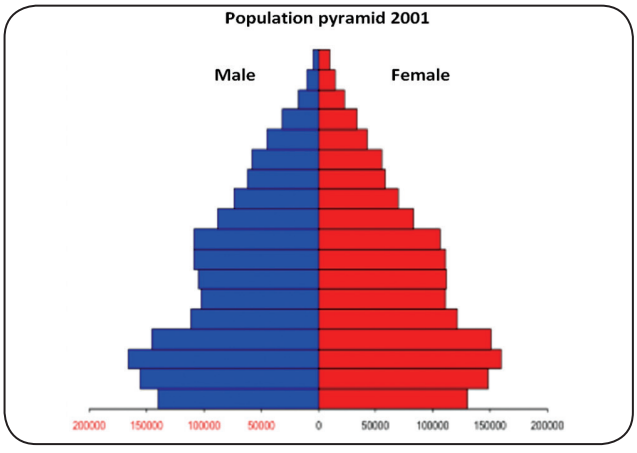
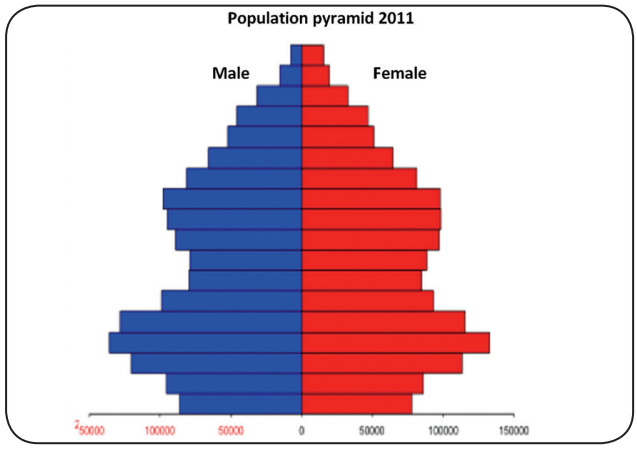


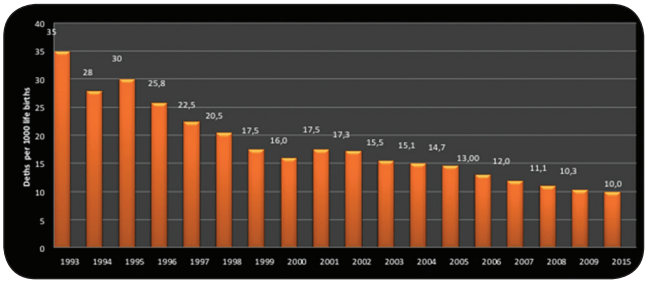
Figure 3





The infant mortality rate in Albania confirms a decreasing trend in the last twenty years, a significant indicator of improved economic and sanitary conditions. Although there is a difference between the estimates of infant mortality compared by government agencies versus assessments carried out by UN agencies specialized on children's health and rights in Albania, there is a common decreasing trend characterizing this twenty years period. Figure 4, according to data sourced from the Ministry of Health, shows the trend of infant mortality which started from a value of 35/1000 in 1993, was reduced in 16/1000 in year 2000 and reaches 10/1000 in year 2009 and we believe it continues to a further decline until the present days [9,10].

Figure 4 The infant mortality trend (per 1000 live births) during the period 1993 – 2009 (the 2015 value shows the millennium objective set for Albania)



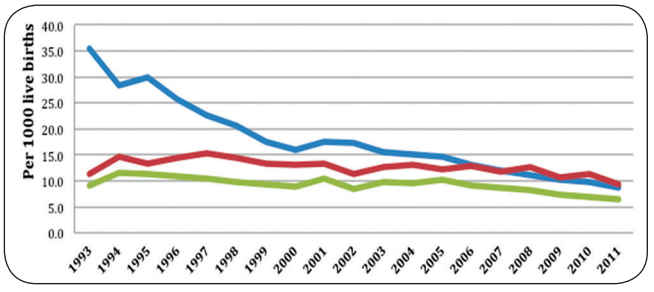
The drastic reduction of child mortality is primarily due to the improvement of socio-economic conditions of the country and is critically related to the excellent control of infectious diseases. The vaccination program has ensured high vaccination coverage rates in childhood age (see Figure 5). This program reflects the renewed National Health Service; plus the continuous enrichment vaccination childhood schedule with new antigens[11]. We must recognize these years were difficult for the country because they were characterized by complex political events - external and internal economic migration, flooding of Kosovo refugees in 1999, local political and economic crisis etc.

There are three different mortality rates, which represent various trends and describe different aspects of paediatric age groups: infant mortality, which shows a drastic reduction during this 2 decades' study and neonatal mortality and perinatal mortality whose reduction rates are minor according to figure 6. The interpretation of each singular trend can be used to identify existing barriers and come up with specific interventions to be implemented accordingly. According to the same figure 6, the neonatal mortality shrinks clearly more slowly and less effectively than the infant mortality. While infant mortality is reduced by almost 70% in twenty years time interval, the neonatal mortality is reduced by only 40% (from 11.5 per thousand it goes to 7 per thousand) for the same time laps. Perinatal mortality shows a similar trend wit neonatal mortality rates because its values from around 15 per thousand during nineties go to around 10/1000 in 2010. These data provide good evidence about specific programs that Ministry of Health need to support in order achieve further improvements relative to neonatal and perinatal mortality rates [13,14].

Figure 5 WHO vaccine-preventible diseases: monitoring system. 2014 global summary (vaccination coverage expressed in percentage rates)
Last updated 15 Jul 2014

Vacciness	2013	2010	2008	2006	2004	2002	2000	1998	1996	1994
BCG	100	100	100	97	97	94	93	87	94	87
DTP1	99	99	99	98	98	98	98	_	_	_
DTP3	99	99	99	97	97	98	97	96	98	100
HepB3	99	99	99	97	99	96	96	94	96	100
HepB	100	100	98	_	99	99	98	_	_	_
Hip3	99	99	_	_	_	_	_	_	_	_
MCV	99	99	98	95	96	96	95	89	92	90
MCV2	99	99	98	94	96	93	_	_	_	_
PCV1	99	_	_	_	_	_	_	_	_	_
PCV3	99	_	_	_	_	_	_	_	_	_
Pol3	99	99	99	97	98	98	97	97	100	98
Rubella 1	99	99	98	95	96	_	_	_	_	_
TT2+	_	85	83	86	85	71	89	65	98	100

Figure 6 Trends of various mortality rates in pediatric age during the period 1993-2011



Although the reduction of paediatric mortality rates were achieved through a better control of infectious diseases in the population, along with maintaining high vaccine coverage, we still observe high incidence of these diseases as a cause of death. As reference we have taken and compared the same indicators in Italy and Albanian in two periods of times close to each other (2011 for Albania and 2007 for Italy). The graph (figure 7) shows the causes

of death during the first year of life, you can see that in Albania still remains a high death rate for respiratory diseases, equivalent to 9.6 deaths per 10,000; while in Italy this ratio is 0.07 for 10,000 deaths. (14,15,16). The cities where these deaths occur mostly are Tirana and Elbasan. This mortality in excess could perhaps be related to major environmental pollution of these two cities. The same mortality in excess for respiratory diseases is also identified in the figure 8,which shows the distribution of causes of death for children in between 1 and 4 years old in both countries. The figure 9 shows the death causes for children between 5 to 14 years old, the first things to note is that the rates between the two countries, for this age group, are quite close. The other evident problem is the mortality in excess due to accidents and incidents in Albania compared to Italy. Based on the reports of the Institute of Public Health there are frequent traffic deaths involving children in the city of Tirana where it is emphasized the urgent need to tackle this problem. [17,18].

Figure 7

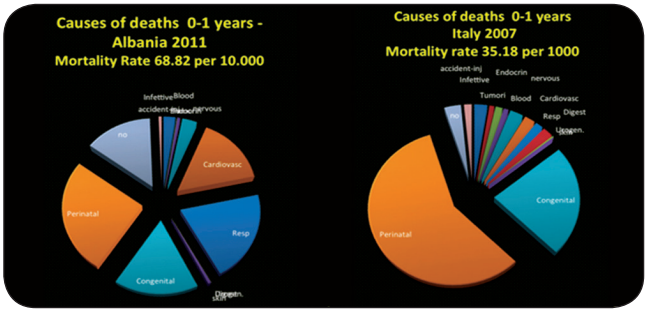


Figure 8

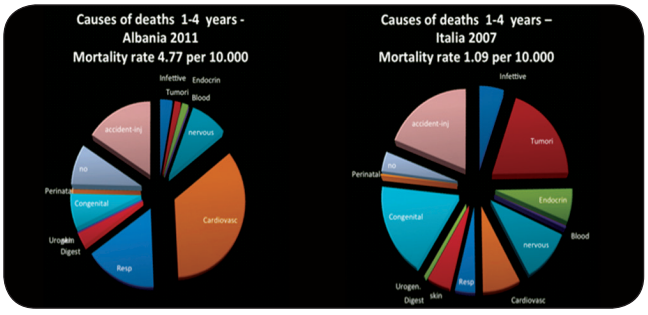
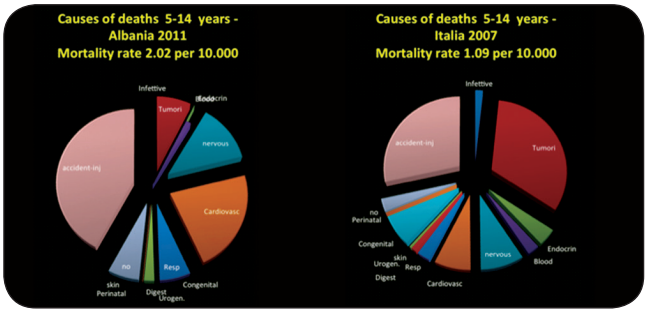


Figure 9



Child malnutrition is considered as another health determinant, and according to data from various sources collected during the period 1994 - 2008, we have noticed an impressive reduction of malnutrition rate among children under-5 years of age. According the figure 10, the malnutrition is recorded at values around 20% in the year 1994, to a value around 10% in 2001 and 6% in 2008 [19,20]. The following figure 11 shows the on-going pattern of under-5 mortality in children Albanians during the same period (1997 – 2007). With surprising punctuality you can see from different sources and studies on children under-5 years, that malnutrition is reduced with a very similar trend to that of mortality rate [21,22,23]. It is important to emphasise a clear difference of malnutrition rate between rural and urban areas, with a higher proportion of malnourished children in rural areas. This disparity highlights the more vulnerable conditions of rural children, which would require more specific interventions in rural and peripheral inhabited areas, in order to remove these conditions.

Figure 10 1077-2008: The Albanian trend of Children Malnutrition Weiht for Age <- zscore (5-69 months)

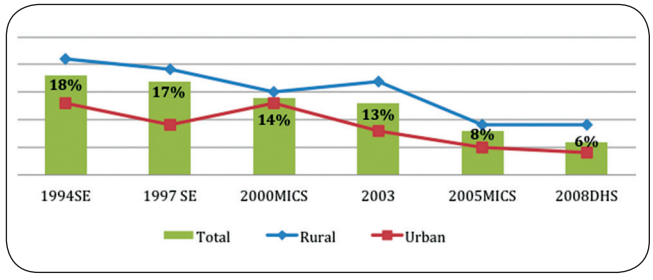
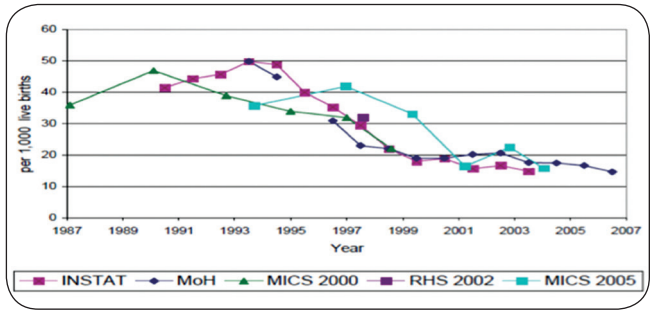


Figure 11 Trend in under-5 mortality rates. Albania, 2005



When analysing nutritional status we have noted another important aspect, which is the emergence, the distribution and trend of overweight and obesity in the paediatric population. As a result of the demographic transition of the Albanian population, it has also been modified the epidemiology of the disease that affect adult population. Today 50% of the causes of death among

adults are due to cardiovascular diseases, strongly related to excess of weight. This condition also affects the paediatric population based on the data coming from the following two studies: the first was conducted in the paediatric population frequenting kindergartens in the city of Tirana which were selected in three different areas of the city. [24]. According to the anthropometric data of the sample, the figure 12 shows a distribution of weight for age where 6% of the sample are overweight or obese and only 1.7% are underweight. Despite this sample is not representative of the paediatric population in Albania (the selected children, all from Tirana, come mostly from families with a certain standard of living), it is interesting to note the increase of obesity in comparison to malnutrition. The other study has recruited school population children between 7 and 10 years old and has estimate the prevalence of overweight and obesity equal to 20% in urban area and 9% in rural area with national rate of around 15% (see figure 13) [25,26]. The very low proportion of underweight index indicates the nutrition transition currently occurring in the paediatric population in Albania. However the overweight and obese rates in Albania are fortunately still far below those in Italians, whose regional prevalence varies amongst 25% and 40% of the paediatric population.

Figure 12 Nutritional Status in Albanian pre-school age children in Tirana - 2003
Distribution of the sample according to „weight to age“

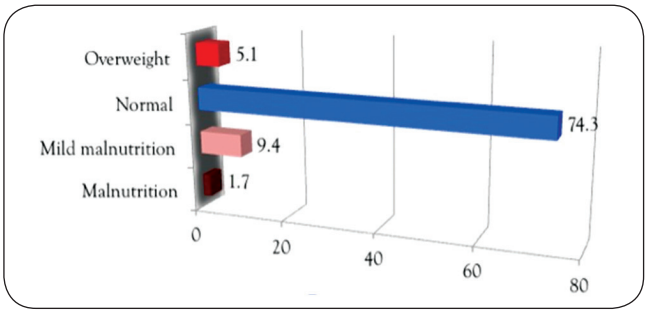
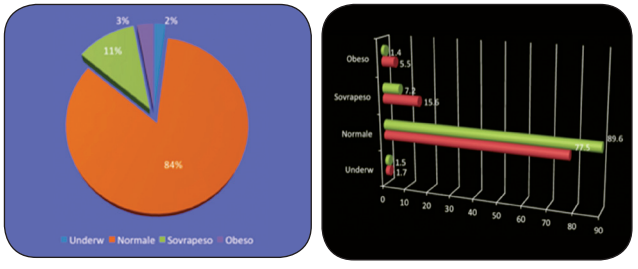


Figure 13 Albania - Obesity 2013: Rural vs Urban 7 to 9 years old



CONCLUSIONS

As a conclusion of this analysis about epidemiological and nutritional transition and its impact on the health status of Albanian population, we can confirm that Albania in the last two decades has profoundly improved the health and nutrition status its paediatric population. On the other side, Albania is currently dealing with problems very similar with other European countries. As an example there are the chronic degenerative diseases such as tumours or excess of mortality for road accidents as well as emerging of overweight and obesity as predictors for diabetes and cardiovascular disease in later ages. Health protection of Albanian children remains a challenge for the national health system and will require better equity, both territorial and social, for health care services targeting especially neonatal age group [27,28]. Among many challenges Albania is facing in health sector, one of them should certainly be the improvement of paediatric care services, which need to build a health care environment that guarantees to all the best possible access to the health care, and is open to research and innovation.

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SFIDAT SHËNDETËSORE PËR FËMIJËT SHQIPTARË GJATË TRANZICIONIT DEMOGRAFIK DHE EPIDEMIOLOGJIK TË PERIUDHËS 20 VJEÇARE (1994 – 2014)

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ABSTRAKTI

Albania gjatë 20 viteve të fundit ka qënë dëshmitare e transofmimeve të mëdha në fushën demografike, politike, ekonomike, shëndetësore dhe atë sociale. Kjo periudhë mund të quhet edhe si tranzicioni demografik, epidemiologjik dhe atij nutricional. Të dhënat e vdekshmërisë foshnjore (VF), pakësimi i popullatës fertilite, zgjatja e viteve të jetës si dhe rritja e moshës mesatare tw popullatws shpjegojnë hyrjen e Shqipërisë në fazën e fundit të tranzicionit demografik. Vihet re një reduktim dramatik dhe i qëndrueshëm i vlerave të VF e cila mund të jetë e lidhur me përmirësimin e kushteve shëndetësore, shoqërore dhe ekonomike të popullatës shqipërtare.

Reduktimi i vdekshmëria neonatale nuk ndjek plotwsisht trendin përmirësues të VF duke përfaqësuar një nga pikat e dobëta të shërbimeve pediatrike. Pavarësisht nga kontrolli shumë i mirë i sëmundjeve infektive, ende shumë prej tyre janë përgjegjëse për një numër të madh rastesh vdekje në popullatën pediatrike.

Gjëndja nutricionale ndjek trendin e VF të vërejtur gjatë 20 viteve të fundit. Prevalenca kequshqyerjes në nivel kombëtar ulet pothuaj 3 herë gjatë kësaj periudhe 20 vjecare. Ndërkohë që mbipesha dhe obeziteti po kthehen në një fenomen gjithmonë e më të shpeshtë ndonëse ky nivel është mjaft më i ulët sesa grup-mosha pediatrike në Italinë fqinjë. Mbrojtja e shëndetit të cdo fëmijë në Shqipëri paraqet një sfidë të madhe për sistemin shëndetësor me qëllim që ky i fundit të ofrojë shërbime mjekësore cilësore dhe të shpërndara në mënyrë homogjene për të gjitha kategoritë sociale në vënd.

Fjalët kyçe: tranzicioni demografik, vdekshmëria foshnjore, kujdesi i kequshqyerjes në moshën pediatrike, obeziteti.

Original scientific paper

KONVULSIONET FEBRILE TRAJTIMI MË EFIKAS PËR PARANDALIMIN E REKURENCAVE

FEBRILE SEIZURE PREVENTIVE TREATMENT OF CONVULSIVE RECURRENCES

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ABSTRAKTI:

Konvulsionet Febrile janë lloji më i shpeshtë i konvulsioneve tek fëmijët nën moshën 5 vjeç. Ato vazhdojnë të jenë subjekt i interesit dhe kundërshtive që vazhdojnë të lidhen me mënyrën se si duhet te trajtohen.

Qëllimi i Studimit: Të evidentojë se cila është mënyra me e mire e trajtimit te konvulsioneve Febrile Komplekse me terapi intermitente apo profilaksi me antiepileptikë.

Materiali dhe Metoda: Në studim u morën 106 fëmijë me Konvulsione Febrile Komplekse. Pacientët u ndanë në 2 grupe. Në grupin e parë përfshiheshin pacientë me Konvulsione Febrile Komplekse tek të cilët terapia e rekomanduar ishte Diazepam dhe Antipiretike sa herë që fëmija paraqiste temperaturë, dhe në grupin e dytë fëmijë me Konvulsione Febrile Komplekse të cilët mjekimi i rekomanduar ishte trajtim profilaktik me Phenobarbital ose Acid Valproic për një vit pa ndërprerje. Pasi u mjekuan për një vit pacientet u monitoruan për një periudhe 3 vjeçare. Te dhënat u hodhën ne një databaze te programuar paraprakisht bazuar ne te dhënat qe dëshironim te analizonim. Te dhënat u analizuan nëpërmjet programit SPSS.

Rezultatet: Nuk u gjenden ndryshime me sinjifikance statistikore midis grupeve përsa i përket riskut për relaps ne te 2 grupet e trajtuara. Pacientet e trajtuar pa AED treguan te dhëna EEG anormale sinjifikante ne krahasim me grupin e trajtuar me AED.

Konkluzion: Ne konvulsionet Febrile Komplex rekomandohet ndjekja nëpërmjet EEG pasi sipas studimit ndryshimet EEG kane lidhje me rikthimin e krizave. Trajtimi me antiepileptike nuk është i rekomandueshëm përveç rasteve me risk te larte.

Fjale Kyçe: Konvulsion febril, Epilepsi, antiepileptikë, EEG

HYRJE

Konvulsionet Febrile janë lloji me i shpeshtë i konvulsioneve tek fëmijët e moshës nën 5 vjeç. Ndonëse ato konsiderohen përgjithësisht beninje, krijojnë moment paniku tek prindërit për shkak të riskut të lartë për përsëritje. Sipas Akademise Amerikane të Pediatrisë (1999), Konvulsionet febrile të thjeshta nuk kërkojnë mjekim [3]. Por përsa i përket Konvulsioneve Febrile komplekse ende ka debate për mënyrën e trajtimin për vete kompleksitetin që ato paraqesin. Ekziston dilema nëse duhen trajtuar me profilaksi antiepileptike apo jo. Kjo për arsye se nga njëra ane ekziston frika në lidhje me efektet anësore që kanë barnat antiepileptike dhe nga ana tjetër dëmtimet që mund të shkaktojnë krizat konvulsive sidomos ato të zgjatura. Studimet tek kafshët kanë treguar se krizat me kohëzgjatje mbi 20 minuta shkaktojnë dëmtime cerebrale permanente [23].

Ndër faktorët që mund të influencojnë në vendimin tonë për profilaksi afatgjatë me antiepileptike mund të përmendim:

- Insistimi i prindërve për shkak të frikës nga krizat

- Risku për përsëritje
- Risku për epilepsi
- Mundësia e statusit epileptik afebril

OBJEKTIVAT

Të evidentojë se cila është mënyra me e mire e trajtimit të Konvulsioneve Febrile Komplekse me terapi intermitente apo profilaksi me antiepileptikë.

METODA

Në studim u morën 106 fëmijë me Konvulsione Febrile Komplekse.

Pacientët e marrë në studim janë trajtuar nga Qershori 2009- Qershor 2011 pranë Poliklinikës së Specialiteteve nr.3 Tiranë. Përveç pacientëve të paraqitur për herë të parë në shërbimin tonë ne kemi analizuar dhe kartela të pacientëve të paraqitur më parë në shërbimin tonë, apo pacientë të klinikave të tjera që paraqiteshin tek ne për arsye të sistemit të referimit.

Kritere përjashtuese nga studimi:

- Fëmijët me Konvulsione Febrile të thjeshta.
- Fëmijët që kishin bërë kriza konvulsive afebrile më parë.
- Fëmijët me ekzaminim neurologjik jonormal.
- Fëmijët me të dhëna Imazherike jonormale.
- Fëmijët me infeksion të SNQ

Në klasifikuam Konvulsionet Febrile Komplekse bazuar në kriteret e vitit 1993:

1) Krize fokale, 2) kohëzgjatja mbi 15 minuta (Berg and Shinnar, 1996; Nelson and Ellenberg,

1978) [5-21] ose kriza të përsëritura brenda 24 orëve nga episodi i parë (Nelson and Ellenberg, 1976; Annegers *et al*, 1987) [1].

Faktorët që kanë ndikim në shfaqjen e konvulsioneve febrile si:

- Mosha, gjinia dhe vendbanimi;
- Histori familjare pozitive për konvulsione febrile;
- Lloji i krizave;
- Numri i krizave;
- EEG [4]

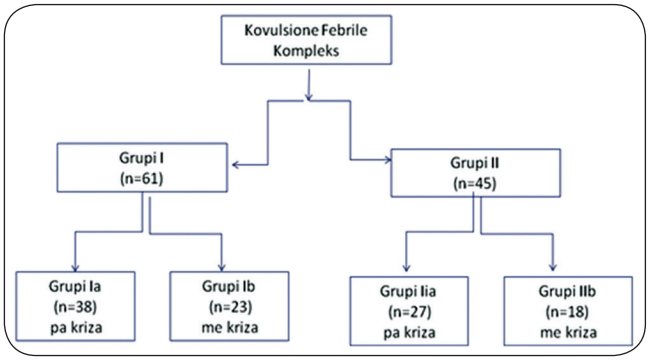
Pacientët u ndoqën për një periudhë 3 vjeçare nga moment që u ndërprenë mjekimet.

Pacientët e marrë në studim (n=106) u ndanë në 2 grupe përkatësisht grupi i parë me 61 pacientë dhe grupi i dytë me 45 pacientë.

Përpara se të vendosnim se në cilin grup do të kategorizonim secilin prej fëmijëve, prindërve të tyre iu sqarua paraprakisht mbi 2 modelet e trajtimit dhe balanca risk përfitim dhe ne mirëkuptim të plotë u mor vendimin se në cilin grup do të vendoseshin.

Arsyeja përse u bë kjo ndarje e pabarabartë ishte pasi u morën në konsiderate disa faktorë si fakti që disa prindër ishin kundër një trajtimi afatgjate për shkak të frikës nga efektet anësore të barnave, apo e kundërta disa prindër të tjerë ishin pro mjekimit afatgjatë për arsye se kishin frike se nuk mund të përballeshin me faktin nëse fëmija do te bënte kriza konvulsive si dhe frika për komplikacione te mundshme.

Figura 1. Ndarja e pacientëve sipas grupeve:



Analiza Statistikore

Te gjitha te dhënat u hodhën ne një databazë te ndërtuar paraprakisht dhe u analizuar në mënyre statistikore me programin SPSS. Vlera P<0.05 u konsiderua statistikisht sinjifikative

REZULTATET

Tabela 1. Karakteristikat e pacientëve të studiuar

Karakteristikat e pacienteve te studiuar (n=106)	
Mosha (muaj)	3-60
Mesatare	21.2
Gjinia	
Mashkull	61 (57%)
Femër	45 (43%)
Histori familjare pozitive për KF	24 (22.6%)
EEG anormal	32(30.2%)
Lloji i krizave	
Parciale	90(84.9%)
Te gjeneralizuara	16(15.1%)
Patientë pa terapi antiepileptike	61 (57%)
Patientë me terapi antiepileptike	45 (43 %)

Në tabelen nr.1 jepen karakteristikat e pacientëve të studiuar. Mosha e 106 pacientëve te marrë në studim ka qenë 3-60 muaj. Numri më i madh i të sëmurëve kanë qenë të gjinisë mashkullore 61/106 (57.5%) dhe 45/106 (42.5%) të gjinisë femërore. 22,6% e pacientëve kanë raportuar histori familjare pozitive për konvulsione febrile. Ne regjistrimet EEG, 30.2% kanë rezultuar me të dhëna EEG jonormale. Krizat parciale janë hasur ne 84.9% te pacienteve dhe krizat e gjenealizuara në 15.1%.

Tabela 2. Risku për relaps sipas grupeve

	Numri i pacientëve që kanë bërë kriza gjatë ndjekjes 3 vjeçare sipas grupeve në raport me totalin e pacienteve N=106				
	Grupi I		Grupi II		
	N	%	N	%	P
Me kriza	23	21%	18	16%	0.34

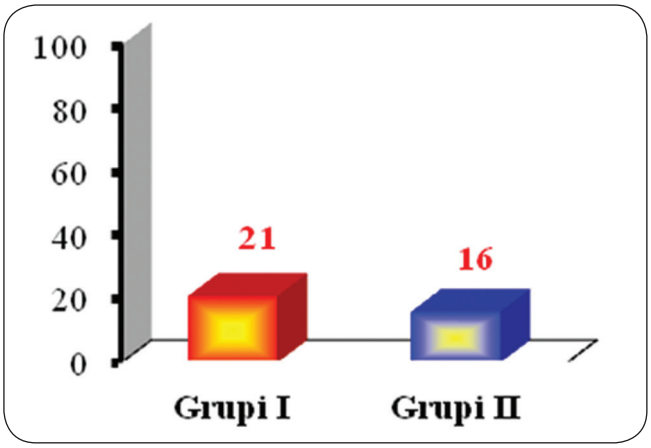


Figura nr.2. Risku per relaps

Shkalla e relapsit mbas ndërprerjes të mjekimit ishte 16% ne grupin me AED dhe 21% ne grupin pa AED. Studime te ndryshme japin shkallë relapsi nga 12-44%.

Tabela 3. Ndjekja 3 vjeçare pas ndërprerjes së mjekimit.

Lidhja e parametrave midis dy gupeve qe kanë bërë kriza gjatë ndjekjes 3 vjeçare					
	Grupi Ib N=23		Grupi IIb N=18		P
	N	%	N	%	
Gjinia					
Mashkull	13	56.5	10	55.5	0.94
Femër	10	43.5	8	45.5	0.89
Histori familjare pozitive per epilepsi	8	34.8	5	27.8	0.64
EEG abormale	14	60%	2	11%	0.002
Lloji i krizave					
Te gjeneralizuara	5	21.8	3	16.6	0.67
Parciale	18	78.2	15	83.4	0.68

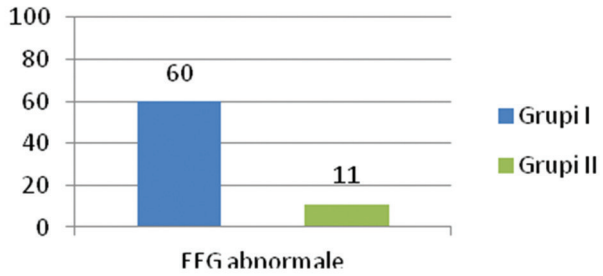


Figura 3. Ndryshimet EEG midis dy gupeve që kanë bërë kriza gjatë ndjekjes 3 vjeçare.

Ne krahasimet e të dhënave EEG midis dy grupeve gjatë ndjekjes 3 vjeçare kemi evidentuar ndryshim sinjifikant statistikor P=0.002.

Tabela 4. Risku për relaps sipas mjekimit.

Lidhja midis grupeve përsa i përket riskut për relaps gjatë ndjekjes 3 vjeçare sipas mjekimeve					
	Me kriza N=41		Pa kriza N=65		P
	N	%	N	%	
Diazepam dhe antipiretikë	23	56,09	38	58,46	0,81
Acid Valproic	10	24,39	14	21,53	0,73
Phenobarbital	8	19,51	13	20	0,95

Ne krahasimet midis 2 grupeve janë vene ndryshime te vogla ne favor te terapisë AED por jo statistikisht sinjifikative.

Tabela 5. Risku për relaps sipas moshës

Mosha	Korrelacioni i moshës së fillimit të krizave përpara fillimit të terapisë me pacientet që kanë bërë kriza gjatë ndjekjes 3 vjeçare.				
	Grupi Ib N=23		Grupi IIb N=18		
	N	%	N	%	P
0-12	9	39,13	10	55,55	0.30
13-24	8	34,78	4	22,22	0.38
25-36	5	21,73	3	16,66	0.68
37-48	1	4,34	1	5.55	0.85
49-60	0	0	0	0	

Ne krahasimet midis 2 grupeve sipas moshave nuk janë vëne ndryshime statistikisht sinjifikative përsa i përket riskut për relaps.

DISKUTIM

Ne studimin tone kemi konstatuar dominim të gjinisë mashkullore. Një dominim i lehtë të gjinisë mashkullore shihet edhe në punimet të tjera [21]. Disa këtë e shpjegojnë me dominim të gjinisë mashkullore në popullatë por kjo nuk shihet në punimet e shumë autorëve Japonez (Tsuboi [25]. Kështu Fois gjen raportin 55.15%-44.85% në favor të meshkujve [28].

Numri më i madh i rasteve kanë qenë të moshës nen 12 muaj (*44.3 %*) përqindje lehtesisht me e larte se grupmosha 13-24 muaj (*25.47 %*). Shifra te përafërta shihen edhe në studime të tjera [24-27]. Duke ardhur ne rend zbritës me rritjen e moshës 25-36 muaj (*18.86 %*), grupmosha 37-48 muaj 9.4%, grupmosha 49-60 muaj 1,8%. Shohim se me rritjen e moshës ulet rreziku për Konvulsione Febrile Komplekse.

Në studimin tone ne evidentuam dy periudha piku në incidencën e konvulsioneve febrile, Nëntor-Janar (që korrespondon me pikun infeksioneve virale që prekin traktin e sipërm respirator, dhe Korrik-Gusht (kohë kur sëmundjet gastrointestinale janë më të shpeshta. Te dhëna te ngjashme përshkruhen ne literature dhe ne studime te tjera [26].

Historia familjare pozitive për Konvulsione Febrile ishte pozitive në 22.6% të rasteve.

Studime te tjera japin shifra 20% deri ne 40% [15-17]

Shkalla e relapsit mbas ndërprerjes të mjekimit ishte 16% ne grupin me AED dhe 21% ne grupin pa AED. Studime te ndryshme japin shkallë relapsi nga 12-44% [2].

Në punimet e autorëve të huaj përqindja e relapsi varion. Ka punime që flasin për relaps deri 30%, deri në përqindje shumë të madhe të relapsit deri 80% te punimet e autorëve japonezë.

Berg gjithashtu precizoi faktorët parashikues të mundshëm për përsëritje te konvulsioneve febrile: mosha e hershme, anamneza familjare pozitive, temperature e ulët në krizën e parë, çrregullimet neurologjike si dhe anomalitë në EEG [8].

Por sidoqoftë shkalla e relapsit varet nga një sërë faktorësh që kanë të bëjnë me mënyrën e dizenjimit të studimit por dhe veçori të ndryshme social ekonomike.

Krizat konvulsive parciale ishin lloji më i shpeshtë i krizave në popullatën e marrë në studim 90(84.9%).

Ne vumë re se prezenca e historisë familjare pozitive për konvulsione febrile, lloji i krizave nuk kishin ndonjë efekt persa i përket riskut për relaps.

Ne pacientet me te dhëna elektroencefalografike abnormale verehet një risk i larte për relaps (statistikisht sinjifikant).

Ndryshimet më të mëdha në EEG i vëren në javën e parë Yamamura. Në studimet në seri të mëdha prezantohen ndryshime anormale në 35%-45% te fëmijët deri në moshën 5 vjeçare, ndërsa ndryshime fokale deri 10% ka vërejtur në studimet te tjera.

Në një studim me 676 fëmijëve Sofijanov ka vërejtur se 22% të fëmijëve kanë pasur ndryshime në EEG [14].

Edhe pse nuk është metodë e sigurt në parashikimin e prognozës së konvulsioneve febrile EEG si metodë jo invazive mbetet e rëndësishme në vërtetimin e ndryshimeve elektrocerebrale si dhe si prediktor i kushtëzuar në prognozën e konvulsioneve febrile dhe kalimin e tyre në epilepsi. Ne studimin tone nuk është evidentuar ndonjë ndryshim sinjifikativ midis grupeve me dhe pa AED ne riskun për relaps.

KONKLUZION

Ne Konvulsionet Febrile Komplekse rekomandohet ndjekja nëpërmjet EEG pasi sipas studimit ndryshimet EEG kane lidhje me rikthimin e krizave. Trajtimi me antiepileptike nuk është i rekomandueshëm përveç rasteve me risk të lartë që kemi përmendur në këtë studim.

REKOMANDIME

Në konvulsionet Febrile te Thjeshta nuk rekomandohet trajtim me AED.

Në konvulsionet Febrile Komplekse, trajtimi me antiepileptikë nuk është i rekomandueshëm përveç rasteve me risk të lartë për rekurenca.

Në konvulsionet febrile Komplekse rekomandohet ndjekja nëpërmjet EEG pasi sipas studimit ndryshimet EEG kanë lidhje me rikthimin e krizave.

Edukimi i prindërve për mënyrën e manazhimimit të fëmijes gjatë krizës konvulsive në kushtet e shtëpisë, në mungesë të ndihmës së specializuar.

Trajtimi me antiepileptike nuk është i rekomandueshëm përveç rasteve me risk të lartë.

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FEBRILE SEIZURE PREVENTIVE TREATMENT OF CONVULSIVE RECURRENCES

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ABSTRACT

Febrile seizures, the most common type of seizures in infants and young children under 5 years. It continues to be the subject of intense interest and controversy among physicians about the treatment.

Aim of study: This study was designed to identify which is the best method of treatment of Complex Febrile Seizure with intermittent or continuous prophylaxis with AED.

Methods:106 children with diagnosis Febrile seizure Complex were included.

Patients was divided in 2 groups. Firs group patients with intermittent prophylaxis treatment Diazepam and antipyretics during fever and second group patients with prophylactic therapy AED. Treatment duration 1 year. All the patients was followed up for 3 years for any new seizure occur. All data were analyzed by SPSS

Results: No significant statistical difference was found between both groups regarding the rate of seizure relapse during follow up.

It is found that presence of significantly abnormal EEG in the group treated without AED.

Conclusion: As a conclusion regarding the treatment of Complex Febrile Seizure first we must evaluate the balance risk-benefit regarding AED treatment.

EEG monitoring in children with complex Febrile Seizure is recommended because in our study we found a correlation between abnormal EEG and seizure relapse.

Key words: Febrile Seizure, Epilepsy, antiepileptic, EEG

FAKTORËT E RISKUT PËR NEFROPATI TË INDUKTUAR NGA KONTRASTI MIDIS PACIENTËVE QË I NËNSHTROHEN KORONAROGRAFISË OSE NDËRHYRJEVE KORONARE PERKUTANE – REZULTATET E STUDIMIT NË QENDRËN SPITALORE UNIVERSITARE "NËNË TEREZA" TIRANË

RISC FACTORS FOR CONTRAST INDUCED NEPHROPATHY IN PATIENTS UNDERGOING CORONARY ANGIOGRAPHY OR PERCUTANEOUS CORONARY INTERVENTION- REZULTS OF THE STUDY FROM "MOTHER THERESA" UNIVERSITY HOSPITAL CENTER, TIRANA

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ABSTRAKT

Objektivat: Ky studim synon të vlerësojë faktorët e riskut për Nefropatinë e Induktuar nga Kontrasti (NIK), në pacientët që i nënshtrohen koronarografisë ose Intervenimit Koronar Perkutan (PCI) në një qendër spitalore terciare, në Shqipëri

Metodat: Midis pacientëve që i nënshtrohen koronarografisë ose PCI në Qendrën e Katerizimit të Zemrës në QSU "Nënë Tereza" Tiranë, u studjuan për faktorë risku për NIK 1231 pacientë, nga 2010 deri në 2014. NIK u përkufizua si një rritje në nivelin e kreatininës serike, më tepër se 0.5 mg/dl ose 25% të nivelit bazal, në 48/72 orë pas ekspozimit ndaj agjentit të kontrastit krahasuar me vlerën bazale të kreatininës. U vlerësuan faktorët konvencionalë të riskut për NIK, më të pranuar në literaturë: lesioni renal pre-ekzistent, Diabeti mellitus, mosha>65 vjeç, anemia, Insuficienca Kardiake, volumi i kontrastit; duke u përdorur analiza e regresionit logjistik binar dhe ajo multivariate. Incidenca e NIK u përllogarit si një përqindje e totalit. U konsiderua sinjifikante vlera e $p< 0.05$

Resultate: Popullata e studjuar ishte 804 pacientë (427 pacientë të përjashtuar; nuk plotësuan kriteret e përfshirjes). Incidenca në total e NIK ishte 14.4% . Faktorët e riskut të shoqëruar me zhvillim të NIK rezultuan: lesion renal pre-ekzistent, [OD: 1.57; CI95%: 1.02-2.41] (*p=0.039*), mosha>65 vjec [OD: 1.52; CI95%: 1.02-2.26](*p=0.038*), Insuficienca Kardiake (*p<0.001*). Faktorët e tjerë si Diabeti mellitus, anemia, volumi i kontrastit nuk rezultuan faktor risku të pavarur për NIK.

Konklusion: Afërsisht 14.4% e pacientëve që ju nënshtruan koronarografisë bën NIK, që përbën dhe incidencën e NIK-ut më të përshkruar në literaturë. Edhe pse incidenca e NIK në prezencën e faktorëve të riskut konvencionalë ishte më e lartë, faktorë të pavarur risku për NIK rezultuan: lezioni renal pre-ekzistent, mosha>65 vjeç, Insuficienca Kardiake. .

Fjalët kyce: faktorë risku, NIK, incidenca, kontrast, koronarografi, PCI

HYRJE

NIK përbën shkakun e tretë të hospitalizimeve për Insuficiencës renale akute (IRK), duke kontribuar në 10% të rasteve të IRK të hospitalizuara [1]. Është e pëkufizuar zakonisht si një përkeqësim akut i funksionit renal karakterizuar nga një rritje sinjifikante e kreatininës serike, me më tepër se 0.5 mg/dl ose më tepër se 25% e vlerës bazale të kreatininës, në 48/72 orë pas ekspozimit ndaj agjentit të kontrastit, krahasuar me vlerën bazale

të kreatininës serike para procedurës[1]. NIK shoqërohet me rritje të vdekshmërisë, sëmundshmërisë dhe kostos së trajtimit[1]. Megjithëse zakonisht është tranzitore, me rikthim në 1-3 javë, çrregullimi i funksionit renal mund të jetë në disa raste i përhershëm me rrezik për sëmundje renale kronike dhe nevojën për dializë të përkohëshme ose të përhershme[1]. Incidenca e raportuar nga literatura për NIK ndryshon gjerësisht nga 2%- 30%, duke u varur nga popullata e studjuar, kriteret diagnostike dhe faktorët e riskut prezentë. Duke qenë se edhe numri i pacientëve të riskuar që ekspozohen ndaj substancës së kontrastit është gjithmonë dhe më i madh, NIK paraqet një problem klinik vazhdimisht në rritje. Parandalimi është çelësi për të reduktuar incidencën e NIK dhe kjo fillon me identifikimin e pacientëve me risk të lartë bashkë me menaxhimin e përshtatshëm periprocedurial. Është gjetur një korelacion i fuqishëm midis faktorëve të riskut dhe lezionit renal preekzistent, Diabetit mellitus, moshës së avansuar, insuficiencës kardiake kongjestive, volumit dhe llojit të substancës së kontrastit, përdorimit konkomitant të substancave nefrotoksike, dehidrimit [1]. Synimi i këtij studimi është të bëjë një profil të pacientëve të cilët zhcillojnë NIK pas koronarografisë dhe/ose PCI, duke synuar marrjen e masave të përshtatëshme parandaluese, nëpërmjet analizës së faktorëve të riskut, të pranuar më gjerësisht në literaturë.

Qëllimet e studimit:

- Të identifikojë dhe vlerësojë faktorët e riskut për NIK në pacientët që i nënshtrohen proçedurave intervencionuese koronare, në Qendrën e Kateterizimit të Zemrës, në QSU "Nënë Tereza" Tiranë, në një periudhën kohore Janar 2010 – Dhjetor 2014.

Kriteret e përfshirjes në studim:

- Pacientë që kryejnë koronarografi ose PCI, në Qendrën e Kateterizmit të Zemrës, QSU "Nënë Tereza" Tiranë (2010-2014).
- Pacientë të cilëve u matet kreatinina para proçedurës invazive koronare dhe në 48/72 orë pas proçedurës me kontrast intra-arterial.

Kriteret e përjashtimit:

- Pacientë në dializë kronike
- Pacientë të cilëve nuk u arrit t'u matet kreatinina serike (KrS) para proçedurës me kontrast dhe të paktën 48/72 orë pas procedurës.

Pikëmbërritjet:

Primare:

- incidenca e NIK në 48/72 orë.
- vlerësimi i faktoreve të riskut për NIK

Sekondare:

- Roli i vlerës absolute të KrS para proçedurës si faktor risku për NIK (KrS >1.5 mg/dl).

MATERIALE DHE METODA

Studimi është prospektiv *case-control*, që përfshiu 1231 pacientë, që realizuan koronarografi dhe/ose ndërhyrjes perkutane koronare (PCI) në Qendrën e Kateterizimit të Zemrës në QSU "Nënë Tereza" Tiranë , prej vitit 2010-2014.

U mat vlera e KrS para proçedurës dhe 48/72 orë pas proçedurës. U monitoruan faktorët e rrezikut madhorë për zhvillimin e NIK më gjerësisht të pranuar në literaturë: (mosha, diabeti mellitus (DM), lezioni renal preekzistent (LRP), anemia, insuficienca kardiake (IK), sasia e kontrastit të përdorur) dhe u vlerësua sinjifikanca e secilit prej tyre.

NIK u konsiderua rritja e vlerës së kreatininës pas 48/72 orësh në vlerë relative me ≥25% dhe/ose në vlerë absolute me ≥0.5 mg/dL krahasuar me vlerën e kreatininës se fundit para proçedurës.

Lezioni renal pre-ekzistent i përkufizuar si GFR (Glomerular Filtration Rate) <60/ml (Shkalla e filtrimit glomerular); gjithashtu pacientët me kreatinine para procedurës >1.5 mg/dL u konsideruan edhe ata me LRP, dhe u përdor si kriter për analizën statistikore referuar LRP, në tjetër mënyrë përkufizimi.

- Në përllogaritjen e GFR u përdor formula Cockcroft-Gault:

Femrat:

$$GFR\left\{\frac{ml}{min}\right\} = 0.85 \cdot \frac{(140 - mosha\{vite\} \cdot pesha\{kg\})}{72 \cdot KrS\{mg/dl\}}$$

Meshkuj:

$$GFR\left\{\frac{ml}{min}\right\} = \frac{(140 - mosha\{vite\} \cdot pesha\{kg\})}{72 \cdot KrS\{mg/dl\}}$$

- Pacient me anemi u konsideruan ata me vlera të hemoglobinës (Hb)<12 mg/dl
- Pacient me insuficiencë kardiake u morën në konsideratë vetëm ata me disfunksion sistolik, me EF<50%.
- Vlerë cutt-off për moshën si faktor risku për NIK u mor 65 vjeç.

Tek pothuajse të gjithë pacientët u përdor lënda e kontrastit Ultravist 370 (iopromide); një lëndë kontrasti jo-jonike, me osmolaritet të ulët.

Analiza statistikore

Incidenca u mat në përqindje ndaj totalit të rasteve dhe u përdor testi Hi katror për variablat kategorike të krahasimit midis grupeve dhe Testi i studentit -t test- për variablat e vazhdueshme. Vlera e p u konsiderua sinjifikante nëse <0.05. Për gjetjen e sinjifikancës së faktorëve të riskut u përdorën analiza e regresionit logjistik binar si edhe multivariabël.

REZULTATET

Numri total i pacientëve që u perfshinë në studim ishte 1231. U përjashtuan nga analiza 427 pacientëm të cilëve nuk ju gjet e vlerësuar KrS në 48/72 orë pas proçedurës me kontrast. Pra pacientë të studjuar që plotësonin kriteret për analizën tonë ishin 804 pacientë. Ndër pacientët e analizuar rezultuan 116 pacientë që kanë bërë NIK 48/72 orë, me një incidencë të NIK prej 14.4%. Përveç nëngrupit të pacientëve me DM, incidenca e NIK në nëgrupet e tjerë me faktorët klasikë të NIK është më e lartë se incidenca e përgjithëshme 14.4% (Tab.1).

Tab.1 Incidenca e NIK në nëngrupe pacientësh me faktorë risku

Faktorët e riskut për NIK	LRP, bazuar në GFR(195 pacientë)	Mosha >65 vjeç (298 pacientë)	Insuficiencë kardiake (91 pacientë)	Anemi (159 pacientë)	Diabet mellitus (236 pacientë)
Incidenca	18.9%	17.7%	18.6%	18.8%	13.1%

Kur faktorët e riskut të njohur, përfshirë këtu edhe sasinë e kontrastit, u analizuan sipas analizës së regresionit logjistik binar ose multivariat, rezultuan të jenë faktorë të pavarur për NIK: LRP (GFR<60 ml/min ose KrS> 1.5 mg/dl, para proçedurës me konstrast), mosha>65vjeç si edhe IK. Faktorët e tjerë si DM, sasia e kontrastit dhe anemia nuk rezultuan faktorë ta pavarur risku për NIK.

Lezioni renal pre-ekzistent (LRP)

Për LRP e përkufizuar si GFR<60 ml/min para proçedurës me kontrast, bazuar në analizën e regresionit logjistik binar, rezulton se ka një lidhje rastësore, statistikisht të rëndësishme mes NIK dhe LRP. Pacientët me LRP, kanë pothuaj 60% më shumë gjasa se ato pa LRP, për të bërë NIK [OD: 1.57; CI95%: 1.02-2.41] (*p=0.039*)(Tab.5) Nga pacientët me LRP, 18.9% prej tyre zhvilluan NIK, ndërsa nga pacientët pa LRP, zhvilluan NIK vetëm 12.9% prej tyre (79 nga 609 pacientë). LRP kishte sensitivitet 31.3% dhe vlerë prediktive pozitive të ulët 18.97%; specificitet të lartë dhe vlerë prediktive negative relativisht të lartë, 87.03%.

Gjithashtu LRP sipas kriterit të përkufizimit të KrS >1.5mg/dL (para procedurës me kontrast) rezultoi faktor risku i pavarur për NIK (Tab.5). Nga pacientët me LRP (Kr>1.5 mg/dl), 21.1%(15 nga 71 pacientë) zhvilluan NIK 48/72 orë, ndërsa nga pacientët pa LRP zhvilluan NIK vetëm 13.7% (101 nga 733pacientë) (*p<0.001*). Pacienët që kanë LRP, bazuar në këtë kriter, kanë 3.3 herë më tepër risk për të zhvilluar NIK në 48 orë. LRP kishte sensitivitet dhe vlerë prediktive pozitive të ulët përkatësisht 12.9% dhe 21.1%, por specificitet dhe vlerë prediktive negative të lartë, përkatësisht 91.1% dhe 86.2%.

Kur krahasohen midis tyre roli e GFR dhe vlera absolute e kreatininës para procedurës (>1.5 mg/dl), si elemente të përkufizimit të LRP, rezulton se LRP e përkufizuar si GFR <60ml/min ka sensitivitet dhe vlerë prediktive negative pak më të lartë; specificitet dhe vlerë prediktive pozitive më të ulur , krahasuar me LRP të përkufizuar në bazë të kreatininës.

Mosha

Gjithashtu duke u bazuar në analizën e regresionit logjistik binar, rezulton se ka një lidhje rastësore, statistikisht të rëndësishme mes NIK dhe moshës mbi 65 vjeç; pacientët me moshë mbi 65 vjeç, kanë pothuajse 52% më shumë gjasa se ata nën 65 vjeç, për të bërë NIK [OD: 1.52; CI95%: 1.02-2.26](*p=0.038*). (Tab. 5)

Insuficienca kardiake (IK)

Bazuar në analizën e regresionit logjistik binar, rezulton se nuk ka lidhje statistikisht të rëndësishme mes NIK dhe IK p=(0.22) (Tab. 5). Por në analizën multivariate të lidhjes së NIK-ut me faktorët e riskut u konstatua se i vetmi faktor risku që kishte lidhje me NIK ishte IK (p<0.001) (Tab.2).

Tab.2 Lidhja e NIK me faktorët e riskut, analiza multivariate

Variablat	Vlera p	OD	95% C.I.	
LRP+DM	.148	4.50	.585	34.679
IK	.000	4.63	2.136	10.049
Mosha >65vjeç	.112	1.80	.872	3.726
Sasia e kontrastit	.753	1.00	.997	1.004
Konstant	.004	4.24		

Diabeti mellitus (DM):

Bazuar në analizën e regresionit logjistik binar, rezulton se nuk ka lidhje statistikisht të rëndësishme mes NIK dhe DM(*p=0.502*)(Tab.5)

Kur u analizuan DM dhe LRP së bashku, u pa se si në grupin me këto dy faktorë risku, edhe në grupin pa këto faktorë risku, zhvilluan NIK përkatësisht 14.49% dhe 14.42%. Gjithashtu, bazuar në analizën e regresionit logjistik binar, rezultoi se edhe shoqërimi i DM me GFR<60ml/min, nuk përbënte faktor risku për NIK(*p=0.987*), një rezultat jo konkordant me rezultatet e studimeve të tjera në literaturë (Tab. 3) .

Tab.3 Lidhja midis DM + LRP dhe NIK

			NIK		Total
			jo	po	
DM+LRP (bazuar GFR)	po	Sasia,	59	10	69
		% me NIK		14.49%	
	jo	Sasia	629	106	735
		% me NIK		14.42%	
Total		Sasia,	688	116	804
		% me NIK	100.0%	100.0%	100.0%

Anemia

Bazuar në analizën e regresionit logjistik binar, rezulton se nuk ka lidhje statistikisht të rëndësishme mes NIK dhe pranisë së anemisë (e përkufizuar si Hb<12 mg/dL) (*p=0.079*)(Tab.5). Edhe kur Hb u mor si një variabël sasior i vazhdueshëm, bazuar ne këtë analizë, rezulton se nuk ka lidhje statistikisht të rëndësishme mes NIK dhe nivelit të Hb(*p=0.171*). (Tab. 5)

Sasia e kontrastit

Bazuar në analizën e regresionit logjistik binar, rezulton se nuk ka lidhje statistikisht të rëndësishme mes NIK dhe sasisë së kontrastit >100 ml (*p=0.479*)(Tab. 5).

Përmes Testit të Studenti (t test) shihet se sasitë mesatare të kontrastit si te pacientët me NIK dhe tek ata pa NIK janë pothuajse të barabarta (*p=0.262*). Pra është e vështirë të përcaktohen vlera *cutt off* për sasinë e kontrastit që të përbëjë faktor risku për NIK (Tab.4). Këtë e vërteton dhe kurba ROC (Fig 1).

Tab.4 Sasia e kontrastit dhe NIK

	NIK	Numri i pacientëve	Mesatare	SD (devijacioni standart	Vlera t	Vlera p
Sasia kontrastit	po	116	189.22	122.44	1.123	0.262
	jo	688	177.37	102.02		

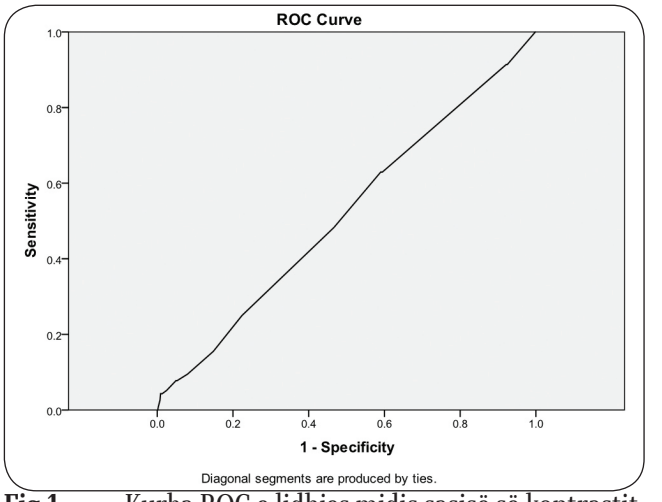

Fig.1. Kurba ROC e lidhjes midis sasisë së kontrastit dhe NIK.

Tab.5 Regresioni logjistik binar i faktorëve të riskut për NIK

	B	S.E.	WALD	df	Sig. (p)	Exp(B)	95% C.I. për Exp (B)	
							I poshtëm	I sipërm
Step 1 LRP_Bazuar_GFR Kostante	.452 -1.903	.219 .121	4.260 249.092	1 1	.039 .000	1.571 .149	1.023	2.413
Step1LRP bazuar KrS para procedurës) Kostante	3.510 .429	.363 .243	93.473 3.121	1 1	.000 .077	3.340 1.536	1.640	6.810
Step 1[a] Mosha_>65 vjeç Kostante	.419 -1.950	.203 .135	4.283 209.82	1 1	.038 .000	1.521 .142	1.022	2.263
Step 1[a] IK Kostante	.354 -1.825	.290 .108	1.491 283.910	1 1	.222 .000	1.425 .161	.807	2.515
Step 1[a] DM Kostante	-.152 -1.737	.226 .118	.451 218.173	1 1	.502 .000	.859 .176	.552	1.338
Step 1[a] DM+LRP bazuar në GFR Kostante	.006 -1.781	.358 .105	.000 287.638	1 1	.987 .000	1.006 .169	.499	2.028
Step 1[a] Anemia Kostante	-.410 1.868	.233 .116	3.078 260.015	1 1	.079 .000	.664 6.477	.420	1.049
Step 1[a] Hemoglobina Kostante	-.090 -.602	.066 .860	1.874 .490	1 1	.171 .484	.914 .548	.804	1.040
Step 1[a] Sasia e Kotrastit>100 ml Kostante	.147 -1.870	.207 .164	.501 130.288	1 1	.479 .000	1.158 .154	.771	1.739

DISKUTIM

Rezultatet e këtij studimi në lidhje me faktorët e riskut sinjifikantë për NIK pas koronarografisë ose PCI përputhen me studimet e tjera vetëm për disa nga faktorët e riskut të studjuar. Variabiliteti i përkufizimit të NIK midis studimeve mund të jetë një nga arsyet bazë të mospërputhjes së rezultateve. Në studimin tonë u përdor si kriter sasior për NIK rritja e kreatininës 48 orë pas proçedurës në vlerë relative ≥25% dhe/ose në vlerë absolute ≥0.5 mg/dL. Në studime të ndryshme përdoret vetëm njëri nga kriteret; në disa studime NIK llogaritet bazuar në vlerat e kreatininës ditën e 3-5-të pas proçedurës, që mund të ndikojnë në ndryshimin e incidencës së NIK si dhe të sinjifikancës së faktorëve të riskut të studjuar [2,3.

Mosha > 65 vjeç rezultoi se kishte lidhje statistikisht sinjifikante me NIK, ndoshta kjo e lidhur me faktin që më të moshuarit kanë veshka më fraxhile dhe më të ndjeshme ndaj lëndëve nefrotoksike si për shembull lënda e kontrastit [4].

Ekzistojnë të dhëna të limituara për të përcaktuar epidemiologjinë e NIK tek të moshuarit. Një meta-analizë e studimeve më të fundit (22 studime, me 186455 pacientë nga të cilët 67831 ishin të moshuar ≥65 vjec) tregoi se incidenca në total për NIK tek te moshuarit ishte 13.6%, (95% CI 10.1–18.2, I^2=0.496). Risku i zhvillimit të NIK tek të moshuarit rezultoi mbi 2 herë më i lartë sesa në pacientët e rinj, edhe pas azhustimit për faktorët e tjerë të riskut [5]; kurse në studimin tonë të moshuarit (>65 vjeç) kishin 52% mw shumw risk pwr NIK.

LRP sido që u përkufizua: GFR para proçedurës <60 ml/min ose KrS para proçedurës >1.5 mg/dl; rezultoi se kishte lidhje statistikisht sinjifikante me NIK. Gjithashtu nga analiza multivariate e faktorëve të riskut për NIK rezultoi se IK kishte lidhje statistikisht sinjifkante me NIK. Këto dy rezultat përputhen me pothuajse të gjitha studimet [7,8,9]. Kjo pasi pacientët me LRP kanë përgjigje vazodilatatore të reduktuar që është një faktor i rëndësishëm në zhvillimin e NIK. Në të njëjtën kohë, reduktimi i filtrimit glomeral te këta pacientë zgjat eliminimin e lëndës së kontrastit nga qarkullimi, duke theksuar në këtë mënyrë efektet e saj citotoksike dhe hemodinamike. Nga ana tjetër insuficienca kardiake karakterizohet nga ulja e debitit kardiak, rritja e aktivitetit neurohumoral vazokonstriktor dhe ulja e vazodilatacionit renal i varur nga NO, që mund të çojë në hypoperfuzion të medulës renale.

Shënojmë që në studimin tonë specificiteti i përdorimit të KrS para proçedurës ishte më i lartë se GFR për zbulimin e pacientëve që bëjnë NIK. LRP bazuar me rritje te nivelit te KrS para proçedurës eshte i njohur si një faktore risku vendimtar per zhvillimin e NIK, i konfirmuar edhe në këtë studim. Në studimin e Gruberg dhe Mehran [24], pavarësisht hidratimit preprocedurial dhe përdorimit të substancës së kontrastit jo-jonike, NIK shfaqet në 1/3 e pacientëve që ju nënshtruan PCI dhe kishin KrS ≥1.8 mg/dL.Sa më e lartë të jetë vlera e kreatininës bazale, aq më i madh është risku për NIK. Në një tjetër studim tregohet se nëse vlera e kreatininës bazale është 1.4-1.9 mg/dL, risku për NIK rritet 5 fish [25]. Edhe në studimin tonë pacientët që kishin KrS para proçedurës >1.5 mg/dl, kishin 3.3 herë më tepër risk për të zhvilluar NIK.

Megjithatë, kreatinina bazale nuk është mjaftueshëm për të identifikuar pacientët në rrezik për NIK. Kjo për arsye se KrS ndryshon me moshën, masën muskulare dhe gjininë. Prodhimi i KrS ulet me moshën: një vlere normale e KrS në pacientët e moshuar korelon në përgjithësi me një ulje të moderuar në funksionin renal. Për të vlerësuar me realisht funksion renal, duhet të realizohet vlerësimi i klirensit te kreatininës [26,27,28]. Edhe në studimin tonë sensitiviteti i GFR për zbulimin e NIK ishte më i lartë se ai i KrS: 31.9 vs12.9.

Fakti që nuk gjetwm një lidhje statistikisht sinjifikante midis sasisë së kontrastit >100 ml dhe NIK; as kur kotrasti merrej si variabwl i vazhdueshëm, nuk na lejon të përcaktojmë një vlerë *cut off* mbi të cilin rritet shumë rreziku për të zhvilluar NIK. Kjo lidhet ndoshta me sasinë jo të madhe të konstrastit të përdorur në pacientët e përfshirë në studim (189±122 ml). Duke qenë e njohur nga literatura që sasia e kontrastit përbën një faktor risku për NIK, mendojmë që mjekët interventionistë kanë synuar të reduktojnë sasinë e kontrastit të përdorur. Gjithashtu duhet përmendur edhe fakti që kontrasti i përdorur është në mënyrë absolute i llojit jo-jonik, me osmolaritet të ulët (Ultravist 370 (iopromide), që ka shkallë të ulët dëmtimi të funksionit renal. Megjithatë shumica e studimeve indikojnë se volumi më imadh i kontrastit ndikon në mënyrë të qartë negativ mbi funksionin renal sidomos në presencë edhe të faktorëve të tjerë të riskut. Edhe doza relativisht të vogla kontrasti (me pak se 100 ml), mund të të induktojnë insuficience renale permanente dhe nevojën për dializë në pacientët me sëmundje renale kronike [10,17,18,19]. Por rezultat të njëjtë me studimin tonë kanë patur edhe në studimin : Radiocontrast nephropathy: is it dose related ?[16],ku është përdorur Ultravist (Iopromide).

Edhe studime të tjera të rëndësishme tregojnë se DM nuk përbën faktor risku të pavarur për NIK. [11,12,13,14]. DM rezulton të jetë një faktor i pavarur për NIK atëherë kur shoqërohet me proteinuri, gjë që në studimin tonë nuk u arrit të përcaktohet; nuk u mat protenuria [11,13,14]. Është e vështirë të gjendet një shpjegim se pse shoqërimi i DM me LRP nuk çoi në incidencë më të madhe të NIK. Një nga arsyet mund të jetë se shumë pacientë me LRP të rëndësishme dhe probabilisht me DM, janë mënjanuar nga kryerja e koronarografisë, duke u konsideruar me risk të lartë për dializë, komplikim që pacienti e pranon me vështirësi. Dhe ngelet vetëm një përqindje jo e madhe pacientësh me LRP dhe me DM (69 pacientë) dhe që kanë bërë NIK -vetëm 10 prej tyre; jo sinjifikante për të ndikuar në rezultate.

Grupi i pacientëve me anemi pavarësisht incidencës së lartë të NIK (18.8 %) gjithsesi nuk rezultoi si faktor risku i pavarur për NIK , as kur u përkufizua si Hgb < 12 g/dL dhe as kur Hb u mor si variabël numëror i vazhdueshëm, rezultat i kundërt me disa studime të tjera [4,15,22,23]. Pacientët me anemi para procedurës janë mjekuar paraprakisht për aneminë (edhe transfuzion gjaku), duke patur vlera të pranueshme anemie. Kjo rezulton edhe nga të dhënat ku në grupin me NIK vlerat e Hb kanë qenë 12.97±1.7 kurse në atë pa anemi rezultojnë 13.18±1.49, duke mos pasur ndonjë diferencë sinjifikative. Kjo mund të jetë një nga arsyet se pse anemia nuk ka rezultuar faktor risku i pavarur për NIK , rezultat i njëjtë edhe me studime të tjera si: Risk factors for contrast induced nephropathy: A study among Italian patients [21].

KONKLUZIONE

Incidenca e NIK në popullatën e pacientëve që ju nënshtruan koronarografisë dhe/PCI në QSU "Nënë Tereza", është e ngashme me incidencën e shumicës së studimeve të tjera në literaturë. Faktorët e pavarur të riskut për NIK si LRP, IK, Mosha>65 vjeç, që u konfirmuan edhe në studimin tonë, duhen të kihen gjithmonë parasysh duke bërë të mundur identifikimin e popullatës me risk të lartë për NIK si edhe për marrjen masave paraprake për parandalimin e saj. Nevojiten punime të tjera , me numër më të madh pacientësh për të studjuar faktorët e tjerë të riskut jo të konfirmuar në studimin tonë si DM, Anemia, sasia e kontrastit. Pavarësisht se KrS para procedurës ka specificitet të lartë për zbulimin e pacientëve me risk për NIK, për të vlerësuar me realisht funksion renal, duhet të realizohet vlerësimi i klirensit te kreatininës (GFR).

Eshtë shumë e rëndësishme unifikimi i përkufizimit në NIK pasi kjo do të lehtësonte krahasimin e incidencës, të sinjifikancës së faktorëve të riskut, por sigurisht edhe të strategjive më të mira për parandalimin dhe trajtimin e NIK.

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RISC FACTORS FOR CONTRAST INDUCED NEPHROPATHY IN PATIENTS UNDERGOING CORONARY ANGIOGRAPHY OR PERCUTANEOUS CORONARY INTERVENTION- REZULTS OF THE STUDY FROM "MOTHER THERESA" UNIVERSITY HOSPITAL CENTER , TIRANA

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ABSTRACT

Objectives: This study sought to evaluate the risk of Contrast Induced Nephropathy (CIN) in patients undergoing coronary angiography or Percutaneous Coronary Intervention (PCI) in a tertiary hospital center, in Albania.

Methods: Among patients undergoing coronary angiography or PCI at Cardiac Catheterization Center in "Mother Theresa" UHC, Tirana, were studied for risk factors for CIN 1231 patients, from 2010 through 2014. CIN was defined as the increase in serum creatinine levels, more than 0.5 mg/dl or 25% of baseline levels, within 48-72 h after exposure to a contrast agent compared to baseline serum creatinine values. Incidence of CIN was calculated as a percentage of total. The Binary logistic and Multivariate logistic regression was used to evaluated risk factors of CIN: Pre-existent renal lesion, diabetes mellitus, age>65 years, anemia, heart failure, contrast volume. A p-value of less than 0.05 was considered statistically significant.

Results: The study population was 804 patients (427 patients were excluded; they didn't met inclusion criterias). The overall CIN incidence it was 14.4%. The risk factors associated with development of CIN included: Pre-existent renal lesion, [OD: 1.57; CI95%: 1.02-2.41] (*p=0.039*), age>65 years [OD: 1.52; CI95%: 1.02-2.26](*p=0.038*), heart failure(*p<0.001*). The other factors as Diabetes Mellitus, Anemia, Contrast volume didn't resulted as independent risk factor for CIN.

Conclusions: Approximately 14.4% of patients undergoing coronary angiography or PCI experience CIN, which is the most incidence of CIN described in other studies. Even the incidence of CIN in the presence of conventionally risk factors is higher, the independent risk factors of CIN resulted: pre-existent renal lesion, age>65 years, heart failure.

Key words: risk factors, CIN, incidence, contrast, coronary angiography, PCI.

Original scientific paper

NDIKIMI I INFEKSIONEVE BAKTERIALE DHE PARAZITARE NË RUPTURAT MEMBRANORE FETALE

THE IMPACT OF BACTERIAL AND PARASITIC INFECTIONS IN FOETAL MEMBRANE RUPTURE

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ABSTRAKT

Hyrje: Infeksionetgenitale me natyrës bakterialdhe/ose parazitare në shtatzani përbëjnë problem madhor të shëndetit publik në shkallë globale. Në rreth 80% të rasteve infeksioni nga chlamydia trachomatisështë jo-simptomatik dhe shkakton shtatzëni ektopike dhe lindje premature.

Qëllimi ikëtij studimi është vlerësimi i ndikimit të vaginozave bakteriale në lindjen e parakohëshme dhe vlerësimi i riskut për të zhviluar ruptur të membranave në femrat me dhe pa Klamidiazë.

Metodologjia: Studimi i tipit kroseksional i kryer në perjudhën Janar - Gusht2015 në spitalin e pergjithshem ne sherbimin obstetrik - gjinekologjik të Stugës. Në studim u përfshijnë 55 femra me moshë gravidance mbi 23-26 javë dhe që vuanin nga vaginoza bakteriale. Instrumenti i përdorur për grumbullimin e të dhënave ishte pyetësori i cili përmbantetë dhënave socio-demografike, anamneza medikale dhe atë ostetrikale. Pacientet u ndoqën deri në përfundimin e lindjes. Lindje parakohe u quajt lindja para 37 javëve dhe pesha e bebit me pak se 2500 gr.Analiza statistikore e të dhënave është kryer nëpërmjet paketës statistikore SPSS vrs.17 dhe sinjifikanca statistikore u konsiderua e rëndësishme për P<0.05

Rezultate: Mosha mesatare e subjekteve në studim ishte 30,22vjeç ±6,491 vjet.Chlamydia trachomatis u diagnostikua në 43,6 % të rasteve, Trichomonas vaginalisnë 23,6 % dhe Gardnerella vaginalisnë 18,2%. 4,6% e femrave me Klamidiazë zhvilluan ruptura të membranës (RR= 2,6 ; CI95%= 1,6-3,4)

Përfundime: Femrat me vaginoza bakteriale kryesisht me Chlamydia trachomatis pozitive kanë risk me të lartë për të patur lindje premature krahasuar me femrat pa klamidiazë.

Fjalë kyçe: rupturë, vaginozë bakteriale

HYRJE:

Infeksionet në shtatzëni me natyrë bakteriale dhe/ose parazitare përbëjnë problem madhor të shëndetit publik në shkallë globale [1].

Literatura të cilës i jemi referuar tregojnë se infeksioni klamidial zë propocionin më të madh midis bakteriozave vaginale. Në rreth 80% të rasteve infeksioni nga chlamydia trachomatis është jo-simptomatik, shkakton shtatzëni ektopike dhe është i lidhur ngushtë me shkolitjen e parakohëshme të mebrananës fetale si dhe lindjen e parakohëshme. Nga të njëjtat studime rezulton se risku i lindjes premature në rastet me vaginozave bakteriale është 2 deti në 11 herë më i lartë krahasuar me rastet pa vaginozë (CI 95%, [1.8- 29.4]) [2].

Sipas një studimi eksperimental, mikroorganizmat e vaginozës bakteriale prodhojnë faktorë duke përfshirë edhe proteazat (IgAse, kolagjenazës, etj) që mund të lehtësojnë transportin e baktereve të membranave fetale dhe dëmtojnë integritetin e cipës së fetusit. [2].

Në Spitalin e pergjithshem ne sherbimin Obstetrik Gjinekologjik të Strugës incidenca e lindjeve premature

ka pësuar ulje dhe vlerësohet për vitin 2014 të jetë 6,3%. Përkundrazi incidenca e vaginozave bakteriale për të njëjtin vit ka pësuar rritje.

Qëllimi i këtij studimi është vlerësimi i ndikimit të vaginozave bakteriale, kryesisht chlamydia trachomatis, në shkolitjen e parakohëshme të mebrananës fetale si dhe lindjen e parakohëshme dhe vlerësimi i riskut për të zhvilluar rupturë të membranave fetale në femrat me dhe pa Klamidiazë.

METODOLOGJIA

Studimi i tipit kroseksional i kryer në perjudhën Janar - Gusht 2015 në Spitalin e pergjithshem ne sherbimin Obstetrik Gjinekologjik të Stugës. Instrumenti i përdorur për grumbullimin e të dhënave ishte pyetësori i cili përmbante të dhënave socio-demografike, anamneza medikale dhe atë ostetrikale. Pacientet u ndoqën deri në përfundimin e shtatzënisë. Lindje parakohe u quajt lindja para 37 javëve dhe pesha e bebit me pak se 2500 gr [4, 5]. Llogaritja e moshës së gravidancës u bazua në ditën e parë të menstruacioneve të fundit duke u konfirmuar edhe me ekografinë e parë.

Vlerësimi i ankesave nga ana klinike është bërë në bazë të shtimit të sekrecioneve vaginale në një shkallë të lehtë ose të moderuar, sekrecione këto me erë të rëndë. Gjithashtu kjo ngjarje shëndetësore shoqërohet edhe me irritimi vulvar, disuri dhe dispareuni [3, 4, 5, 6, 7, 8].

Analiza statistikore e të dhënave është kryer nëpërmjet paketës statistikore SPSS vrs.17 dhe sinjifikanca statistikore u konsiderua e rëndësishme për P <0.05

REZULTATE

Në studim u përfshijnë 55 femra me moshë gravidance mbi 23-26 javë dhe që vuanin nga vaginoza bakteriale.

Tabela 1. Shpërndarja sipas grup - moshës së pacienteve

Variabli	Frekuenca	Përqindja
21 deri në 25 vjeç	15	27.3 %
26 deri në 30 vjeç	15	27.3 %
31 deri në 35 vjeç	15	27.3 %
36 deri në 40 vjeç	4	7,1 %
Mbi 40 vjeç	5	9.0 %
Mosha Mesatare	30,22 vjeç ± 6,491 vjet	

Për të lehtësuar kryerien e analizës statistikore, subjektet i kemi grupuar sipas moshës. Kemi një shpërndarjen thuajse të barabartë midis grup moshave 21 deri në 25 vjeç, 26 deri në 30 vjeç dhe 31 deri në 35 vjeç. Gjithashtu i njëjti fenomen haset dhe për grupmoshat mbi 35 vjeç. Mosha mesatare e subjekteve në studim ishte 30,22 vjeç ± 6,491 vjet.

Tabela 2. Shpërndarja sipas vendit të banimit dhe etnisë

Variabli	Frekuenca	Përqindja	Variabli	Frekuenca	Përqindja
Qytet	24	43,6	Shqipëtare	31	56,4
Fshat	31	56,4	Maqedonase	24	43,6
Total	55	100,0	Total	55	100,0

Afërsisht 56% e femrave i përkisnin etnisë shqiptare dhe 43, 6% i përkisnin etnisë maqedonase.

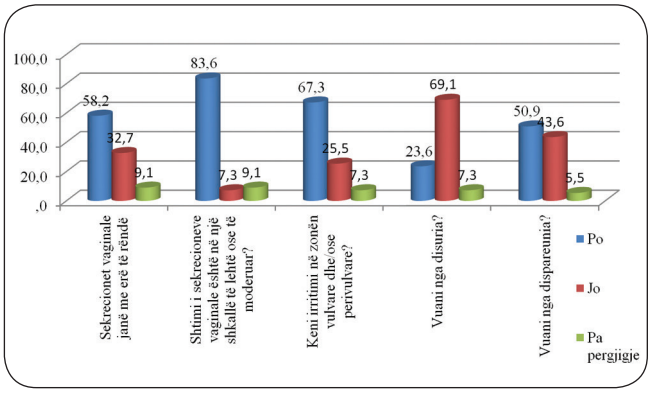
Më shumë se 54 % e subjekteve të hospitalizuar e të përfshira në studimin tonë raportuan të jetojnë në qytet ndërsa 43 % në fshat dhe propocioni më i madh këtyre grave shtatzëna janë me arsim të mesëm (54,5 %). Një përqindje relativisht e vogël (1,8%) janë me arsim universitar.

Përdorimi i antibiotikeve mund të eleminojë bakteriozën vaginale ose të modifikojë efektin e tij në rezultatin e gravidancës. Rezultatet e të dhënave janë mbledhur tek grate të cilat nuk kanë përdorur antibiotike gjatë periudhës së studimit deri në 37 javë [4, 5].

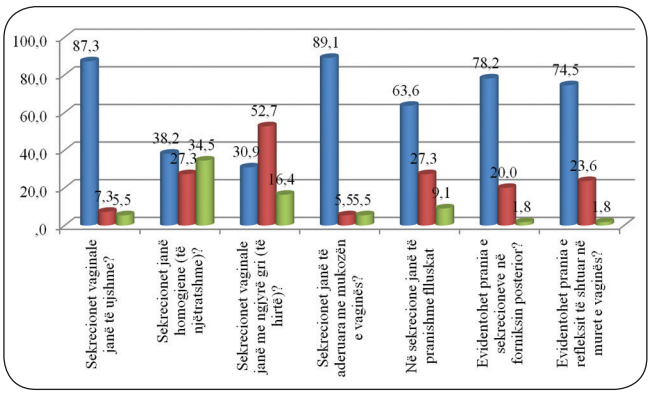
Tabela 3. Shpërndarja sipas diagnozës përfundimtare

Diagnoza	Frekuenca	Përqindja
Klamidia	24	43,6
Trikomonas	13	23,6
Gardnerella	10	18,2
Te tjera	8	14,5
Total	55	100,0

Chlamydia trachomatis u diagnostikua në 43,6 % të rasteve, Trichomonas vaginalis në 23,6 % dhe Gardnerella vaginalis në 18,2%.



Grafiku 1. Shpërndajra sipas shenjat klinike prezente në pacientet me bakterioza vaginale



Grafiku 2. Shpërndajra sipas shenjat klinike prezente në pacientet me bakterioza vaginale. Sekrecionet vaginale

Mosha e gruas nuk përbën faktor risku për të zhvilluar Klamidiazë ndërsa vendi i banimit sipas studimit ka gjasa të ndikoj në vaginozat bakteriale (RR 1,4).

Afërsisht 5 % e femrave me Klamidiazë zhvilluan ruptura të membranës (RR 2,6 dhe CI95% [1,6-3,4]).

DISKUTIMI

Ne gjetëm një lidhje të rëndësishme midis kolonizimit bakterial të traktit gjenital në gravidancë dhe rupturave të membranës fetale. Ne theksojmë se efekti i florës jo normale vaginale është një parashikues i mirë i lindjes parakohe.

Infeksionet genitale me natyrë bakteriale janë një faktor risku i rëndësishëm për të shkaktuar shkolitje të membranës fetale e si pasojë edhe lindje prematur.

Gjithashtu infeksionet bakteriale në gravidancë janë një faktor risku i pavarur nga faktorët e tjerë që kemi marrë ne siç është p.sh. mosha, edukimi dhe/ose punësimi për rupturën fetale membranore. Por, duke krahasuar këto gjetje me rezultatet e publikuara në literaturë boterore, duhet të theksohet se ka patur raste ku infeksionet bakteriale kanë qenë të lidhur me statusin socio-ekonomik dhe vendin e banimit. Disa arsye që nuk kemi parë të njëjtën tendencë në rezultatet tona për lidhjen e infeksionet genitale me natyrë bakteriale me statusin socio-ekonomik përmbledhin: 1) numrin e kufizuar të pacienteve të përdoruara në këtë studim; 2) zonat e botes ku u gjet një lidhje e tillë, e cila mund të mos ketë qenë shkak direkt ekonomik, por pasoj e bias-it të pjesëmarrës; dhe 3) lloji i të dhënave të përmbledhura nga studime të ndryshme dhe mënyrat e përkufizimit të statuseve.

Në këtë studim femrat me Chlamydia trachomatis kishin risk 2,6 here më të lartë për lindje prematur krahasuar me femrat pa Klamidiazë.

Studimet rast-control dhe studimet kohort rreth temës tonë në USA, Angli, dhe Indonezi e përforconë më shumë besueshmërinë e gjetjeve tona duke përmbushur edhe kriterin e konsistencës.

Risku i lindjes premature ndërmjet grave me bakteriozë vaginale i shkaktuar nga Chlamydia trachomatis është gjetur të jetë 2,6 në studimin tonë, varion nga 2.0 deri ne 11 në studimet e tjera.

Këto gjetje janë të rëndësishem edhe sepse do të shërbejnë në të ardhmen si bazë për kryerjen e hulumtimeve më të detajuar rreth kësaj ngjarje shëndetësore.

Gjithashtu ne mund të japim një përgjigje për shëndetin publik në lidhje me parandalimin e abortit spontan dhe në përfundimin jo te mirë të shtatzënisë në lidhje me floren vaginale.

PËRFUNDIME

1. Ky studim ka prezantuar të dhëna signifikante për një lidhje të fortë midis vaginozave bakteriale dhe rupturës membranore fetale.
2. Në shtatzëni, vaginozat bakteriale janë faktor të fuqishëm rreziku për të patur lindje të parakohëshme.
3. Femrat me Chlamydia trachomatis pozitive kanë risk me të lartë për të patur lindje premature krahasuar me femrat pa klamidiazë.

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THE IMPACT OF BACTERIAL AND PARASITIC INFECTIONS IN FOETAL MEMBRANE RUPTURE

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ABSTRACT

Background: Bacterial infections and/or parasitic infections in pregnancy represent a major public health problem on a major scale. In 80% of cases Chlamydia trachomatis infection is non-symptomatic, causes ectopic pregnancies and is highly connected with premature rupture of foetal membrane and premature birth.

The purpose of this study is to evaluate the impact of bacterial vaginosis, mainly Chlamydia trachomatis, in premature rupture of foetal membrane and premature birth and risk evaluation on rupture development of foetal membranes in women with or without Chlamydia.

Methodology: The cross-sectional study conducted in the period January - August 2015 in the obstetric - gynaecologic hospital of Struga. The study involved 55 pregnant women over 23-26 weeks and suffering from bacterial vaginosis. The patients were followed during the whole pregnancy and birth. Preterm birth was called birth before 37 weeks and the baby weight less than 2500gr. Statistical analysis of data is performed through statistical package SPSS vrs.17

Results: The average age of subjects in the study was 30.22 ± 6,491 years old. Chlamydia trachomatis was diagnosed in 43.6% of cases, Trichomatis vaginalis in 23.6% and Gardnerella vaginalis in 18.2%. 4.6% of women with Chlamydia developed membrane rupture (RR=2.6; CI 95% .

Women's age is not a risk factor for developing Chlamydia, while the place of residence according to the study is likely to affect in bacterial vaginosis .

Approximately 5% of women with Chlamydia developed membrane rupture (RR 2.6 and CI 95%).

Conclusions: Women with bacterial vaginosis mainly with positive Chlamydia trachomatis have a higher risk of having premature birth, compared to women without Chlamydia.

Key words: membrane rupture, bacterial vaginosis.

Original scientific paper

ПРОМЕНИ ВО ХЕМОДИНАМСКИТЕ СОСТОЈБИ КАЈ РОДИЛКИТЕ ВО ОПШТА И СПИНАЛНА АНЕСТЕЗИЈА ВО ТЕК НА ЦАРСКИ РЕЗ

MATERNAL HEMODYNAMIC CHANGES IN GENERAL AND SPINAL ANESTESION DURING CESAREAN SECTION

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АБСТРАКТ:

Резиме: Бројот на царски резови е значително зголемен и затоа го испитуваме влијанието на видот на анестезијата врз хемодинамските параметри на родилките.

Цел: Да се споредат ефектите на спиналната со општата анестезија преку хемодинамско следење на родилките и да се утврдат можните компликации.

Материјал и методи: Испитани се 120 родилки кои се поделени во две групи.Група 1 се состоеше од 60 родилки во ОА. За премедикација: амп.метоклопрамид од 10mg. За вовед :пропофол (2,0-2,5 мг/кг/тт) .За олеснување на интубација сукцинил холин (1-1,5 мг/кг/тт), или рокуроиум бромид (Есмерон) (0,4 - 0,6 мг/кг/тт).По екстракција на плодот, дававме анелгетик Фентанил (0,005 мг/кг/тт) и деполаризантен релаксант. Односот на гасовите O_2 и N_2O беше 3:3 Л/мин.Група 2се состоеше од 60 родилки во СА. Лумбалната пункција беше изведувана помеѓу $Л_2$ и $Л_3$ или $Л_3$ и $Л_4$, со игла 26 или 27 G. Беше аплициран Бупивакаин 0.5% (2-3мл). Родилките беа хидранисо 500-1000мл NaCl0.9% или Рингеров раствор. Беше следен волуменот на дадени раствори,вкупно и по видови од почетокот до крајот на интервенцијата. Кај двете групи беа следени: АП ,пулсот, бројот на респирации во минута и сатурацијата на периферната крв со кислород (SpO_2).

Резултати: Групата со СА покажа поголем пад на АП во однос на групата со ОА.Количината на ординирани раствори во групата со ОА изнесуваше 1000-1500 мл, додека во групатасо СА беше во распон од 2000-2500 мл. Немаше сигнификантни разлики во срцевата фрекфенција и бројот на респирации, како и во SpO_2.

Заклучок: Компарирано со општата анестезија, спиналната анестезија има приоритет.

Клучни зборови: Царски рез. Анестезија, општа, спинална, хемодинамскипромени

ВОВЕД

Царскиот рез претставува породување на детето по пат на оперативна интервенција со инцизија на стомачниот ѕид и ѕидот на матката. Водењето на анестезија при царски рез е специфично. Тоа се должи на посебната улога која ја има анестезиологот: да се грижи истовремено за животот и на мајката и на детето. Ургентноста на царскиот рез го ограничува изборот на видот на анестезија. Се користат две анестезиолошки техники, општа и регионапна анестезија.

Предностите на спиналната анестезија, како и на останатите централни невроаксијални блокови, се состојат во фактот што пациентката е свесна во текот на интервенцијата, лесно се следат виталните функции и може да се воспостави контактот меѓу мајката и бебето веднаш по породувањето.

Во текот на последните две децении, праксата за анестезија при царски рез во светот драстично е променета. Во Германија, во мултицентрична студија од 1994-1995 година Hamza J. и сор. [1] утврдиле дека општата анестезија била дадена во 66.5% случаи за елективен царски рез а во 90.8% случаи за неелективен царски рез. Спиналната анестезија била применета само кај 9.8% од родилките. Наспроти тоа, во 2007 година Held F. и сор. [2] врз основа на пополнети прашалници за типот на анестезијата при царски рез, утврдиле дека дури 90% од родилките се анестезирани со спинална анестезија, а само 10% со општа анестезија. И во другите европски земји е присутен истиот тренд на пораст на спиналните анестезии [3,4,5]. Заради тоа во 2003 Кралскиот колеџ на Анестезиолози од Велика Британија ги постави стандардите за типот на анестезијата при царскиот рез. Според овие стандарди 85% од царските резови во една институција треба да бидат водени во регионални анестезии [6].

ЦЕЛ НА ТРУДОТ

Да се споредат ефектите на спиналната и на општата анестезија врз хемодинамиката кај родилките во текот на царскиот рез.

МАТЕРИЈАЛ И МЕТОДИ

Истражувањето претставува проспективна, компаративна студија која се изведе во Службата за Анестезија, реанимација и интезивно лекување при Клиничката болница - Битола. Испитани се 120 родилки кај кои гинекологот индицирал царски рез, а кои се поделени во 2 групи од по 60 родилки.Пациентките се одбирани рандомизирано, според редоследот на доаѓањеза интервенција.Инклузиони критериуми во студијата беа: родилки од 18 до 35 годишна возраст, здрави, без органски заболувања (ASA I), и со уредно контролирана бременост. Ексклузиони критериуми во студијата беа: родилки кои не се во оваа возрасна група, родилки со кардиоваскуларни или други заболувања, родилки со неконтролирана бременост,како и родилки кај кои на ехо гинеколошки преглед е видено дека се работи за аномалии на плодот.

Првата група се состоеше од 60 родилки кои беа водени во општа анестезија. Родилките во премедикација добијаметоклопрамид од 10мг. За вовод се користеа пропофол (2,0-2,5 мг/кг/гт/), а за олеснување на интубацијата сукцинил холин (1-1,5 мг/кг/тт), или рокурониум бромид (Esmeron) (0.6 мг/кг/тт). Во текот на анестезијата родилките добиваа аналгетик (Фентанил, 0.005мг/кг/тт) после вадење на бебето и деполаризантен релаксант рокурониум бромид (Esmeron,0.4-0.6 мг/кг/тт). Односот на гасовите O_a и N_20 беше 3 : 3 Л/мин.до екстракцијата на плодот а потоа 2 : 1. На крајот на интервенцијата родилките беа декураризиранисо Атропин и Простигмин.

Втората група се состоеше од 60 родилки кои беа водени во спинална анестезија. Лумбалната пункција се изведе во средната линија на р'бетниот столб во висина на интервертебрапниот простор помеѓу $Л_2$ и $Л_3$ или $Л_3$ и $Л_4$,со игла 26 или 27 G, Пациентките беа поставувани во лева странична или седната положба со испакната кичма со цел да се отворат интервертебралните простори. Аплицирани беа 2-3 мл Бупивакаин 0,5% во зависност од височината на пациентката и посакуваната височина на блокот. Сензорната блокада се проверуваше со проверка на чувството за топло-ладно (со тупфер со алкохол) а степенот на моторната блокада по Bromage скалата. За успешен блок се сметаше ако се добиеше II или III степен по Bromage, (пациентката воопшто не може да ги движи долните екстремитети или прави само движења на стопалото). Оксигенацијабеше ординирана преку транспарентна лицева маска во текот на интервенцијата. Родилките беа хидрирани пред почетокот на царскиот рез со 500-1000 мл NaC1 0,9% или Рингеров раствор. Кај родилките во обете групи во текот на истражувањето беа следени следните параметри за функцијата на кардиоциркулаторниот систем на родилките :артериски притисок (АП), систолен и дијастолен, фрекфенција на пулсот (број на удари/мин), број на респирации во минута, пулс оксиметрија.

За статистичка анализа на добиените резултати направена е база на податоци во програмот Statistica for Windows 7, 0 и SPSS 13.0.

РЕЗУЛТАТИ

Пациентките од двете испитувани групи не покажаа статистички значајни разлики во однос на возраста и антропометриските параметри. Во нашето истражување покажаа дека видот на анестезија кај елективен царски рез, спинална или општа, нема значајно влијание на вредноста на пулсот. Овој заклучок се базира на тестираната разлика во просечната

вредност на срцевата фреквенција меѓу родилките од двете групи, која што разлика статистичката анализа ја потврди како несигнификантна (p=0,67). Просечната вредност на пулсот во групата родилки водени во спинална анестезија изнесува 97,58±10,5 удари во минута, и е незначајно пониска од просечниот пулс регистриран во групата родилки водени во општа анестезија, а чија што просечна вредност изнесува 98,48±12,42 удари во минута. Беа презентирани минималните и максимални вредности на срцевата фреквенција во двете групи испитанички. Така, се забележува дека 73 удари во минута е најнизок пулс, регистриран во групата родилки водени во спинална анестезија, додека максимална вредност на пулсот од 132 удари во минута е нотиран во групата родилки водени во општа анестезија.

Табела 1. Вредности насрцевата фреквенција (удари во минута) кај испитуваните пациентки

Тип на анестезија	N	Дескриптивна статистика – Пулс			
		mean±SD	Clformeans	Min - Max	Std. error
Спинална	60	97,58 ± 10,41	94,89 – 100,27	73 - 120	10,41
Општа	60	98,48 ± 12,42	95,27 – 101,69	75 - 132	12,42

t-тест= 0,43 p=0,67

Бројот на респирации се движи во интервал од 12 до 14. Просечниот број на респирации во групата родилки водени во спинална анестезија изнесува 12,77±0,93, а во групата родилки водени во општа анестезија изнесува 12,63±0,88. Тестираната разлика во просечниот број на респирации е несигнификантна (p=0,42). Можеме да заклучиме дека бројот на респирации на родилките кои се породуваат со елективен царски рез не зависи значајно од типот на анестезија која им е дадена во текот на породувањето.

Табела 2. Број нареспирации во групите водени во општа и спинална анестезија

Тип на анестезија	N	Дескриптивна статистика – Респирации			
		mean±SD	Cl for means	Min - Max	Std. error
Спинална	60	12,77 ± 0,93	12,53 – 13,01	12 - 14	0,12
Општа	60	12,63 ± 0,88	12,40 – 12,86	12 - 14	0,11

t – test = 0,8 p=0,42 p>0,05

Во групата родилки водени во спинална анестезија, просечната периферна капиларна сатурација со кислород се движи од 90 до 100%, додека во групата водени во општа анестезија минималната сатурација со кислород изнесува 98%, максималната е 100%. Можеме да заклучиме дека сатурацијата на периферната капиларна мрежа со кислород во тек на елективен царски рез не зависи сигнификантно од типот на анестезија.

Табела 3. Периферна капиларна сатурација со кислород

Тип на анестезија	N	Дескриптивна статистика – SpO_2			
		mean±SD	Cl for means	Min - Max	Std. error
Спинална	60	99,23 ± 1,60	98,82 – 99,65	90 -100	0,21
Општа	60	99,22 ± 0,58	99,06 – 99,37	98 - 100	0,07

t – test = 0,07 p=0,94 p>0,05

Во однос на артериският притисок беа презентирани резултатите кои се однесуваат на вредностите на почетниот систолен артериски притисок, почетниот дијастолен артериски притисок, максималниот пад на артериски систолен притисок, како и на интервенцијата при пад на артериският притисок кај родилките во тек на елелктивен царски рез. Родилките породени со елективен царски рез, а водени во спинална или општа анестезија, не се разликуваат значајно во однос на просечниот почетен систолен притисок (p=0,67). Во групата испитанички со спинална анестезија, просечниот почетен систолен притисок изнесува 125,72±15,66 mmHg, наспроти просечната вредност од 126,9±15,03 mmHg во групата испитанички со општа анестезија. Разликата од 1,18 mmHg меѓу двете групи е недоволна за да се потврди статистички како сигнификантна.

Табела 4. Вредности на почетниот АП (систолен) кај испитуваните групи

Тип на анестезија	N	Дескриптивна статистика – Почетна АП систолен			
		mean±SD	Cl for means	Min–Max	Std. error
Спинална	60	125,72 ± 15,66	121,76 – 129,76	98 – 170	2,02
Општа	60	126,90 ± 15,03	123,02 – 130,78	105–180	1,94

t – test = 0,42 p=0,67 p>0,05

Во тек на операцијата беше регистриран пад на систолниот притисок во двете групи. Во групата родилки водени во општа анестезија, беше помал во однос на групата водена во спинална анестезија. Истото се однесува и за дијастолниот притисок.

Просечните вредности на систолниот и дијастолниот притисок како и распонот на измерените вредности во двете групи се прикажани на табела 4 и табела 5.

Табела 5. Вредности на почетниот АП (дијастолен) кај испитуваните групи

Тип на анестезија	N	Дескриптивна статистика – Почетен АП дијастолен			
		mean±SD	Cl for means	Min - Max	Std. error
Спинална	60	81,22 ± 9,48	78,77 – 83,67	65 - 108	1,22
Општа	60	84,27 ± 7,99	82,20 – 86,33	67 - 105	1,03

t – test = 3,91p=0,0006** p<0,01

Беше регистриран просечен максимален пад на ситолниот притисок на 105,8±13,95 mmHg во групата родилки водени во општа анестезија, и на 110,38±10,46 mmHg во групата родилки водени во општа анестезија. Разликата во максималниот пад на АП систолен од 4,58 mmHg статистички се потврди како сигнификантна за ниво на p=0,04. Заклучок е дека давањето на спинална анестезија во тек на елективен царски рез е асоцирана со значајно поголем просечен пад на систолниот притисок во споредба со давањето на општа анестезија.

Табела 6. Максимален пад на АП (систолен) кај испитуваните групи

Тип на анестезија	N	Дескриптивна статистика – Максимален пад на АП систолен			
		mean±SD	Clformeans	Min - Max	Std. error
Спинална	60	105,80 ± 13,95	102,19 – 109,40	68 - 140	1,80
Општа	60	110,38 ± 10,46	107,68 – 113,08	90 - 134	1,35

t – test = 2,03p=0,044* p<0,05

Родилките кои се породиле со царски рез во општа анаестезија имаат значајно помал просечен максимален пад на дијастолниот притисок во споредба со родилките од групата со спинална анестезија (p=0,003). Просечниот максимален пад на дијастолниот притисок изнесува 72,75±10,68 mmHg во групата родилки водени во спинална анестезија, и 77,78±7,43 mmHg во групата родилки водени во општа анестезија.

Максимален пад на дијастолниот притисок е регистриран во групата родилки водени во спинална анестезија од 40 mmHg. Просечниот максимален пад на дијастолниот притисок е идентичен во двете групи родилки, и изнесува 99mmHg.

Табела 7. Максималниот пад на артерискиот притисок (дијастолен) кај испитуваните групи

Тип на анестезија	N	Дескриптивна статистика – Максимален пад на АП дијастолен			
		mean±SD	Clformeans	Min - Max	Std. error
Спинална	60	72,75 ± 10,68	69,99 – 75,51	40 - 99	1,38
Општа	60	77,78 ± 7,43	75,86 – 79,70	55 - 99	0,96

t – test = 3,0p=0,003** p<0,01

Во нашето испитување во случаите кај кои имаше пад на артерискиот крвен притисок е интервенирано е кај 9(15%) родилки по давање на спинална анестезија, и кај 2(3,34%) родилки по давање на општа анестезија. Оваа разлика се потврди како сигнификантна за ниво на p<0,05.(таб 8).

Табела 8. Приказ на честотата на интервенции при пад на АП кај испитуваните групи

Интервенција при пад на АП	Спинална анестезиолошка техника		Општа анестезиолошка техника	
	N	%	N	%
Не	51	85	58	96.66
Да	9	15	2	3.34
Вкупно	60	100	60	100

Chi square = 4,91 df=1 p=0,027* p<0,05

Интервенциите во случај на пад на крвниот притисок се состојат од примена на вазоконстор Ефедрин и давање на плазмаекспандер Гелофундин.Нашите резултати се на табела 9. Оттука, може да се заклучи дека кај пациентките кај кои е направен царски рез со спинална анестезија се јавила поголема потреба за интервенција.

Табела 9. Интервенции и терапија при пад на АП

Интервенција и терапија при пад на АП	Спинална анестезиолошка техника		Општа анестезиолошка техника	
	N	%	N	%
Нема	51	85,00	58	96,67
Ефедрин 5+5	2	3,33	1	1,67
Гелофундин	1	1,67	1	1,67
Ефедрин 5+ Гелофундин	5	8,33	/	/
Ефедрин 10	1	1,67	/	/
Вкупно	60	100	60	100

ДИСКУСИЈА

Од приложените резултати може да се види дека не постојат разлики во почетниот систолен и дијастолен притисок меѓу пациентките од обете групи.

Во текот на анестезијата и операцијата кај обете групи на пациентки настана пад на крвниот притисок во однос на почетните вредности кој е статистички значаен ($p<0,05$). Но, статистички значајна разлика постои и помеѓу групите. Падот на АП (систолен/дијастолен) значајно се разликува помеѓу групите, односно тој е значајно поголем во групата на родилки водени во спинална анестезија. Овие резултати се во корелација со најголемиот број на трудови од литературата во кои е истражуван овој проблем [7,8,9]. Maayan-Matzger A. и сор. потенцираат дека повеќе од половина од родилките кои примаат спинална анестезија имаат намалување на притисокот за повеќе од 30% од почетната вреднотс, додека Shearer и сор. констатирале дека кај 70% од родилките се развила хипотензија по спиналната пункција [10].

Кај општите анестезии се очекува исто така извесно намалување на АП во однос на АП измерен пред почетокот на анестезијата, како резултат на возбуда пред интервенција и хипотензивните ефекти на анестетикот (пропофол, рокурониум) ефекти на поголемиот број анестетички средства кои се употребуваат во воведот на анестезијата (пропофол, рокурониум, хипервентилација

Додека пак кај групата пациенти водени во спинална анестезија и покрај очекуваниот пораст на хемодинамските параметри (АП и пулс) има пад поради специфичното дејствување на анестетикот врз симпатикусот. Тој резултира со пад на АП (систолен и дијастолен).Причина за ова е отсуството на парасимпатички нервни влакна во торакоабдоминалниот дел на medulla spinalis.

Интензитетот на падот на АП најмногу зависи од висината на блокот. Физиолошката корекција на хипотензијата се врши со вазоконстрикција на незафатените делови од човечкото тело и разбирливо е дека високите блокови ќе го намалат овој физиолошки одговор. Заради тоа непотребно високиот блок ќе доведе до симпатоплегија на поголемиот дел од телото која консекутивно ќе доведе и до поголем пад на крвниот притисок.Намалувањето на АП (систолен/дијастолен) и на пулсот во нашето испитување не беше толку драстичен колку што би се очекувало. Дури ни екстремните вредности (68/40 ммХг) кај пациентката со најголем пад на АП сеуште не се во ранг на животозагрозувачка состојба. Ова зборува дека дозирањето на анестетиците, позиционирањето на пациентките за време и по лумбалната пункција, а пред се навременото реагирање на хипотензијата правилно сме ја изведувале, не дозволувајќи пациентките да се најдат во критични ситуации.

Во нашето испитување за параметарот пулсна фреквенција не најдовме сигнификантни разлики меѓу пациентките од двете испитувани групи. Просечната пулсна фрекфенција кај пациентките во спиналната група беше 97,5 удари/мин, додека кај оние од групата со општа анестезија 98,4 удари/мин. Лесната тахикардија кај спиналната анестезија е резултат на возбудата која е очекувана кај пациенти со очувана свесност, а кај групата во општа анестезија таа е резултат на релативно површната анестезија која се дава до моментот на клемувањето на папчаникот на новороденото.

Кај параметарот „респирации во минута“ не забележавме разлики помеѓу групите бидејќи во општа анестезија беше диктиран од наша страна (респираторен апарат), а кај спиналната анестезија како резултат на респираторниот центар на пациентката.

Во секој случај кај ниту една родилка во испитувањето не забележавме епизоди на тешка хипооксија пропратени со хиперкапнија и ацидоза.

ЗАКЛУЧОК

Двата видови анестезија доведоа до благ пад на крвниот притисок без значајно влијание врз пулсот и периферната сатурација со O_2 кај родилките. Падот на крвниот притисок беше поизразен во групата водена во спинална анестезија, но беше во дозволените граници. Препорачуваме во иднина за породување со елективен царски рез да се форсира спиналната анестезија како подобра и поквалитетна анестезиолошка техника.

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MATERNAL HEMODYNAMIC CHANGES IN GENERAL AND SPINAL ANESTESION DURING CESAREAN SECTION

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ABSTRACT

Background: Number of caesarean sectionshas drastically increased and thus arose the idea to research the effect of the type of anesthesia.

The aim of the study: To compare SA and GA through overseeing the hemodynamics of the birthmother and to define and compare the incidence and type of complications.

Material and methodology: 120 patients divided in two groupshave been examined.Gorup 1 was with 60 patients with GA. The patients received 10mg i.v. of metoclopramide as premedication. For introduction propofol (2.0-2.5 mg/kg/bm),and for intubation succinyl choline (1-1.5 mg/kg/bw), or rocuronium bromide (Esmeron) (0.4 – 0.6 mg/kg/bw). During the course of the anesthesia, after the extraction of the fetus, the patients were given Fentanyl (0.005 mg/kg/bw) and a depolarizing relaxant. The gas ratio of O_2 and N_2O was 3:3 L/min. Group 2 was with 60 patients withSA. The lumbar puncture was performed between L_2 and L_3 or L_3 and L_4, with a needle with 26 or 27 G width. Bupivacain 0.5% (2-3 ml) was applied. The patients were hydrated with 500 – 1000mL of 0.9% NaCl or Ringer solution. The volume of administered solutions, both in total and by type was monitored from the beginning to the end of the procedure. The following parameters were observed in both groups: AP, pulse frequency, the number of respirations per minute and the peripheral blood oxygen saturation (SpO_2).

Results: The group with SA showed a larger fall in AP compared to the group lead with GA. The quantity of administered solutions in the group with GA was 1000 – 1500 ml, whereas in the group with SA it ranged from 2000 – 2500 ml. There were no significant differences in heart rate and respirations per minute, as well as in SpO_2. Conclusion: SA has a priority over GA.

Key words: Caesarean section, Anesthesia, general, spinal, hemodynamic changes

Review

METHODS USED IN DETERMINING THE AGE OF BRUISES

МЕТОДИ ЗА ОДРЕДУВАЊЕ НА СТАРОСТА НА КРВНИТЕ ПОДЛИВИ

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ABSTRACT

Bruises are common skin lesions that can be found in persons died a violent death and therefore have a forensic significance. In practice there are cases of violent death when it is difficult to determine with certainty the age of the bruises. But according to the biological processes associated with the reparation of the bruises, we could get reliable information about their age. Common methods for determining the age of the bruises, such as observation, colorimetry, spectrophotometry and patho-histological analysis are presented in this review paper.

Determination of the age of bruises according to their color is a method used by most experts in the initial analysis. The observation of the yellow color, not brown or orange, points out a bruise that is not fresh. However, the possibility of visual observation is limited by the morphology and physiology of the human eye. Spectrophotometric analysis of data can offer useful and objective information. Histological analysis is suitable as a method only in post-mortem examinations. In this field of work there is a lack of published information on the histological analysis about the aging of bruises, which restricts the information for more precise determination of their age.

Keywords: bruises, methods for determining the age of bruises

INTRODUCTION

A bruise represent extravasation of blood in the connective tissue of the skin [1]. Upon the occurrence of the bruise, smaller blood vessels in the connective tissue of the skin are damaged, macroscopic recorded as a red spot on the skin. Usually blood is extravasated between the dermis and hypodermis, because there is a greater amount of rare connective tissue. If blood is deeper into the skin then, macroscopic, the bruise is seen as blue or purple patch on the skin. Old bruise is seen as yellow spot on the skin, with vaguely defined border to surrounding healthy tissue. There have to be fulfilled 3 criteria to occure the bruise. The first criterion is the force acting on the skin, it should cause laceration of the blood vessels in it, but without thereby damaging the integrity of the skin. The pressure force is usually from a blunt object, otherwise it would cut the skin [2]. The second criterion is the blood pressure. Once lacerated blood vessels, there should be sufficiently high blood pressure which allows extravasation of blood in the connective tissue of the skin. The third criterion is the location of the extravasated blood. Blood should be close enough to the surface of the skin, and so could be observed as bruise [3]. Bruise occured during life may not be visible due to the effect of opalescentness of the skin [3,4], but post mortal will be revealed due to the emergence of reflection in it [5]. Early manifestation of bruise depends on two factors: extravasation of blood from the blood vessels into the surrounding tissue and depth in the skin where blood is found [6,7,8].

Bruises are not insignificant injuries because they can lead to death if extensive [9]. They are very common injuries and determining their age is one of the most significant data in forensic investigations, especially when it comes to cases of violent death and abuse in children [10].

In the interpretation of the age of the bruises are used different methods, some of which are used in post-mortem analysis. The simplest, but not the most accurate method is visual observation by direct inspection of the bruise or interpretation of the bruise seen on photograph. Histological analysis offers precise data on the age of the bruises. Previous analyzes mainly are based

on visual observation and monitoring of the change in the color of the bruises. Patho-histological analysis includes determining of the cell population found in the area of bruise and also specific permanent changes of the tissue. Immunohistochemical method in determining the age of bruises detects the presense of specific enzym in the inflammatory cells found in the area of bruises. These methods offer exact information in determining the age of bruises.

The purpose of this paper is to review the literature data and previously published results that provide information about the different methods applied in the interpretation of the age of bruises.

MATERIAL AND METHODS

This paper presents analysed results of the searched databases Google scholar and Pubmed central, made on May 15, 2014, in order to get published data about the research field to determine the age of the bruises. Also are analyzed and discussed studies cited in the review article of Langlois (2007).

RESULTS AND DISCUSSION

Most commonly applied method in the interpretation of the age of bruises is the method of visual observation. The good side of this method is the convenience and non-invasiveness for application in clinical forensic medicine. But the weakness is the fact that often this method is quite accurate because it is affected by several factors, such as the color perception of observers, the current lighting and pigmentation of the skin of the victim. [1] When we analyze the color of the bruise, we should consider that it could be presented with a delay, it could migrate and it could take different time of resolution [10].

The presence of hemoglobin near the surface of the skin will appear red, but if hemoglobin is located deeper in the tissue it is noticed blue, the effect which is associated with Raighley phenomenon of dispersion, the absorption coefficient of the skin and visual interpretation system [6,8,17,18]. Extravasation of blood in connective tissue causes an inflammatory reaction [14] and this reaction can be aggravated by tissue damage from blunt injury [15,16]. Neutrophils are the first cells that infiltrate the bruise, but they probably can not metabolize the hemoglobin in erythrocytes [2.19]. Other inflammatory response cells, the macrophages, can phagocytose erythrocytes [20], because they possess the enzyme heme oxygenase (HO) which provides the first step in metabolism of hemoglobin. This enzyme converts hemoglobin in biliverdin [21]. Biliverdin is green pigment and is quickly converted to bilirubin, a yellow pigment, mediated by the enzyme biliverdin reductase (BVR). BVR is an enzyme that is found in all tissues under normal conditions, but especially in reticulocytes and macrophages of the liver and spleen [22 23].

The initial appearance of the bruise is associated with presence of blood into the skin. The bruise may become visible as early as 15-20 minutes of injury [24]. According to published data, the initial color of the bruise depends on the location where blood is extravasated into the skin [8,17,25]. We can see the red, blue, purple, black or green, but these colors are not indicators about the age of the bruise [26]. Color change in bruises can occur due to alter of the position of blood against the surface of the skin [27] and can be emphasized by hemoglobin released during conversion of the oxyhemoglobin to deoxyhemoglobin [28]. It takes time for influx of macrophages, induction of enzyme HO and metabolism of hemoglobin at site of the bruise for the production of bilirubin and hemosiderin that give the color of the bruise [29]. The development of yellow color in bruise is due to local production of bilirubin [22,30] that can be demonstrated in the serum with it`s concentration [48]. There is a significant difference in the average time of appearance of the yellow color in people younger than 65 years [20]. Literature data with experimental animal studies suggest that bruises recover faster in younger individuals [11] and that the function of macrophages is impaired in older individuals [12,13].

According to the metabolism of hemoglobin and changing the color of bruise, it has been concluded that only the appearance of yellow color in the bruise can provide information about its age, when using observation as a simple method for determining the age of the bruise [20]. Stephenson in his paper outlines the five schemes of different authors to interpret the age of bruises, according to their color [55], table 1. The initial color of bruise is almost always red, unless the bruise is deeply into the skin and then it is purple or blue. Yellow coloration can not be seen earlier than 18 hours after the occurrence of the bruise [20]. This color is usually noticed after a week and disappears at the end of the second week. In interpretation of the age of bruises very important role have anamnestic data, or time of occurrence of the injury which is different from the time of occurrence of the bruise [33].

Table 1. Classification of the age of bruises by color, by 5 schemes published by different authors

	Adelson	Rentoule	Camps	Poison	Spitz
Initial colour	Red/blue	Violet	Red	Red, black	Blue/red
1-3 days	Blue/ brown	Dark blue	Blue/ brown	Purple, black	Purple, black
1 week	Yellow/ green	Green	Green	Green	Green/ yellow
8-10 days		Yellow	Yellow		Brown
2 weeks		Normal	Normal	Yellow	Normal

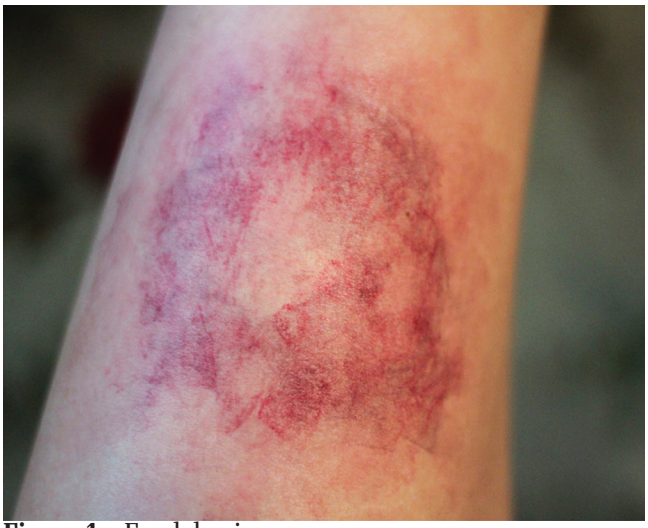

Figure 1. Fresh bruise

There is irregular formation with red coloration on the skin

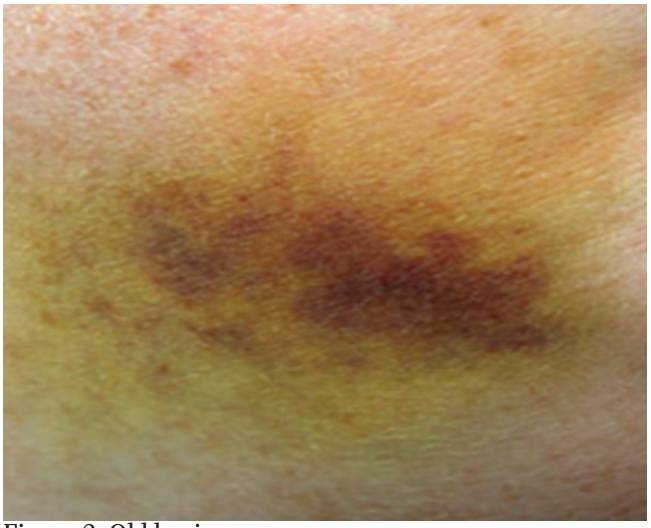

Figure 2. Old bruise

There is a formation in yellow coloration on the skin

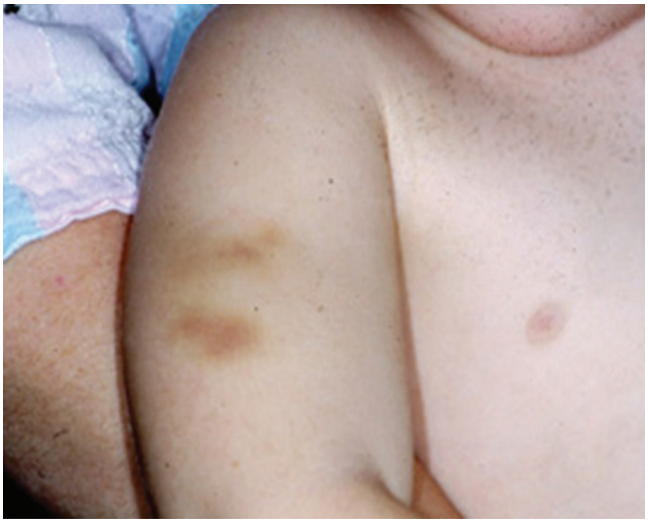

Figure 3. Bruise in children in regression.

Intermediate between the red and yellow coloration on the skin

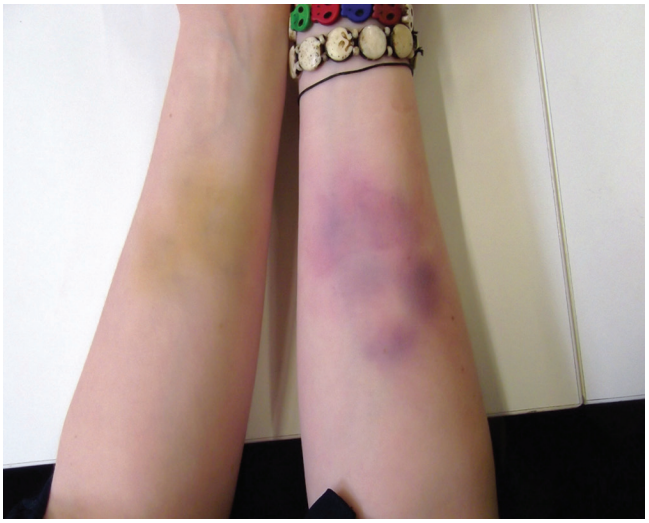

Figure 4. Old bruise and new bruise

Spectrophotometry and hyperspectral imaging can be used in the interpretation of the age of bruises. Spectrophotometry provides objective data analysis of color, while avoiding individual variations during the interpretation of the color of bruises [43,44]. This method allows measurement of multiple points in the eyesight field [45]. Their intensity can be measured at intervals of 1 nm for the entire field of red (700 nm) and blue (400 nm) color [46,47,48]. Data obtained from spectrophotometric analysis of tissue with bruise can provide guidelines in determining its age [49,50]. Outgoing published experimental data in the literature on the application

of spectrophotometry using advanced mathematical analysis offers promising results in determining the age of bruises [51].

Hyperspectral imaging has the potential to provide spectrophotometric data of large areas of the body where bruises are located [52]. The location and extent of bleeding and the presence of bilirubin in the bruise can be measured, but also the bleeding can be isolated and analyzed in relation to the imaged area [53,54].

An accurate method for determining the age of bruises is histological analysis of the tissue where the bruise is located. This method is used only in the post-mortem analysis of bruises in forensic medicine. Histological analysis monitor cellular response upon the occurrence of a bruise. Besides the initial signs of tissue damage, such as edema near haemorrhage resulting in expansion of the fibrous septa, erythrocytes outside the vessels activate the body's inflammatory response, thus in connective tissue soon appears infiltration by inflammatory cells [2]. For approximately 4 hours of the occurrence of the bruise, there is migration of polymorphonuclear neutrophils in it, but they can not phagocyte erythrocytes. Neutrophils are not present in normal skin and because of it, their presence is considered significant in findings [34]. Later, after nearly nine hours of the occurrence of the bruise, there is migration of mononuclear leukocytes, macrophages [35]. Erythrocyte phagocytic macrophages are noted after 15-17 hours of the occurrence of bruises [35]. Macrophages are present in normal skin [34] and it hinders their determination when the infiltration in bruised area is assessed. In human skin lessions, macrophages migrate after 3 [36], or 7 hours, with peak of migration of 1-2 days after injury [37]. Erythrophagocytosis occurs later, after 3 days [36]. Macrophages filled with hemosiderin as residue from phagocyted erythrocytes, detected by staining Perl`s Prossian Blue (Figure 5), can clearly be seen earliest 24-48 hours from the occurrence of the bruise, but usually are observed after 4-8 days. Haemosiderin is usually located in the tissue 90 hours after the occurrence of the bruise, while hematoidin is found occasionally 9 hours after the occurrence of the bruise [35]. The hematoidin is a pigment which is chemically identical with bilirubin. It occurs in the tissues due to metabolism of the hemoglobin, especially in conditions of reduced oxygen concentration. Hematoidin contains iron, and is formed intracellular, presumably in the reticuloendothelial cells, but often located extracellular after 5-7 days prior foci of bleeding. Histological it is noted as refractile, yellow-brown or orange-red granules, but the characteristic diamond tiles are arranged in a radial pattern, etc. hematoidin burrs. The finding of hematoidin is sign of bleeding in the direction of resolution. Staining method Perl`s Prossian Blue easily makes difference between hematoidin and haemosiderin. Haemosiderin gives blue colored particles in the field of bleeding while hematoidin remains as light brown staining [35].

Betz and Eisenmenger in their morphometric study describes a significant amount of hemosiderin, about 20% more in the visual field, which indicates the age of the bruise of about 1 week [38].

Raekallio J. found the presence of fibrin in subcutaneous hemorrhages, but concluded that clot in tissue hemorrhage can occur and posthumously and that it is not evidence of a vital reaction. Because postmortem fibrinolysis occurs one day after hemorrhages, finding a well-preserved fibrin network in subcutaneous hemorrhages, analyzed by autopsy 2-3 days after death, indicates vital or agonal origin of the hemorrhage or bruise [35].

Accurately determining the age of bruises is extremely important when dealing with cases of child abuse, accompanied with violent death.

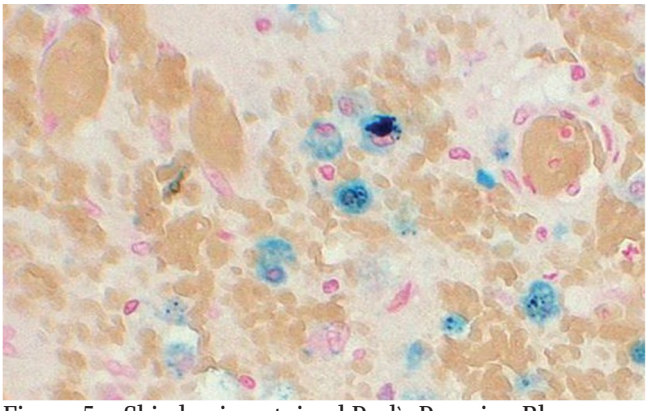

Figure 5. Skin bruise, stained Perl`s Prossian Blue, x 100

Microphotograph shows presence of macrophages filled with hemosiderin in the connective tissue of the skin

Another method used to determine the age of the bruises is determination of the activity of the enzyme heme oxygenase (HO), expressed in macrophages that infiltrate bruises. This method is used only in the post-mortem analysis of bruises in forensic medicine. Expression of HO can be demonstrated and measured by immunohistochemistry, using ELISA technique. This enzyme has a potential role in modulating the immune response [19]. There are two forms of the enzyme, inducible form heme oxygenase-1 (HO-1) and

constitutively form heme oxygenase-2 (HO-2), which has been detected in many tissues [21,39]. Form HO-1 is present in macrophages and is normally found in small amounts in them [29]. Heme oxygenase enzyme is also present in fibroblasts, in inducible form, but these cells do not have a role in the metabolism of hemoglobin in bruises [40]. The amount of enzyme HO-1 in macrophages increases in red-blood-cell phagocytosis [19,20,41] or in the exposure only of hemoglobin [22]. In HO-1 positive cells, which correspond to the field of bleeding, the enzyme can be early detected 3 hours after bleeding, but a peak of expression is noticed after 3 days. [35]. Nakajima T et al. in the paper of subcutaneous bleeding analyzed the expression of HO-1 enzyme and infiltration by macrophages. They came to the conclusion that defining the HO-1 expression may provide useful information in determining the age of bruises [42].

CONCLUSION

Of all the methods used for analyzing bruises and determining their age, often applied is the method of visual inspection for quick orientation about the age of the bruise. However, this method is not specific and here is considered subjectivity by the expert.

Accurately to determine the age of the bruises is necessary to apply histological analysis of the tissue. Data published in the literature suggest that iron in the bruise can be demonstrated by histological staining after 3 days of injury.

The precise determination of the age of bruises is often sought information in court expertise and has great importance in cases of child abuse when analyzing subsequent bruises and when required the exact cause of death.

Also in forensic investigations is required to confirm the fact whether bruises occured during life or posthumously. In these cases, the increased presence of macrophages in the bruise may indicate that it occured during life. However all authors advise caution to interpret the age of bruises due to the multiplicity of factors involved in their creation, presentation and resorption.

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МЕТОДИ ЗА ОДРЕДУВАЊЕ НА СТАРОСТА НА КРВНИТЕ ПОДЛИВИ

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АБСТРАКТ

Крвните подливи се чести повреди на кожата кои се среќаваат кај лицата починати од насилна смрт и затоа имаат судско-медицинско значење. Во праксата се јавуваат случаи кога е дискутабилно да се одреди со сигурност старост на крвните подливи. Меѓутоа со познавањето на биолошките процеси асоцирани со репарацијата на крвните подливи би можело да се добијат посигурни информации за нивната старост. Распложливите методи за одредување на старост на крвните подливи како што се опсервација, колориметрија, спектрофотометрија и пато-хистолошка анализа се ревиски презентирани во овој труд.

Одредување на старост на крвните подливи според бојата е метод кој го користат повеќето вештаци, при првичната анализа. Опсервацијата на жолтата боја, притоа не кафеава или портокалова, асоцира на крвен подлив кој не е свеж. Меѓутоа, можноста за визуелна опсервација е ограничена со морфологијата и физиологијата на човечкото око. Анализата на спектрофотометриските податоци може да понуди полезни и објективни информации. Хистолошката анализа е погодна како метод за одредување на старост на крвните подливи само во постморталните иследувања. Во ова поле на работа постои недостаток од публикувани информации за хистолошката анализа на крвните подливи што ги ограничува сознанијата врз кои би се темелоло попрецизното одредување на нивната старост.

Клучни зборови: крвни подливи, методи за одредување на старост на подливите

SEASONAL VARIATION IN GRAM-NEGATIVE BACTERIA AS AGENTS OF INTRA-HOSPITAL INFECTIONS

СЕЗОНСКИ ВАРИЈАЦИИ НА ГРАМ-НЕГАТИВНИ БАКТЕРИИ – ПРЕДИЗВИКУВАЧИ НА ИНТРАХОСПИТАЛНИ ИНФЕКЦИИ

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ABSTRACT

Seasonal variations in community-acquired infections are well-studied, while little is known about seasonal variations in healthcare-associated infections. Seasonal variations in bacteria are important environment condition in hospital eco-systems because they can predict infection, adequate diagnosis and therapy. Seasonal variations can influence on decisions for infection prevention. The aim of this study was to determine seasonal variation in Gram-negative bacteria, as agents of intra-hospital infections in correlation with seasonal changes. Literature research was performed for the purpose of this study, with combinations of the keywords: „seasonal variations“, „Gram-negative bacteria“, „intra-hospital infections“ and „climate“, to retrieve full-text articles written in English published in peer-review journals from March 1979 to September 2015. Results from 25 scientific studies have shown that certain climate parameters correspond with seasonal variations in nosocomial Gram-negative bacterial infection and bacterial acquisition in health-care environment. The highest incidences of these infections occur in the warmest months and the months with the highest humidity. These findings lead to conclusion that stronger preventive precautions are necessary in the critical seasons to prevent Gram-negative bacteria acquisition in the hospital environment.

Keywords: seasonal variations, Gram-negative bacteria, intra-hospital infections, climate

INTRODUCTION

Intra-hospital infections (IHI) are significant public health problem in developed countries, as well as in developing countries [1].

Most IHI occur in the Intensive Care Unit (ICU). Treatments in ICU require use of intravenous catheters, urinary catheters, respirators, which depress resistance mechanisms and make patients susceptible to infections [1, 2].

The most common isolated pathogens related to hospital acquired infections are Gram-negative bacilli [3].

There are data for seasonal variations of nosocomial infections.

Seasonal variations in community-acquired infections are well-studied, while little is known about seasonal variations in healthcare-associated infections [4].

Seasonality is defined as a periodic surge in disease incidence corresponding to seasons or other predefined calendar periods [5].

Seasonal variations in bacteria are important environment condition because they can predict infection, adequate diagnosis and therapy and can influence on decisions for infection prevention. The occurrence of seasonal variation is associated with certain meteorological parameters and climate changes.

Seasonal variations are especially noticeable for Gram-negative bacteria. They have seasonal trends in infections incidence. In Eber *et al.* study, *Acinetobacter spp.* infections exhibited the greatest seasonal variations, with a 52% increase in the summer as compared with the winter months [6].

AIM

The aim of this study was to determine seasonal variation in Gram-negative bacteria as agents of intra-hospital infections in correlation with seasonal changes.

MATERIAL AND METHODS

A literature research was performed with combinations of the keywords: „seasonal variations", „Gram-negative bacteria", „intra-hospital infections" and „climate", to retrieve full-text articles written in English published in peer-review journals from March 1979 to September 2015.

RESULTS

This review study presents results from 25 scientific studies where seasonal variations are well-identified in these Gram-negative bacteria: *Acinetobacter spp.*, *Klebsiella spp.* and *Escherichia coli*.

Acinetobacter spp.

The most known trend of seasonality is seen in *Acinetobacter* species.

Acinetobacter is a harmless coloniser on the mucosal surfaces and skin of healthy people. While *Acinetobacter spp.* affect few risks to healthy individuals, they are an important cause of nosocomial infection, with a tendency for developing multidrug resistance [7].

These Gram-negative bacteria are important nosocomial pathogens in hospitals and they are associated with seasonal variation in isolation and infection rates.

Surviving environmental conditions for weeks, a characteristic that promotes transmission through fomite contamination in hospitals, gives *Acinetobacter* special importance as nosocomial pathogen. This is due to its ability to maintain long periods of high humidity or under dry conditions [8].

Seasonal increasing isolation of *Acinetobacter baumannii* in warm months, especially summer has been reported since 1970s. Gaynes and Edwards study of *Acinetobacter* infections reported to the National Nosocomial Infections Surveillance (NNIS) System of USA between 1974 and 1977 was based on hospital-wide surveillance data. Findings included a rate of 3 infections per 10,000 patient discharges and an unexplained increase in infection rates during the late summer months. Infection rates were twice as high in late summer months as in early winter months [9, 10].

Another study of seasonal variation of *Acinetobacter* infection reported to the National Nosocomial Infections Surveillance (NNIS) System of USA was made between 1987 and 1996 by McDonald *et al*. Study findings represented a total of 3447 *Acinetobacter* infections during 5.5 million patient-days of ICU-component surveillance and increase in infection rates during the late summer months of July-October. Incidence rate of infections was higher for 54% during the warmest months (July–October) in comparison with the other months of the year [11].

Same results were represented by study made in Queen Mary Hospital, Hong Kong, P.R. China in the period from 1990 to 1993. Siau *et al*. study represented increase infection rates during the late summer months (July-October) [12].

Also, there are data for its outbreak in Intensive Care Units in Queen's Medical Centre, Nottingham, Great Britain, that indicates spring and winter as critical seasons when patients with acute and chronic lung disease require admission to the ICU for artificial ventilation [13, 14].

Seasonal variation of *Acinetobacter baumannii* isolated from intubated surgical ICU patients was estimated for three years period (2010-2012) at the Clinic for anestesiology, reanimation and intensive care, Skopje, Republic of Macedonia. Seasonal index pointed the highest rates of isolation during the spring months (March to June) and winter months (December, January and February) when the humidity was on the highest level during each year of the investigated period (Figure 1).

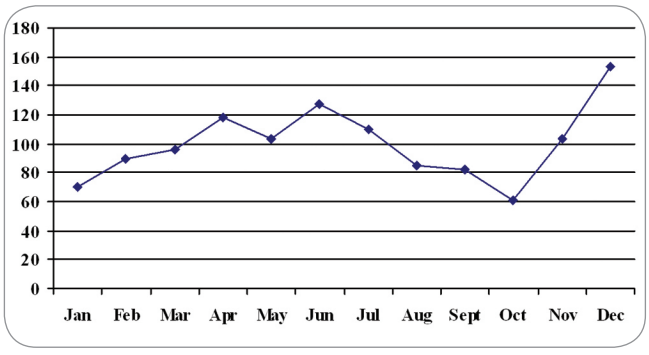

Figure 1. *Acinetobacter baumannii* seasonal index (2010-2012)

Acinetobacter isolates in investigated period showed variety of seasonal variations. In 2010, largest number of isolates was recorded during winter months, early spring and early autumn. High isolation incidence was observed in spring and winter months in 2011. The highest rates of isolation in 2012 were detected in summer and winter [15].

Klebsiella spp.

Klebsiella spp. invades rapidly the hospital environment and often causes nosocomial outbreaks. These outbreaks are especially observed in neonatal ICU [16, 17].

Seasonal variations are also seen in *Klebisella spp.*

Anderson *et al*. made large study on four continents (Europe, Australia, North America and Asia) to determine seasonal variation in *Klebisella* bloodstream infections. The authors analysed surveillance data from 2001 to 2006 at four hospitals (Durham, North Carolina, USA; Marseille, France; Melbourne, Australia; and Taipei, Taiwan).

Incidence rate of *Klebsiella* from bloodstream infections varied between institutions, but highest incidence was recorded during the warmest four months of the year. The study results showed that summer months are most critical for acquisition for *Klebsiella spp.* [5, 17].

Escherichia coli

Escherichia coli is the most well-studied Gram-negative bacteria in microbiology. *Escherichia coli* is one of the most frequent isolated Gram-negative bacteria and cause most of community and nosocomial urinary tract infection (UTI) [18, 19].

Trend of seasonality in infections with *Escherichia coli* are also described.

A study made in Minnesota from 1998 to 2007, presented results that *Escherichia coli* is mostly isolated from urine samples, during the warmest 4 months of the year (June through September). Incidence rate was a 44% higher in the two warmest months in the year in comparison with the other 10 months [6, 20, 21].

Results from the original scientific studies have shown that certain climate parameters correspond with seasonal variations in intra-hospital Gram-negative bacterial infection and bacterial acquisition in health-care environment. Seasonality of the Gram negative bacteria and correlation with the temperature are shown on Table 1.

Table 1. Microorganism seasonality and correlation with temperature

Microorganism	Seasonality	Correlation with temperature
Acinetobacter spp.	Yes	Yes
Klebsiella spp.	Yes	Yes
Escherichia coli	Yes	Yes

DISSCUSION

The heterogeneity of these studies made their synthesis difficult. They are difficult to compare because they represent different places of the world and different periods of time.

Differently designed studies made analysis of the data more difficult.

Drawback of these studies is not presenting extensive meteorological parameters. Studies should contain detailed information about the temperature and humidity of the air [22, 23].

All available studies for seasonal variations of *Escherichia coli* and *Klebsiella spp.* highlighted warmest months as critical for acquisition of these bacteria.

High incidence of *Acinetobacter* isolation and infections was registered during periods of high humidity but also during summer months. Winter is also critical season for *Acinetobacter* infection. Number of patients which require admission to the ICU, for artificial ventilation, increases in winter.

The incidence of endemic *Acinetobacter spp.* isolated from intubated surgical patients from Clinic for anesthesiology, reanimation and intensive care, Skopje, Republic of Macedonia in the last two decades was in range between 29-40%. High percentage of isolation characterizes this organism as the most important nosocomial pathogen in the intensive care unit.

Seasonal index of *Acinetobacter baumannii* estimated for the 3 year period (2010-2012) had shown that *Acinetobacter* has been isolated mostly in spring (April to June) and beginning of winter (December). These seasons have the highest humidity which correlates with the ecology of *Acinetobacter spp.* This is due to the ability of the bacterium to disseminate rapidly in wet environmental conditions.

High rate of isolation was observed in the summer months in 2012. Increasing isolation incidence in summer months is correlated with the most findings from scientific literature [6, 15].

Seasonal variation data from the Republic of Macedonia comply with the data from foreign literature.

In accordance with all obtained literature data, results pointed the highest rates of Gram-negative bacteria infections during summer months. Summer season and higher monthly temperature are associated with nosocomial infections caused by Gram-negative bacteria.

Higher temperature promotes growth of Gram-negative bacteria. Ecology and epidemiology of these bacteria enable them to maintain in the hospital environment. Lack of hospital staff during the summer is also a reason for increasing of intra-hospital infections [6, 7, 13-15, 23-25].

These findings can be used for infection prevention, diagnosis and empirical therapy against Gram-negative bacteria and as prevention for bacterial acquisition in hospital in correlation with seasonal changes.

CONCLUSION

Preventive prediction of seasonal variations in Gram-negative bacteria could prevent intra-hospital infections and it would improve the health of patients, reduce hospital days, and costs of treatment. It would reduce the risk of transmission and infection of other patients and hospital staff.

Stronger precautions are necessary in the critical seasons to prevent Gram-negative bacteria acquisition in health care centers.

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СЕЗОНСКИ ВАРИЈАЦИИ НА ГРАМ-НЕГАТИВНИ БАКТЕРИИ – ПРЕДИЗВИКУВАЧИ НА ИНТРАХОСПИТАЛНИ ИНФЕКЦИИ

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ИЗВАДОК

Сезонските варијации кај инфекциите стекнати во заедницата се добро проучени, додека малку се знае за сезонските варијации кај интрахоспиталните инфекции. Сезонските варијации на бактериите се важни случувања во болничките еко-системи, бидејќи врз основа на нив може се предвиди инфекција и да се одреди соодветна дијагноза и терапија. Тие можат да влијаат врз мерките за превенција на одредени инфекции. Целта на ова истражување е да се одредат сезонските варијации на Грам-негативни бактерии - предизвикувачи на интрахоспитални инфекции во корелација со сезонските промени. За изработка на оваа студија беше изведено електронско пребарување на литературни податоци на англиски јазик, објавени во рецензирани часописи, издадени во периодот: од март 1979 до септември 2015 година, со комбинација на следните клучни зборови: „сезонски варијации", „Грам-негативни бактерии", „интрахоспитални инфекции" и „клима". Резултатите од 25 научни студии покажаа дека одредени климатски параметри кореспондираат со сезонските варијации на болничките инфекции предизвикани од Грам-негативни бактерии. Најголем процент на овие инфекции се јавуваат во најтоплите месеци и месеците со најголема влажност. Овие сознанија доведуваат до заклучок дека се потребни посилни превентивни мерки во критичните сезони за да се спречи развојот на Грам-негативните бактерии во болничката средина.

Клучни зборови: сезонски варијации, Грам-негативни бактерии, интрахоспитални инфекции, клима

THE APPLICATION OF GENE THERAPY AS CURRENT CHALLENGE IN WISKOTT- ALDRICH SYNDROME

APLIKIMI I TERAPISË GJENIKE SI NJË SFIDË AKTUALE NË SINDROMIN WISKOTT-ALDRICH

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ABSTRACT

Background: Wiskott-Aldrich syndrome (WAS) is a rare X-linked primary immunodeficiency (PID) characterized by micro-thrombocytopenia, recurrent infections, eczema.

Methods: Clinic, immunologic and genetic examinations and gene therapy were performed.

Results: We report a 11 years old, boy, who was admitted for the first time in the Onco-Hematologic Service on the UHC, eight years ago. He, continuously, showed frequent cutaneous manifestations, diffuse petechiae and ecchymosis of the skin, oral mucosa and bloody diarrhea, recurrent cutaneous infections, bronchopneumonia. No HLA-identical donor sibling. He had presented inclusion criteria to be enrolled in the experimental protocol of treatment with gene therapy for WAS when he was 10 years old. He was performed upon premedication, the infusion of the transduced autologous bone marrow cells, engenireed with the lentiviral vector containing the WAS cDNA.

Conclusion: Hematopoietic stem/progenitor cell (HSPC) transplants can be curative, but, when matched donors are unavailable, infusion of autologous HSPCs modified ex vivo by gene therapy is an alternative approach. WAS is amenable to hematopoietic stem cell gene therapy. New trials using lentiviral vectors are expected to improve efficacy and safety profiles.

Key words: WAS, boy, infections, gene therapy.

INTRODUCTION

Wiskott-Aldrich syndrome (WAS) is an X-linked recessive immunodeficiency disorder characterized by the triad of recurrent bacterial sinopulmonary infections, eczema (atopic like dermatitis), and a bleeding diathesis caused by thrombocytopenia and platelet dysfunction, which is associated with a high incidence of auto-immunity and lymphoreticular malignancy [1,2,13]. Wiskott-Aldrich syndrome (WAS) was first described by Wiskott in 1937 and was further characterized by Aldrich in 1954. It has joined the list of Primary Immune Deficiency Diseases in the 1960's.[15]

It is WAS arises from mutations in the Wiskott-Aldrich Syndrome protein (WASp), a cytoplasmic protein that links signaling by cell surface receptors such as the T-cell receptor and integrins to actin polymerization. WASp promotes the functions of multiple cell types that support immune responses, but also is important for the function of regulatory T cells and in TCR-induced apoptosis, two negative mechanisms of immune regulation that maintain peripheral immune tolerance. [6,7,11] WASP has been reported to interact with many cytoplasmic molecules linking cellular signaling to the

actin cytoskeleton. [2,3,4,5] Studies of Wiskott-Aldrich syndrome protein-deficient cell lines and wasp-knockout mice have paved the way for possible gene therapy [11]. One of the first diseases to be successfully treated by allogeneic hematopoietic stem cell transplantation, WAS is currently the subject of several phase I/II gene therapy trials for patients without HLA-compatible donors [17]. Since Wiskott-Aldrich syndrome protein is expressed exclusively in hematopoietic stem cells, and because Wiskott-Aldrich syndrome protein exerts a strong selective pressure, gene therapy is expected to cure the disease [16, 18]. Hematopoietic stem/progenitor cell (HSPC) transplants can be curative, but, when matched donors are unavailable, infusion of autologous HSPCs modified ex vivo by gene therapy is an alternative approach[9].

AIMS

To describe clinic, laboratory; immunologic examinations and genetic features of the patient with Wiskott –Aldrich before and after gene therapy.

CASE REPORT

Patient SH.G, 11 years old, boy, who was admitted for the first time in the our unit of the UHC, eight years ago. He, continuously, showed frequent cutaneous manifestations, diffuse petechiae and ecchymosis of the skin, oral mucosa and bloody diarrhea, recurrent cutaneous infections, bronchopneumonia, otitis, faringitis and eczema (very dry skin), some episodes of hives, since he was 4 months. An hemorragic ocular infection was appeared at the age of 3 years old with visual impairment, photophobia. On 2013 another ocular infection was occurred, involving both eyes. This infection brought to a corneal ulceration on the right eye with desmatocele, so he underwent performant keratoplastic. He is regularly followed for his issues in our center. Blood picture revealed microthrombocytopenia, high IgA, IgE and normal IgG, and low IgM levels, congenital defect of antithombin (40-50%). Platelet levels average around 15000/microl (10000- 20000). Bone Marrow aspirate morphology: Hematopoietic series are present in all maturative stages. Molecular analisis of mutation of the WAS'gene of patient: presence of alteration c[735-2A>G];[0]. The analisis of mutation of the WAS'gene of patient's mother: c[735-2A>G];[=]. In the citofluorimetric analisis, there was evidenced a several deficit of WASp in the level of all leucocyte populations evaluated. Non-consanguineous parents. His maternal uncle died at the age 25 of a cerebral hemorrhage, three pro-maternal uncles (brothers of his maternal grandmother) respectively 51; 53 and 72 years old, died intracranial hemorrhage.

Our data confirmed a WAS'diagnosis, that was based in the familiar, personal history; the clinic and the immunologic parameters; and severely reduced WAS protein expression are consistent with a severe phenotype. No HLA-identical donor sibling, so he had presented inclusion criteria to be enrolled in the experimental protocol of treatment with gene therapy for WAS.

The patient started the anti-infective prophylaxis in 2013 with co-trimoxazole, acyclovir, nystatin, intravenous Imunoglobulin, antibioticotherapy, etc. The patient performed blood tests and instrumental tests required by the baseline phase of the protocol. He started the peripheric mobilization of CSE with G-SCF with Myelostim on July 2014 with a good response, then he was performed upon premedication, the infusion of the transduced autologous bone marrow cells, engenireed with the lentiviral vector containing the WAS cDNA.

The patient received gene therapy with autologous CD34+ cells transduced with a lentiviral vector encoding WAS at the Scientific Institute HS Raffaele, Milan, Italy.

He performed hemograms once a month with platelets value around 80000-180000/microl., with normal platelet volume, he is showing a progressive recovery of lymphocyte counts, after transient lymphopenia following conditioning. At the present, total lymphocyte count is still below normal level for age, as are T cells, but they are expected to progressively increase in next months. As a number of CD4+ and CD8+ cells raised. B and NK cell counts are instead normal for age. Over the course of several months, the patient has always been in good general conditions, the cutaneous manifestations of viral disease resolved completely and a patient remains clinically well and free of infectious complications and no bleeding episodes at 1 year, after transplantation.

DISCUSSION

Wiskott-Aldrich syndrome (WAS) is an X-linked recessive immunodeficiency disorder characterized by the triad of eczema (atopic like dermatitis), recurrent bacterial infections and a bleeding diathesis caused by thrombocytopenia and platelet dysfunction. WAS is caused by various mutations in the gene that code for the WASp.[9]

The incidence of WAS in the USA is 4 in 1 000 000 live male births [14]. The frequency in the European population is similar to that of the United States. The same study also

examined the prevalence of Wiskott-Aldrich syndrome in several national registries (ie, Italy, Japan, Switzerland, Sweden) and found that this condition occurred in 2-8.8% of patients with primary immunodeficiencies [8,14]. WAS is an X-linked disorder that is manifest in males, with an absence of clinical symptomatology in obligate female carriers[12].

Examination for Wiskott-Aldrich disease includes evaluation for signs of bleeding, infection, malignancy and atopy, general appearance and vital signs, dermatologic, pulmonary, neurologic assessment. Laboratory studies used in the evaluation of Wiskott-Aldrich syndrome, CBC count supports the diagnosis, quantitative serum immunoglobulin levels, functional testing of the humoral and cellular components of the immune system, genetic testing, major histocompatibility tests of the patient, parents, and siblings to determine feasibility for stem cell transplantation, screening of patient and potential donor for infectious agents (HIV, CMV, hepatitis viruses, etc), radiography, particularly of the chest, is part of the assessment for new infections [12, 14]. Without appropriate care and intervention, morbidity and mortality are frequent. With appropriate care and timely intervention, patients with WAS have an excellent prognosis. As an example, long-term survival following the use of allogeneic HSCT is >80%. WAS is amenable to hematopoietic stem cell gene therapy. It is very important to draw the attention of pediatricians to suspect WAS in cases of children with a long history of recurrent infections, cutaneous manifestations, bleeding episodes that do not respond to standard therapy, moreover when they see the life-threatening complications such as gastrointestinal hemorrhage, intracranial hemorrhage. Hematopoietic stem/progenitor cell (HSPC) transplants can be curative, but, when matched donors are unavailable, infusion of autologous HSPCs modified ex vivo by gene therapy is an alternative approach[10]. New trials using lentiviral vectors are expected to improve efficacy and safety profiles [5].

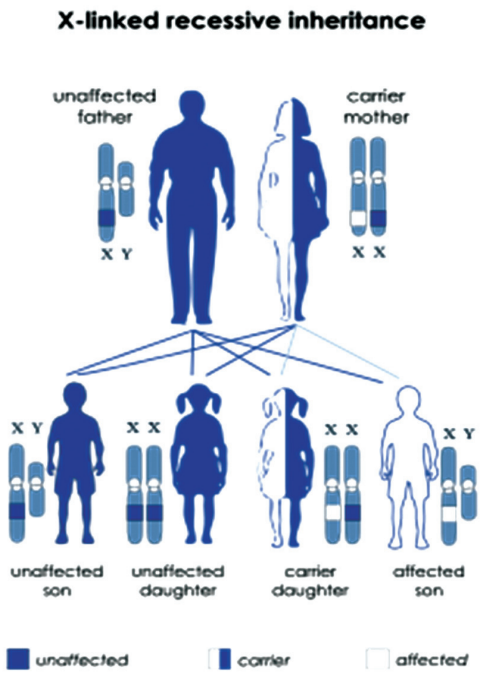


Fig. 1. X-linked recessive inheritance

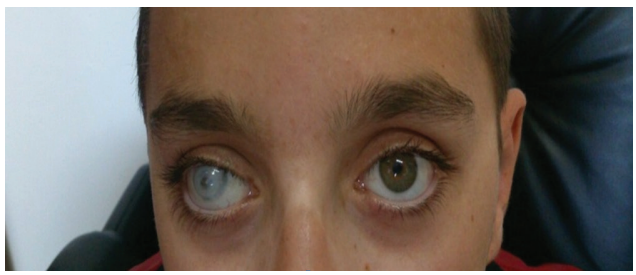
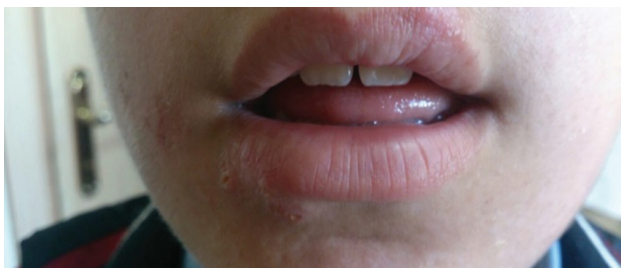


Fig. 2. Corneal transplantation in the boy affected by Wiskott-Aldrich Syndrome



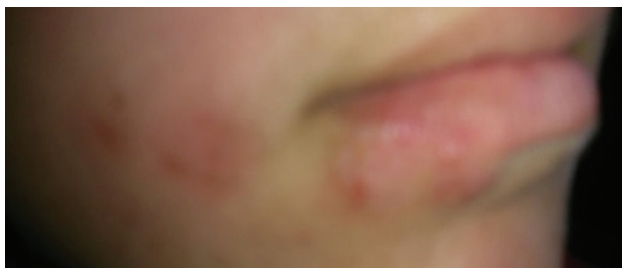


Fig. 3 and 4. Eczema in the boy affected by Wiskott-Aldrich Syndrome

CONCLUSION

Understanding the types of Primary Immunodeficiency (PI) and the related clinical manifestations can help pediatricians see beyond the presenting symptoms and lead to improved recognition and diagnosis of PI. Timely diagnosis is of utmost importance in PI, as recent advances in bone transplantation and immunoglobulin replacement therapy, as well as future gene therapies, provide effective ways to prevent significant mortality and morbidity. Gene therapy is a good treatment alternative in patients with WAS, because it gives them chance for long remission and improvement of quality of life. Beyond proof of principle, ongoing international efforts to coordinate trials of gene therapy for the WAS may also provide a model for the expedited development of new treatments for other rare diseases. It should be noted that thanks to the close cooperation with the Italian colleagues, it was made possible performing this important procedure, being the first Albanian patient with WAS who has committed gene therapy.

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APLIKIMI I TERAPISË GJENIKE SI NJË SFIDË AKTUALE NË SINDROMIN WISKOTT-ALDRICH

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APSTRAKTI

Hyrje: Sindromi Wiskott-Aldrich (WAS) është një imunodeficiencë primare e rrallë e lidhur me X që karakterizohet nga mikro-trombocitopenia, infeksione të përsëritura, ekzema.

Metodat: U kryen ekzaminimet klinike, imunologjike, gjenetike si dhe terapia gjenike.

Rezultatet: Ne raportojmë një djalë 11 vjecar, i cili u pranua për herë të parë në Shërbimin e Onko-hematologjisë në QSU, tetë vjet më parë. Ai vazhdimisht paraqeste manifestime te shpeshta në lëkurë, petekie dhe ekimoza të përhapura në lëkurë e në mukoza te gojës dhe diarre me gjak, infeksione të shpeshta në lëkurë, bronkopneumoni. Nuk ka donator familjar për HLA-në (motër ose vëlla). Ai plotësoi kriteret e përfshirjes në protokollin eksperimental të trajtimit me terapi gjenike për WAS dhe u përfshi në të në moshën 10 vjecare. Ai iu nënshtrua premedikimit, infuzionit me qeliza autologe të palcës së kockës, me vektor lentiviral që përmban WAS cDNA.

Konkluzion: Transplantet me qeliza staminale mund të jenë kurative, por, kur nuk ka donator familjar, transplanti autologi modifikuar ex vivo nga terapia gjenike eshte nje qasje alternative. WAS është i përshtatshëm per aplikimin e terapise gjenike. Përdorimi i vektorëve lentiviral pritet të përmirësojnë efikasitetin dhe sigurinë e mëtejshme.

Fjalëtkyce: WAS, djalë, infeksione, terapi gjenike.

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ANGINA PECTORIS WITH SLOW CORONARY FLOW PHENOMENON: A CASE REPORT

ANGINA PECTORIS СО БАВЕН КОРОНАРЕН ПРОТОК -ПРИКАЗ НА СЛУЧАЈ

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ABSTRACT

Objectives and background: Coronary slow flow phenomenon (CSFP) was identified as an exclusive clinical entity in 1972 [1] where the distal opacification of the coronary artery is delayed on angiography in the absence of significant coronary artery disease. It is a frequent finding, typically observed in patients presenting with acute coronary syndromes. Although it is well known to interventional cardiologists, but the pathogenic mechanisms remain unclear. The clinical implications are significant, with over 80% of patients experiencing recurrent chest pain, resulting in considerable impairment in quality of life.

Methods, procedures and results: We present a clinical case of 54 years old female patient complaining of recurrent chest pain. Physical examination showed non-specific signs. She had a history of high blood pressure, dislipidemia more than 5 years, and a genetic history of coronary artery disease. At the beginning she was treated with antihypertensive therapy with ACE inhibitors and beta blokers. We performed blood laboratory, ECG, echocardiography (ECHO), 24h ambulatory blood pressure monitoring (ABPM), coronary exercise stress test, coronary angiography and myocardial perfusion scintigraphy (MPS) after two years of hospitalisation. After coronary angiography, the diagnosis of slow coronary flow of LAD was confirmed. She was followed up two years after and treated with antihypertensive and antihyperlipemic therapy-statins and dipiridamol.

Conclusion: Coronary slow flow phenomenon is not an infrequent angiographic finding and contributes to morbidity. This phenomenon should be considered a separate clinical entity with peculiar characteristics, pathogenic mechanisms, and defined diagnostic criteria.

Keywords: coronary slow flow phenomenon, coronary artery, chest pain.

INTRODUCTION

Although a number of formal definitions have been proposed, the CSFP essentially consists of a delay in the progression of the contrast injected into the coronary arteries during coronary angiography [1, 2]. This condition, which may affect one or all coronaries, was originally described by Tambe *et al.* in 1972 [5]. Since then it has been accepted as an independent clinical entity, which is called "CSFP", "coronary slow flow syndrome" "syndrome Y", or "primary" coronary slow flow [6-9]. Importantly, "primary" CSFP should be distinguished from the delay in the contrast progression in the context of coronary reperfusion therapy such as angioplasty or stenting for acute myocardial infarction, or other "secondary" causes of coronary slow flow [8-10], coronary ectasia or spasm, ventricular dysfunction, valvular heart disease and connective tissue disorders. Incidence of coronary slow-flow is reported to be 1-7% of all coronary angiograms.

Clinically, this phenomenon occurs most commonly in young men and smokers, and patient admitted with acute coronary syndrome [12]. The clinical course is complicated, with over 80% of patients experiencing recurrent chest pain, most occurring at rest, necessitating readmission to the coronary care unit in almost 20% of affected patients [12]. Most importantly, coronary slow flow has been described to be associated with life-threatening arrhythmias and sudden cardiac death [3, 4], probably due to increased QTc dispersion in these patients.

Further, Yilmaz *et al.* [14] recently delineated the clinical and laboratory features of CSFP compared to the control subjects without CSFP. Metabolic syndrome was more frequent in CSFP in the presence of higher total cholesterol, low-density lipoprotein-cholesterol, fasting glucose and body mass index levels. These data are in line with the observations that insulin resistant states [15] and impaired glucose tolerance [16] correlate with CSFP occurrence. These data suggest that a common underlying pathophysiologic mechanism of the metabolic syndrome and CSFP may be endothelial dysfunction.

Diagnosis and evaluation of CSFP in coronary angiographic studies was initially described subjectively by visual judgement [5]. A semi-quantitative assessment of coronary blood flow is the thrombolysis in myocardial infarction (TIMI) flow grade classification, which reflects the speed and completeness of the passage of the injected contrast through the coronary tree [17,19]. Although this widely used method of grading coronary flow has been a valuable tool for comparison of flow data in clinical trials, variability in the visual assessment may limit the broad clinical applicability. In contrast, as an objective, quantitative index of coronary flow, corrected TIMI frame count (CTFC) facilitates the standardization of TIMI flow grades and flow assessment. It represents the number of cine-frames required for contrast to first reach standard distal coronary landmarks [18]. Currently, by using CTFC as a quantitative index of coronary flow, coronary angiography is the only tool for the diagnosis and assessment of CSFP. Despite good prognosis of CSFP patients, the subsequent progress is frequently characterized by remitting, relapsing anginal episodes resulting in considerable impairment in quality of life. Unfortunately, currently available anti-anginal agents are of limited clinical value. It was shown that dipyridamole and mibefradil, which both influence functional obstruction in arteries <200 μm, normalized CTFC but nitroglycerine, which dilates arteries with diameters >200 μm, did not [20,21]. Importantly, statins appear beneficial for patients with CSFP, likely in part due to their anti-inflammatory properties [22-24]. More recently, several studies demonstrated that nebivolol can both improve endothelial function and markedly ameliorate symptoms, thereby improving quality of life in patients with CSFP [25-27]. Besides its beta-receptor blocking activity, nebivolol can cause endothelium-dependent vasodilatation through increased nitric oxide release [25].

CLINICAL PRESENTATION

A 54-year-old female was admitted to the cardiology department with a history of exertional angina for one year duration and past medical history of hyperlipidemia and hypertension. Chest pain was described as a pressure-like sensation in the middle of her chest. Right upon admission vital signs were stable. Her blood pressure was 150/90 mmHg, heart rate was 94/min, and heart sounds were normal. Systematic examination showed no further significant symptoms. There was a family history of coronary artery disease, her father died from myocardial infarction. She was not a smoker. The resting 12-lead ECG was unremarkable. (Fig.1). We performed ABPM (Fig.2) and results showed that blood pressure was not well controlled.

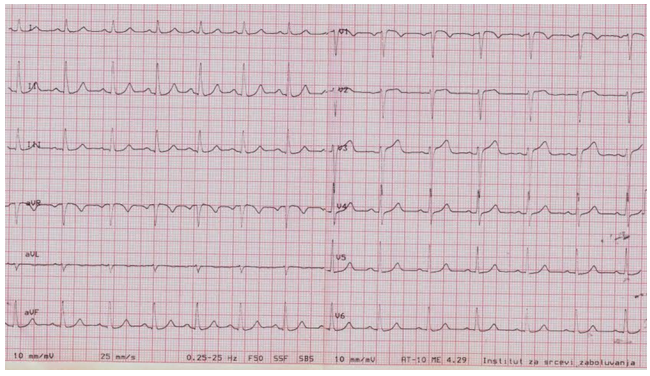

Fig.1 ECG on admission

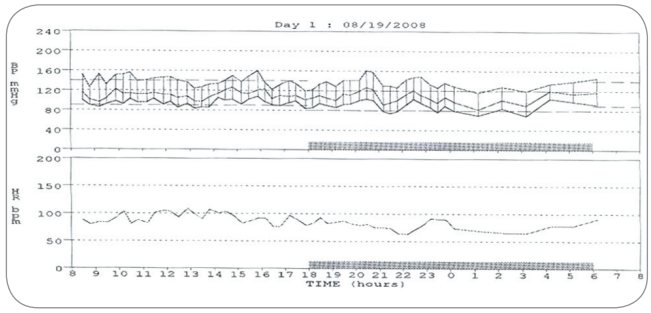

Fig.2. ABPM

Transthoracic echocardiographic evaluation showed a normal left ventricular function and no regional wall motion abnormality. The patient underwent a

treadmill exercise stress test using the Bruce protocol. He experienced typical angina at 6. min of exercise, with nearly a 2-mm ST-segment depression in V4-V6 derivations and coronary test was interpreted as a positive (Fig 3).

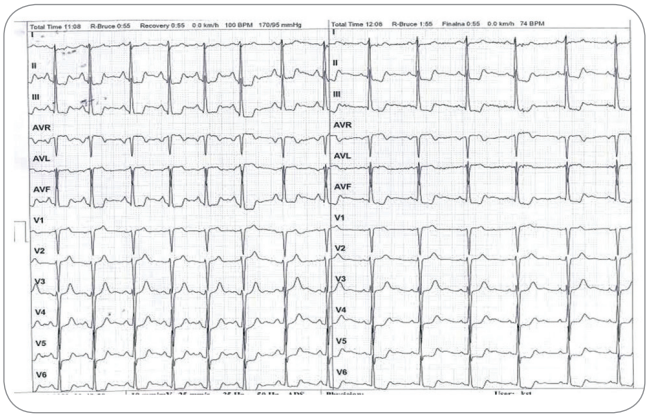

Fig. 3 ECG changes (V4-V6) during exersice coronary test

Coronary angiography was performed for suspected coronary artery disease. During left heart catheterization, systemic arterial pressure was normal and there was no gradient across the aortic valve. A left ventricular angiogram obtained in the right anterior oblique view revealed no regional wall motion abnormality. The Thrombolysis in Myocardial Infarction (TIMI) frame-count method was used to evaluate the degree of the slow antegrade filling. The corrected TIMI frame counts were observed to be 41 frames for the left anterior descending coronary artery (LAD) (Fig 4, 5). Coronary angiography revealed no stenosis of the right coronary artery (RCA) and left circumflex coronary artery (LCx). The angiogram showed normal coronary arteries without evidence of coronary vasospasm or an existing myocardial bridge. Slow flow, however, was noted in the left anterior descending artery (LAD). After 4 days of hospitalization patient was discharged from the hospital with advise for regular use of antihypertensive therapy, statins, dipiridamol and regular controls.

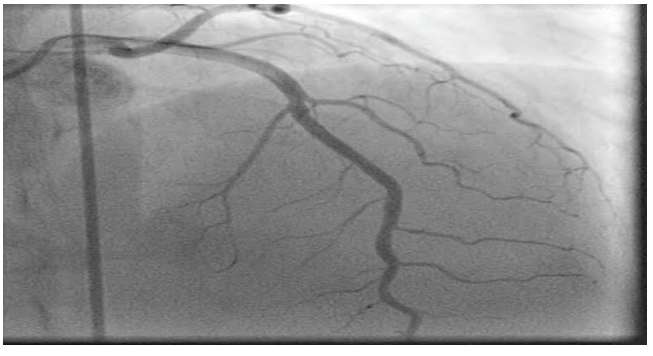

Fig.4 Coronary anatomy and flow of LAD

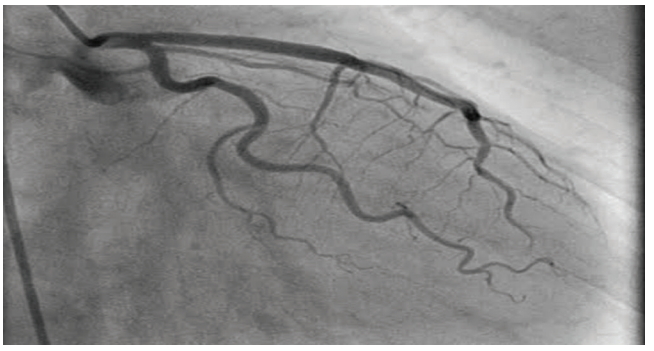

Fig.5 Coronary anatomy and flow of LAD

After two years of follow-up and regular ambulatory check-ups, patient continued to have occasional chest pain and we have decided to perform MPS. Myocardial perfusion scintigraphy showed reversible perfusion abnormalities of apical segment of anterior wall (6%) with good ejection fraction (Fig.6, Fig 7).

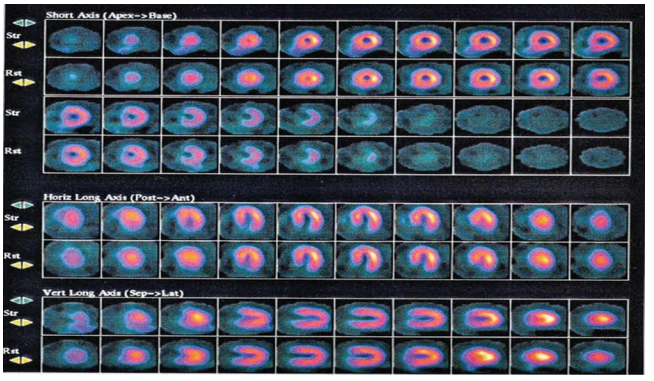

Fig .6 Segment analysis during MPS

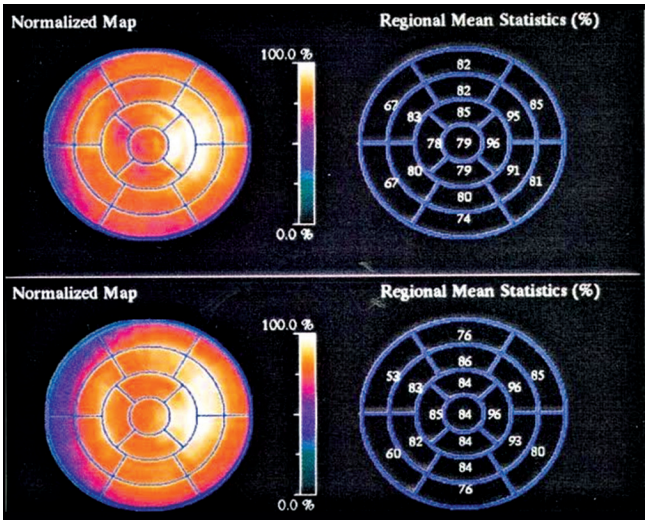

Fig.7 Regional wall abnormalities during MPS

DISCUSSION

This is a case of female patient with coronary slow flow phenomenon which is manifested with chest pain and

need further investigations to determine its etiology. Past medical history of dislipidemia and hypertension as well as family history of coronary artery disease increase her total risk for coronary artery disease development. She was treated with antihypertensive therapy, statins and occasionally aspirin. Clinical investigations especially treadmill exercise stress test was positive without regional wall motion abnormality on transthoracic echocardiographic evaluation. Coronary angiography showed normal coronary arteries without evidence of coronary vasospasm or significant stenosis but slow flow was noted in the left anterior descending artery (LAD). The possible pathophysiological mechanism for CSFP in our case may be a small vessel dysfunction based on observations including microvascular tone dysfunction, endothelial thickening of the small vessels, and impaired endothelial release of nitric oxide (NO). Patient was treated with regular medical therapy consisting of antihypertensive medications, statins and dipiridamol and further follow up showed improvement in her exercise tolerance.

CONCLUSION

Coronary slow flow phenomenon is not an infrequent angiographic finding and it contributes to higher cardiovascular morbidity. Coronary slow flow phenomenon usually has a benign long term outcome but may be associated with relapses. Occasional ventricular arrhythmias and even sudden cardiac death have been reported. Treatment modalities for CSFP are not well established and further studies are necessary.

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ANGINA PECTORIS СО БАВЕН КОРОНАРЕН ПРОТОК -ПРИКАЗ НА СЛУЧАЈ

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АБСТРАКТ

Цели: Феноменот на бавен коронарен проток е идентификуван како посебен клинички ентитет во 1972 кога дисталната опацификација на коронарната артерија е одложена на ангиографија во отсуство на значајна коронарна артериска болест.Тоа е чест наод, типичен кај пациенти кој имаат презентација на акутен коронарен синдром. Иако овој ентитет е добро познат кај интервентите кардиолози,патолошкиот механизам останува нејасен. Клиничките импликации се значајни,со повеќе од 80% од пациентите имаат повторувачки епизоди на градни болки резултирајќи со значајно нарушување на квалитетот на живот.

Методи, процедури и резултати: Презентираме клинички случај на пациент на 54 годишна возраст, женски пол кој се жали на повторувачки епизоди на градна болка. Физикалниот преглед е без специфични знаци. Пациентката има историја на покачени вредности на крвен притисок, дислипидемија повеќе од 5 години, генетска предиспозиција за коронарна артериска болест. Направивме лабораториски испитување, ЕКГ, ехокардиографија, 24 часовен холтер за крвен притисок, коронарен стрес тест, коронарна ангиографија и миокардна перфизуона сцинтиграфија после две години од хоспитализација. По направената коронарна ангиографија дијагнозата за феномен на бавен коронарен проток на LAD е потврдена. Пациентката беше следена две години и беше поставена на антихипертензивна, антилипемична терапија-статини и дипирадамол.

Заклучок: Феноменот на бавен коронарен проток не е редок ангиографски наод и придонесува за морбидитет. Овој феномен треба да биде сметан како посебен клинички ентитет со специфични карактеристики, патогенетски механизми и дефинирани дијагностички критериуми.

Клучни зборови: феномен на бавен коронарен проток, коронарна артерија, градна болка

АКУТЕН ПАНКРЕАТИТ ИНДУЦИРАН ОД ЛЕК

DRUG INDUCED ACUTE PANCREATITIS

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АПСТРАКТ

Акутен панкреатит е тешка болест со значителен морбидитет и морталитет. Акутниот панкреатит индуциран од лек е редок, со проценета инциденцата од 0,1-2%. Повеќе од 100 лекови биле вмешани во предизвикувањето на болеста: ацетаминофенот е поврзан со акутен панкреатит во случаите каде што има предозираност со овој лек. Сепак, честотата е мала. Врз основа на анализа на нивото на докази, 4 класи на лекови можат да бидат идентификувани.

Ви презентираме случај на 28-годишниот маж кој презентираше абдоминална болка и покачени панкреасни ензими укажувајќи на акутен панкреатит, тешка метаболна ацидоза и системски инфламаторен одговор синдром по предозирање на лек што содржи ацетаминофен. Тој земаше ацетаминофен повеќе од 5 g секој ден две недели. Дијагностицирањето вклучувајќи ултразвук, КТ скен, микробиолошки и серолошки анализи не успеа да открие никаква очигледна етиологија за панкреатитисот. Можноста за панкреатитис предизвикан од лекови се зеде во обзир и ацетаминофенот се мислеше дека е веројатно етиолошкиот агенс и беше прекинат. Преглед на релевантна литература исто така е претставена.

Акутениот панкреатит индуциран од лекови е предизвик за лекарите и деталениот механизам е непознат. Многу е важно да се исклучи панкреатитис предизвикан од лекови кога се лекува панкреатитис со непозната етиологија.

Клучни зборови: Приказ на случај. Лек индуциран. Ацетаминофен. Акутен панкреатитис.

ВОВЕД

Акутен панкреатит е воспалително заболување на панкреасот со ненадеен почеток. Може да биде во блага форма па до мултиорганска инсуфициенција. Дијагнозата се базира врз клиничките знаци поткрепени со лабараториски и радиолошки техники.

1,4% Од сите регистрирани панкреатити отпаѓа на акутен панкреатит индуциран од лекови, каде доминира женската популација и помладата возраст. Механизмите на повреда на панкреасното ткиво кај овај вид на панкреатит како и дијагностичките постапки се дискутабилни.

Целта на овај труд е да се прикажат дел од пронајдените податоци во врска со механизмот и дијагнозата на акутен панкреатит предизвикан од лекови, како и касификација на лековите предизвикувачи.

ПРЕЗЕНТАЦИЈА НА СЛУЧАЈ

28-годишниот маж кој презентираше абдоминална болка и покачени панкреатични ензими укажувајќи на акутен панкреатит, тешка метаболна ацидоза и системски инфламаторен одговор синдром по предозирање на лек што содржи ацетаминофен. Тој земал ацетаминофен повеќе од 5 g секој ден две недели. На прием крвен притисок 80/40 mmHg, пулс 150 удари во минута, диуреза помала од 0.5 ml/kg. Лабораториски анализи: RBC = 4.56, Hgb = 160, Hct = 0.46, ALT = 579 (0-40), AST = 525 (0-40), LDH = 5367 U/L,

Ca = 1.63, Na =141, K = 5.89, BUN = 9.25, Kreatinin = 396, Amylase = 3446; CRP = 376. pH = 7.15, pCO_2 = 3.47, pO_2 = 12.54, Be = - 19.7; Lactate = 14.59, Glucose = 7.78 , aPTT = 46s (33s).

Дијагностицирањето вклучувајќи ултразвук (панктеатит со едематозен панкреас и перипанкреатичен едем), КТ скен (ексудативен панкреатит со голема количина на течност околу панкреасот), микробиолошки и серолошки анализи не помогнаа во откривање на јасна етиологија за појавата на панкреатитот. Можноста за лек - индуциран панкреатит беше разгледана и ацетаминофенот се сметаше за можен етиолошки агенс поради што беше прекинат.

ДИСКУСИЈА

Акутен панкреатит е воспалително заболување на панкреасот со ненадеен почеток. Клиничките знаци може да варираат од блага форма кај повеќето пациенти до мулти - органска инсуфициенција и сепса кај околу 20% од пациентите [1, 2]. Дијагнозата на акутен панкреатит се базира врз внимателно клиничко испитување со супортивни докази од лабораториски и радиолошки техники [3]. Третманот на акутен панкреатит зависи од неговата тежина. Неколку прогностички модели се развиени со цел да се идентификуваат пациентите со висок ризик за развој на тежок степен на панкреатит. APACHE II скорот е прецизен и може да биде проценет во првите 24 часа по приемот. Ц-реактивниот протеин (CRP) е најпрактичниот предиктор, но е прецизен само по 48 часа [4]. Мерењето на трипсиноген активирачки пептид во урина е со ветувачки развој [5]

Лек - индуциран акутен панкреатит (АП) е ретко заболување. Првите извештаи се објавени уште во 1950 години на минатиот век, од Zion и соработниците и секоја година се зголемува листата на лекови поврзани со АП.(6) Постојат многу етиолошки ризик фактори за АП, вклучувајќи анамнеза за злоупотреба на алкохол, камења во жолчно кесе, ендоскопска ретроградна холангиопанкреатографија и манометрија, траума или хируршки процедури во близина на панкреасот, одредени лекови, хиперлипидемија, инфекција и хронична хиперкалцемија [7,8].

Дефиниција: „Значително штетна или непријатна реакција, која произлегува од интервенција поврзана со употреба на медицински производ, кој предвидува опасност од понатамошно администрирање и налага превенирање или специфичен третман, или менување на режимот на дозирање, или повлекување на производот“ [9].

Познавањето на вистинската инциденца на лек - индуциран АП зависи од клиничарите кои ги исклучиле другите можни причини и го пријавиле настанот. Може да биде тешко да се исклучат останатите причинители за АП, посебно кај пациентите кои имаат повеќе коморбидитети, користат повеќе лекови и имаат потенцијални непознати базични ризик фактори. Ретроспективна студија спроведена во Германија констатира дека инциденцата на лек - индуциран АП е 1,4% [10]. Едно национално истражување извршено во Јапонија во 1999 година, објави дека 1,2% од сите случаи на АП биле предизвикани од лекови [8]. Лек - индуциран АП е редок, но треба да се земе во обзир кај пациент кој презентира идиопатски АП. Неколку популации со висок ризик биле идентификувани при истражување на лек - индуцирани панкреатити. Предиспонирачки демографски карактеристики се женски пол и помлада возраст. Односот маж/жена е обратен во однос на другите типови на акутен панкреатит, најмалку 1:1.3. Исто така почесто се среќава кај помлади пациенти, со исклучок кај деца [11,12]. Зголемениот ризик кај постери пациенти кои користат повеќе лекови се смета за бајас: ризикот е во употербата на повеќе лекови кај поголемиот дел од оваа популација отколку самата возраст [13]. Три видови на заболувања биле препознаени како најчести предиспонирачки здравствени фактори: воспаленија на мочен меур, ХИВ инфекција и карцином третиран со комбинирана хемотерапија [14]. Помеѓу причините зошто не се знае вистинската инциденца на лек - индуцираниот акутен панкреатит, најверојатно најзначајни се потешкотиите во поставувањето на дијагнозата. Како што е вообичаено со поголемиот дел од идиосинкратски несакани реакции на лекот, не е достапен специфичен тест за поставување на дијагноза за лек - индуциран панкреатит [15]. Според тоа, дијагнозата обично се базира врз следниве критериуми:

А. Акутен панкреатит се појавува во тек на администрирање на лек;

Б. Сите останати чести причинители се исклучени;

В. Симптомите на акутен панкреатит исчезнуваат после повлекувањето на лекот;

Г. Симптомите повторно се појавуваат по повторното вклучување на суспектниот лек.

Знаеме дека активирањето на трипсинот може да доведе до автодигестија на панкреасот и последователно до акутен панкреатит, но механизамот со кој одредени лекови може да предизвикаат панкреатит не е познат [16, 17]. Обично се среќаваат два можни механизми на повреда на панкреасот предизвикана од лекови, но уште три механизми исто така треба да се споменат:

А. Директен токсичен ефект врз панкреасното ткиво;

Б. Идиосинкратска реакција;

В. Влијанието на лекот врз протокот на жолчката;

Г. Засилување на директниот токсичен ефект на етанолот врз панкреасното ткиво;

Д. Секундарно оштетување на панкреасот.

Директното токсично оштетување на панкреасното ткиво е слично на хепаталното оштетување предизвикано од некои лекови или нивните метаболити (на пр. парацетамол). Иако акутен панкреатит понекогаш се развива во услови на предозирање со некои лекови, неговата инциденца останува толку ретка што основната предиспозиција мора да игра улога кај овие случаи - Генетски предиспонирачки фактор. Само неколку видови на лекови се пријавени како предизвикувачи на DIP, при предозирање со: парацетамол (или ацетаминофен), еритромицин и карбамазепин. Исто така, се претпоставува кумулативен дозно - зависен ефект на токсични метаболити - валпроат, диданосин, тамоксифенот, хлоротиазид и естроген [18].

Идиосинкратска реакција - Силна корелација со некои имунолошки заболувања (главно Кронова болест и ХИВ инфекции) имплицира имунолошки посредувана реакција како главен предизвикувачки фактор на болеста. Имуно - посредуваниот процес е несомнено патогенската природа на многу чести несакани реакции поврзани со лековите споменати погоре, како лек - индуциран перикардитис, лупус налик синдром како и некои типови на лек - индуцирани оштетувања на црниот дроб. Можно е сите овие реакции да имаат заедничка имуно - посредувана природа и специфичниот орган е повреден всушност „случајно“ како моментално место со помал отпор (*locus minoris resistentiae*) [19].

Останатите три механизми не се толку ирелевантни како што изгледаат. Неколку лекови инволвирани во акутен панкреатит се вклучени предизвикувајќи холестатска повреда на црниот дроб, на пр. азатиоприн, цитарабин, естрогени и еритромицин. Кодеинот, морфинот и некои други лекови можно е да предизвикаат спазам на Оди - евиот сфинктер. Исто така, е опишана појавата на лек - индуциран панкреатит кај пациенти кои конзумираат алкохол, но на ова прашање не е посветено многу внимание. Секундарна повреда на панкреасното ткиво исто така е можно кај некои лекови. Индиректните ефекти на лековите врз панкреасот опфаќаат исхемија (азатиоприн, диуретици), хиперкалцемија (тиазидни диуретици), тромбоза на панкреасните крвните садови (естрогени), како и зголемување на вискозноста на панкреасот сок (диуретици, пентамидин) [20].

За жал, податоците за лек - индуциран панкреатит остануваат оскудни и повеќето се собирани од експериментални истржувања, прикази на случаи како и контролни студии.

Во 1991 година Mofenson HC, Caraccio TR пријавиле случај на акутен панкреатит поврзан со предозирање со ацетаминофен. Исто така, во 2009 година Roman Fernandes пријавил панкреатит предизвикан од ацетаминофен.

Осумстотини и четиринаесет пациенти со труење со парацетамол биле анализирани и само триесет и три пациенти биле дијагностицирани со парацетамол асоциран акутен панкреатит [21].

Друга студија спроведена во Данска испитала 602 пациенти примени со предозираност со парацетамол. Студијата открила 33 случаи на парацетамол - асоциран акутен панкреатит [22].

Bulera открил: Кај глувци, парацетамол - арелирани протеини се детектираат во панкреасното ткиво уште по 4 часа од администрирањето на токсична доза на парацетамол, што оди во прилог дека панкреасот е директно подложен на токсичноста на парацетамолот [23].

Su и соработниците во 2006 година, откриле појава на умерен панкреатит кај глувци, стаорци и кучиња после администрација на церулин [24].

Dawra и соработниците во 2007 година, кај глувци и стаорци утврдиле појава на панкреатит после интраперитонеална апликација на Л- аргинин [25].

Во критички осврти од 1980, потенцијалот на лекот да предизвика АП бил проценет како дефинитивен, веројатен и можен [26, 27]

Во 2005 Trivedi и Pitchumoni ги класифицирале ризичните лекови врз база на истражување на пријавени случаи во Националната библиотека за Медицина / Пабмед од 1966 до 2004. Лековите биле групирани во Класи I-III [14].

Исто така, Badalov и сор. разгледале Medline извештаи на лек - индуциран АП од 1955 до 2006. Авторите ги класифицирале пријавените лекови во четири класи врз база на објавената тежина на доказ за секој агенс и моделот на клиничка презентација. Класа I вклучуваат лекови кои најмалку во еден случај е опишано повторување на акутниот панкреатит при повторно конзумирање на лекот. Класа II вклучуваат лекови кај кои постои латентност во 75% или повеќе од пријавените случаи. Класа III вклучуваат лекови кои имаат два или повеќе случаи објавено, но ниту при повторно конзумирање, ниту до присутен латентен период. Класа IV се лекови слични со калса III, но само еден случај бил објавен [28].

До денес, постојат 525 различни лекови во базата на податоци на СЗО, кои можат да предизвикаат акутен панкреатит. Но, само неколку лекови имаат доволно силна база на докази за да бидат јасно поврзани со оваа ретка несакана реакција. Тие се наведени во:

Класа на лекот	Име на лекот	Ризична класа Trivedi	Ризична класа Badalov	Вообичаен почеток на латентност
Аналгетици	кодеин*	I	Ia	1 ден
	Парацетамол	II	II	1 ден
	Сулиндак	I	Ia	“/ 30 дена
Анестетици	Пропофол	III	II	1 ден
Антидијабетици	ексенатид*	-	-	
	ситаглипин*	-	-	
Анти - инфективни				
Антивирални	Диданозин	I	II	“/ 30 дена
	Ламивудин	II	Ib	
Антибактериски	Котримоксазол	I	Ia	1 – 30 дена
	Еритромицин	II	II	1 ден
	Тетрациклин	I	Ia	
Антипаразитски агенси	Пентамидин	I	Ib	1 – 30 дена
	стибоглуконат*	I	Ia	1 – 30 дена
Антиконвулзиви	Валпроат	I	I и II	“/ 30 дена
Антинеопластични агенси	Аспарагиназа	I	II	1 – 30 дена
	Цитарабин	I	Ib	1 – 30 дена
Кардиоваскуларни лекови				
АЦЕ инхибитор*	Еналаприл	II	Ia	“/ 30 дена
Диуретици	Фуросемид	I	Ib	
Статини*	Правастатин	III	Ia	“/ 30 дена
Гастроинтестинални лекови	месалазин	I	Ia	1 – 30 дена
	Омепразол	III	Ib	“/ 30 дена
Стероидни хормони	естрогени*	I	Ib	“/ 30 дена
	глукокортикоиди*	I	Ib	1 – 30 дена
Имуносупресиви	Азатиоприн	I	Ib и II	1 – 30 дена
	Сулфасалазин	I	Ia	1 – 30 дена

Лекови обично асоцирани со лек - индуциран панкреатит (* класа ефект веројатен) [28]

Третманот на лек индуциран панкреатит не се разликува од третманот на панкратитите од друга етиологија. Дискутабилна и загрижувачка е употребата на лекови во случаевите каде немаме сигурна потврда на лек пердизвикувач. Се препорачува лековите со помал ризик да се вклучат први, да не се внесуваат

повеќе лекови истовремено, а суспектните лекови да се заменат со нивните аналози со друга хемиска структура [29].

Ако ацетаминофенот е докажан како причинител и станува збор за предозирање веднаш се започнува со N-acetylcystein. Исто така нотиран е еден случај на употреба на континуирана артериовенска хемофилтрација за третманот на метаболната ацидоза предизвикана од ацетаминофенот но и континуираната хемодиафилтрација може да биде ефикасна [30,31,32].

ЗАКЛУЧОК

Лек - индуцираниот акутен панкреатит е многу ретка причина за панкратитит. Патофизиологијата на болеста не е детално позната. Голем предизвик е за лекаририте и е многу важно да се исклучи лек - индуциран панкреатит при лекување на панкреатит со непозната етиологија.

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DRUG INDUCED ACUTE PANCREATITIS

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ABSTRACT

Acute pancreatitis is a severe disease with considerable morbidity and mortality. Drug-induced acute pancreatitis is rare, with an estimated incidence of 0.1-2%. More than 100 drugs have been implicated in causing the disease: acetaminophen has been associated with acute pancreatitis in cases where there has been an overdose of drugs; however, the frequency is rare. Based on analysis of the level of evidence, 4 classes of drugs could be identified.

We report the case of a 28-year-old man who presented abdominal pain and elevated pancreatic enzymes suggesting acute pancreatitis, severe metabolic acidosis and systemic inflammatory response syndrome after overdosing on a drug containing acetaminophen. He was taking acetaminophen more than 5 g every day two weeks.Workup including an ultrasound,CT scan, microbiological and serological analysis failed to reveal any obvious etiology for the pancreatitis. The possibility of drug-induced pancreatitis was considered and acetaminophen was thought to be the probable etiologic agent and discontinued. A review of the relevant literature is also presented.

Drug-induced acute pancreatitis is challenging for clinicians and a detailed mechanism is unknown. It is very important to rule out drug-induced pancreatitis when treating pancreatitis with an unknown etiology.

Keywords: Case report. Drug induced. Acetaminophen, Acute pancreatitis.

VASA PREVIA-RËNDËSIA E DIAGNOSTIKIMIT

VASA PREVIA, THE IMPORTANCE OF DIAGNOSIS

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ABSTRAKTI

Vasa Previa është një gjendje e rrallë por mjaft e rëndë në të cilën enët e gjakut të kordonit umbilikal të fetusit kalojnë përgjatë orificiumit uterin të brendshëm (hapja e brendshme e qafës së mitrës). Këto enë të gjakut shpërndahen brenda membranave amnionale, të pambrojtura nga kordoni umbilikal ose indi i placentës dhe paraqesin një rrezik për rupturë në rast të dëmtimit të pjesës së membranave ku janë të ngjitura. Vasa previa bartin një përqindje të lartë të mortalitetit, 50% e rasteve të padiagnostikuara mbarojnë me vdekje të fetusit. Fatmirësisht kjo gjendje është e rrallë dhe paraqitet 1 në 2000 shtatzani.

Qëllimi i punimit: Qëllimi i punimit ishte të fokusohet mbi rëndësinë e zbulimit të hershëm të pranisë së vasa previa tek një grua shtatzënë dhe në këtë mënyrë të kemi mundesinë që të planifikojmë lindjen në kohe si dhe të intervenohet në mënyrë korrekte pas zbulimit të kësaj patologjie.

Materiali dhe metodat: Kemi paraqitur një paciente e cila u shtrua në spitalin tonë pasi u diagnostikua me pëlcitje të parakohshme të membranave amnionale dhe gjakderdhje ex utero në javën e 35 të shtatzanisë.

Rezultati: Gjatë ekzaminimit te placentës dhe cipave amnionale me sy të lirë, janë konstatuar ndryshime të dukshme të enëve të gjakut të kordonit umbilikal, prania e enëve të gjakut në membrana dhe inserimi velamentoz i kordonit.

Përfundimi: Është e rëndësishme që të vlerësohet prania e gjakderdhjeve gjatë shtatzanisë për të përcaktuar saktë origjinën e saj dhe për të përshtatur në kohë trajtimin adekuat të rastit.

Fjalët kyç: kordoni umbilikal, vasa previa, gjakderdhje ex utero.

HYRJE

Një ekzaminim i shtatzanës me kujdes të vecantë për gjendjen e placentës dhe membranave amnionale sidomos gjatë fazës aktive të lindjes, në dhomën e lindjes së pacientes, jep një informacion të rëndësishëm për nënën dhe frytin. Gjatë ekzaminimit të placentës duhet të vlerësohet: madhësia, trashësia, konsistenca dhe tërësia e saj e gjithashtu edhe prania e lobeve shtesë, infarktet placentare, hemoragjitë, tumorët dhe nodulet. Kordoni umbilikal duhet të vlerësohet për gjatësinë, kapjen apo ngjitjen e tij, numrin e enëve të gjakut, praninë e nyjeve dhe praninë e substancës Wharton. Duhet të vlerësohet edhe ngjyra, tejdukshmëria dhe aroma e membranave fetale si dhe prania e enëve të gjakut në membrane [1,3,8].

Placenta pas daljes së saj në lindjet në kohë, është e gjatë 22 cm dhe 2.5 cm e gjerë, peshon përafërsisht 470 gram. Sipërfaqja maternale e placentës është me ngjyrë të mbyllur dhe e ndarë në lodule ose siç quhen ndryshe kotiledone. Kjo strukturë e kotiledoneve duhet të jetë komplete pa mungesë të tyre. Sipërfaqja fetale e placentës është e shëndritshme me ngjyrë të hirtë dhe të tejdukshme. Në lindjet në kohë, gjatësia e kordonit umbilikal është 55 deri 60 cm dhe gjërësi 2.0 deri 2.5 cm [2,4,5,7].

Kordoni normal umbilikal përbëhet prej dy arterieve dhe një vene. Abnormalitetet e inserimit të kordonit umbilikal:

Kordoni umbilikal normalisht është i ngjitur afër qendrës së sipërfaqes fetale të placentës. Ngjitja Furcate: Në raste të rralla enët e gjakut të kordonit umbilikal ndahen nga substanca e kordonit para ngjitjes brenda në placentë. Ngjitja Marginale: Është ngjitje e kordonit në pjesën marginale të placentës. Është gjetur në 7% të

placentave të lindura pas lindjes në kohë (Benirschke dhe Kaufmann 2000). Ngjitje Velamentoze: Kordoni umbilikal është i ngjitur në membranat amnionale. Benirschke dhe Kaufmann (2000), ndoqën 195,000 lindje dhe gjetën këtë ngjitje vetëm në 1.1% te rasteve. Ngjitja velamentoze shfaqet më shumë tek shtatzanitë binjake ndërsa Feldman me bashkpunëtorë (2002) e gjetën në 28% të shtatzanive me trenjakë [1,10].

Vasa Previa paraqet një patologji e cila e shoqëruar me ngjitje velamentoze të kordonit ka të bëjë me praninë e vazave fetale të gjakut në membranat amnionale dhe pikërisht në regjionin e pjesës prezantuese të fetusit. Lee me bashkpunëtorë (2000) ekzaminuan regjionin e qafës së mitrës me ekografi 94,000 gra shtatzana në tremujorin e tretë të shtatzanisë. Vasa previa u gjet ne 18 paciente pra një incidence prej 1 në 5200 shtatzani. Gjysma e tyre u diagnostikuan edhe me inserimin velamentoz të kordonit umbilikal, kurse gjysma tjetër i përkisnin inserimit marginal dhe inserimit në lobin succenturiate të pranishëm të placentës [1,4,10].

Për shkak të sensitivitetit të ulur të pamjeve të vasa previa me ultratingull, ekzaminimi me color Doppler është i rekomanduar nëse ka dyshime për vasa previa (Harris dhe Aleksander, 2000; Lee me bashkpunëtorë, 2000; Nomiyama me bashkpunëtorë, 1998). Në një studim tek 155 raste nga Oyelese me bashkpunëtorë (2004), diagnoza prenatale u shoqërua me rritje të mbijetesës tek keto paciente prej 97 deri ne 44% [1,5,6,9].

Në një studim tjetër Fung dhe Lau (1998), gjetën se në rastet e pranisë së placentës me inserim të ulur (low-lying placenta), rreziku për praninë e vasa previa shkonte deri në 80%. Ata gjithashtu gjetën që diagnoza antenatale shoqërohej me ulje të mortalitetit fetal krahasuar me diagnozën gjatë lindjes. Oyelese me bashkpunëtorë (1999) rekomanduan bërjen e ekzaminimit me ultratingull bashkë me color Doppler për pacientet ku ishin të pranishëm faktorët e rrezikut. Këta faktorë përfshijnë: placenta me dy lobe, succenturiate, inserim i ulur i placentës, shtatzani multifetale dhe shtatzani përmes IVF.Në një studim 8 vjeçar ku u përfshinë 90,000 paciente dhe tek të cilat ishte bërë ekzaminimi me ultratingull dhe ku ishe parë prania e "linjave ehogjenike paralele ose cirkulare afër cervixit", u preferua të bëhej edhe ekzaminimi me color Doppler. Kështu u bë e mundur që të detektohet vasa previa tek pacientet asimptomatike qysh në tremujorin e dytë.Në rastet e hemoragjise antepartum ose intrapartum, ekziston mundësia e pranisë së vasa previa dhe ruptures së enëve të gjakut të fetusit [1,9,10].

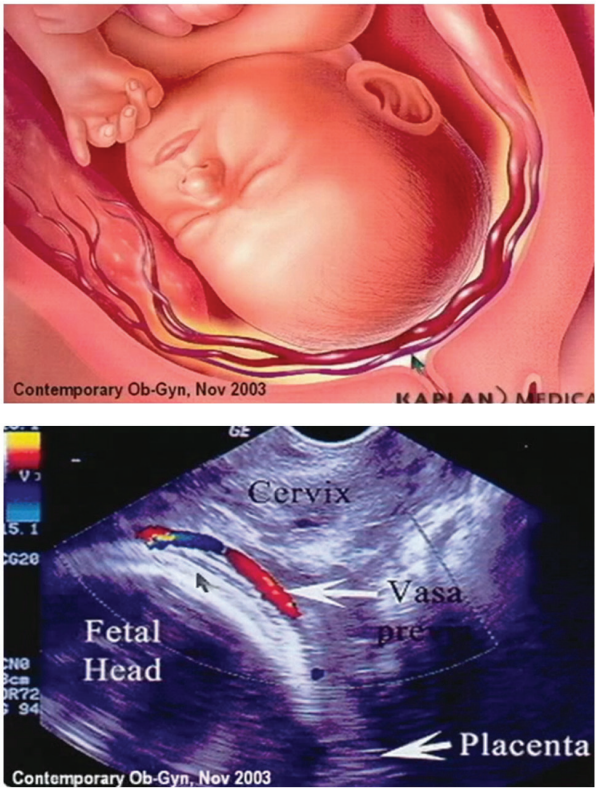

Fig.1. Paraqitje skematike e enëve të gjakut poshtë pjesës prezantuese dhe pamje e color Dopplerit në enët e gjakut

QËLLIMI I PUNIMIT

Qëllimi i punimit ishte të fokusohet mbi rëndësinë e zbulimit të hershëm të pranisë së vasa previa tek një grua shtatzënë dhe në këtë mënyrë të kemi mundesinë që të planifikojmë lindjen në kohe si dhe të intervenohet në mënyrë korrekte pas zbulimit të kësaj patologjie.

MATERIALI DHE METODAT

Është marrë në studim pacientja në javën e 35 të shtatzanisë, me gjakderdhje ex utero, në Spitalin Special për Gjinekologji dhe Obstetrikë në Çair-Shkup. Janë bërë analizat e nevojshme laboratorike, hematologjike, urinare, ekzaminimi me ultrasonografi, ekzaminimi i frytit in utero me anë te kardiotokografisë si dhe ekzaminimi bimanual i pacientes. Placenta dhe cipat amnionale kanë shërbyer për dallimin makroskopik të pranisë së vasa previa si dhe për ngjitjen velamentoze të kordonit umbilikal.

PREZANTIMI I RASTIT

Pacientja N.Z. e lindur në vitin 1991, e martuar, me shkollim të mesëm dhe amvise me profesion është paraqitur në Spitalin Gjinekologjik-Obstetrik " Nëna

Tereze" në Çair me datë 02.09.2015 në ora 21:40. Ankesat: gjakderdhje ex utero menjëherë pas pëlcitjes spontane të membranave amnionale, rrjedhje e lëngut amnional i përzier me gjak të freskët dhe dhimbje të lehta në pjesën e poshtme të barkut dhe pjesën e poshtme të shpinës. Bëhet ekzaminimi gjinekologjik bimanual (me anë të dy gishtave) dhe gjendja ka qenë: Vagina me thellësi normale e kalueshme për 3 gishta, porcioni i vaginës dhe mitrës i gjatë 1cm, orificiumi i jashtëm uterin 3 cm, dhe prekën pjesë të imta të frytit si pjesë prezantuese, cipat amnionale të pëlcitura para 15 minutave (ashtu siq referon pacientja). Nga vagina rrjedh gjak i freskët.

Në ndërkohë mirret edhe anamneza prej pacientes. Pacientja gjatë kësaj shtatzanie e cila ishte e dyta me rradhë (shtatzania e parë ka përfunduar në termin me lindje spontane, gjinia mashkull me peshë totale të lindjes 3550 gram), ka bërë gjithsej 6 ekzaminime me ultrasonografi, gjithashtu është ekzaminuar edhe për skrining dhe Doppler në javën e 21 të shtatzanisë. Pacientja pin cigare (deri në 15 në ditë), dhe nuk pin alkool. Mohon sëmundjet e kaluara gjatë fëmijërisë si dhe sëmundjet në familje. Bëhet majta e tensionit arterial i cili ishte 135/70 mmHg, pulsi 70 rrahje në minutë.

Mirret gjaku për pasqyrë të gjakut (Le: 12.06, Er: 3.92, Hgb: 102, Hct 0.30, PLT: 185), dhe bëhet ekzaminimi me echo për të verifikuar rrahjet e zemrës fetale dhe biometrinë. Biometria i përgjigjej moshës së shtatzanisë për 35 javë gestative dhe rrahjet e zemrës fetale ishin pozitive.

Pacientja pranohet në spital me diagnozën e pranimit: *Graviditas 35 javë gestative. RVS. Partus praetemporarius incipiens. Metrorrhagia.*

Pas kësaj pacientja transportohet në repartin e sallës së lindjes dhe pas përgaditjes së shpejtë (kateterizimi i fshikzës urinare), dërgohet në sallë të operacionit dhe vendoset që lindja të kryhet me operacion për shkak të gjakderdhjes ex utero. Lindja përfundohet me prerje Cesariane, fryti tërhiqet për këmbësh pasi ato ishin pjesë prezantuese dhe në ora 22:20 të po kësaj date nxirret fryt i gjallë i gjinisë mashkull me peshë totale të lindjes 2350 dhe gjatësi 48 cm, Apgar Score 4/7 të vlerësuar nga ana e Neonatologut që ishte prezent gjatë lindjes. Placenta nxirret me dorë dhe pas nxjerrjes së saj vlerësohet me kujdes ajo. Vihet re që kordoni umbilikal kishte inserim velamentoz dhe gjithashtu enët e gjakut të kordonit ishin të vendosura në membranat amnionale.

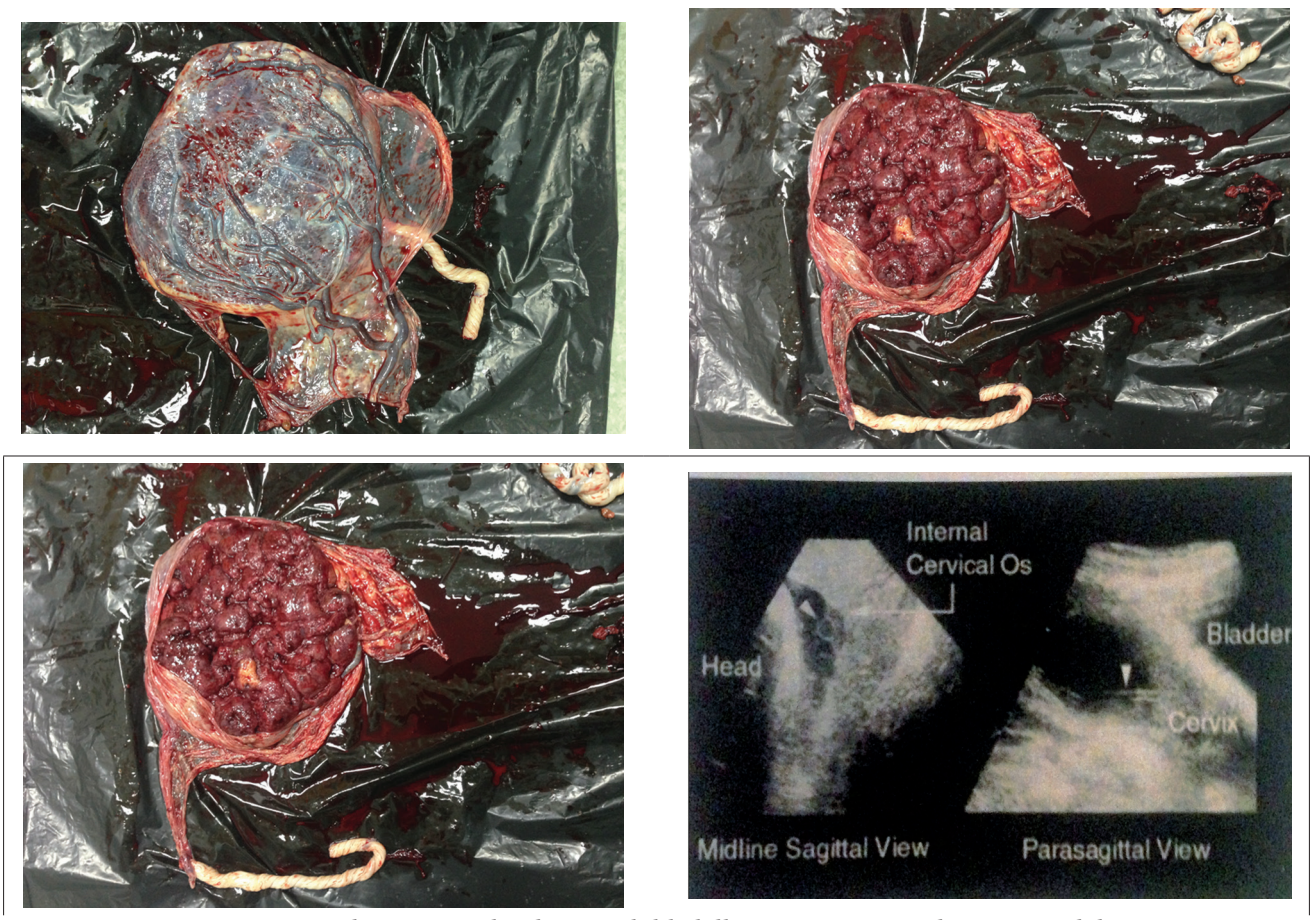

Fig.2. Pamje e inserimit velamentoz të kordonit umbilikal dhe vasa previa në placentë pas daljes së saj.
Reparti: Sallat e Operacionit, Spitali Special Obstetrik-Gjinekologjik, Çair, Shkup

Si përfundim, pacientja e përballoi mirë intervenimin ndërsa fëmiu përcillet për në repartin e Neonatologjisë për trajtim të mëtutjeshëm. Në fazën postoperative është ordinuar terapia me uterotonikë, antibiotikë, analgjezikë dhe infuzione. Pasqyra e gjakut e datës 03.09.2015: Leukocitet: 14.85, Eritrocitet: 3.81, Hemoglobina: 99, Hematokriti: 0.29, Trombocitet: 185. Diagnoza e lëshimit: *Graviditas 35 javë gestative. RVS. Praesentatio pedes. Insertio velamentosa funiculi umbilicalis.Vasa Previa. Partus praetemporarius cum Sectio Cesarea sec. Dorfler. Laparatomia transversalis sec. Pfannenstiel.*

DISKUTIMI

Autorët preferojnë që kur diagnostikohet vasa previa, duhet të bëhet Sectio Cesarea para fillimit të lindjes për të shpëtuar jetën e frytit. Sectio Cesarea duhet të bëhet sa më herët për të shmangur urgjencat e ndërhyrjes por edhe sa më vonë që të jetë e mundur për ti shmangur problemet që vinë nga prematuriteti [6.9,10].

Gjithashtu në rast të diagnostikimit të hershëm të vasa previa sipas autorëve tjerë, duhet te mirret në konsideratë administrimi i kortikosteroideve prej javës së 28 deri në të 32 dhe pacienjta duhet të hospitalizohet në javën e 30-32 [11].

Madje disa autorë preferojnë të bëhet screening rutinë për vasa previa në javën e 18 deri 20 të shtatzanisë për të parë lokalizimin e kordonit umbilikal dhe vlerësimin se a ekziston një lob shtesë i placentes apo jo [1,4,8,9,10].

Ashtu si në spitalin tonë edhe autorët tjerë mendojnë që lindja detyrimisht duhet të kryhet me Sectio Cesarea të planifikuar dhe ate para fillimit të lindjes. Për aq kohë sa qafa e mitrës është e mbyllur pacientja duhet të monitorohet me ultratingull kurse hospitalizimi i pacientes dhe eventualisht kryerja e lindjes bëhet nga java e 35 [2,3,6,11].

PËRFUNDIMI

Triada e njohur në rastin e vasa previa: Pëlcitje spontane ose artificiale e membranave amnionale, gjakderdhje vaginale dhe bradikardi fetale. Gjakderdhja në këto raste është gjak fetal ndërsa inserimi i placentës është normal, kordoni umbilikal merr origjinën në membrana e jo në diskun e placentës siç ndodh normalisht (janë enët e gjakut të cilat kalojnë nëpër cervix e jo placenta). Faktorët e rrezikut janë: Inserimi velamentoz i kordonit, prania e lobit shtesë të placentës dhe shtatzanitë multiple. Trajtimi është operativ me Sectio Cesarea, ndërsa komplikim serioz është vdekja fetale që vjen si rezultat i hipovolemisë.

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VASA PREVIA, THE IMPORTANCE OF DIAGNOSIS

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ABSTRACT

Vasa previa is rare but devastating condition in which fetal umbilical cord blood vessels cross or run in close proximity to the inner cervical os (the internal opening in the cervix separating the uterine cavity from the vagina). These vessels course within the membranes, unsupported by the umbilical cord or placental tissue, and are at risk of rupture if the supporting membranes are damaged. Vasa previa carries a high mortality rate, 50 % of undiagnosed cases end in the death of the fetus. Fortunately this condition is rare, occurring in only one out of every 2000 pregnancies.

The aim: The aim was to focus on importance of early discovery of vasa previa in pregnant women and by this to have an opportunities to plan delivery in time and to do the correct intervention after this.

Methods: We presented a pregnant women hospitalizated in our hospital after she was diagnosed with premature rupture of membranes and ex utero bleeding at the 35 weeks of pregnancy. Placenta, umbilical cord and membranes were examinated for macroscopic changes of vasa previa.

Results: During the macroscopic examination of the placenta and membranes we determine significant changes of vessels of umbilical cord, the presence of blood vessels through the membranes and the velamentous insertion of cord.

Conclusion: It is very important to evaluate the bleeding during pregnancy to defined the origin of blood and to undertake appropriate ways for adequate and effective treatment.

Key words: umbilical cord, vasa previa, ex utero bleeding.

OCULAR DISORDERS IN DOWN SYNDROME

ОКУЛАРНИ ПОРЕМЕТУВАЊА КАЈ ДАУН СИНДРОМ

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ABSTRACT

Introduction: Down syndrome is the most common chromosome anomaly. Patients with Down syndrome have an increased risk of a number of health problems including ocular disorders.

Aim: To identify the ocular disorders in patients with Down syndrome.

Material and methods: Seven patients with Down syndrome were treated for a period of 18 months at the University Eye Clinic in Skopje. The patients were at the age between 3 years and 39 years.

Results: Ocular findings in our patients were the following: epicanthal folds, cataract, hypermetropia, strabismus, astigmatism, myopiaalta, blepharitis and blepharoconjunctivitis.

Conclusion: Early diagnosis and treatment of the ocular disorders at the patients with Down syndrome has enabled them improved quality of life and has minimized their disability.

Key words: Down syndrome,ocular disorders.

INTRODUCTION

Down syndrome is the most common chromosome anomaly [1,2]. This syndrome is caused by a duplication of all or part of chromosome 21 by making three copies of the chromosome rather than the usual two copies. The possibility of having a baby with Down syndrome increases with the age of the parents, primarily the mother [3]. Recent advances in prenatal diagnosis have allowed the earlier detection, in utero, of chromosomal anomalies [4]

The frequency of Down syndrome is approximately 1 in every 800 to 1000 births [5]. Patients with Down syndrome nearly always have physical and intellectual disabilities [6-8]. They have also an increased risk of a number of other health problems including congenital heart disease, leukemia and thyroid disorders [1]. Current data suggests that these patients are at risk for variety ocular disorders [1,5,9]. Fortunately, many of these eye problems can be treated, especially if discovered at early age.

Life expectancy is around 50 to 60 years in the developed world with proper health care [9].

AIM

To identify the ocular disorders in patients with Down syndrome.

MATERIAL AND METHODS

Seven patients with Down syndrome were treated for a period of 18 months at the University Eye Clinic in Skopje. The patients were at the age between 3 years and 39 years. The ophthalmological examination included:

- global inspection of orbit and bulbus oculi,
- evaluation of visual acuity,
- evaluation of ocular motility,
- cover test,
- slit-lamp biomicroscopy,

- tonometry,
- cycloplegicskiascopy and
- ophthalmoscopy.

Snellen letters, numbers, or picture charts were used to assess visual acuity.

Tonometry was performed through using of contactless tonometer.

Cycloplegicskiascopy was performed, 45 minutes after three to five installations of one drop cyclopentolate 1%.

Emmetropia was defined as a refractive error between -0,75diopter (D) spherical equivalent and +0,75 D spherical equivalent [1]. Myopia was defined as less than -0,75Dspherical equivalent, and hypermetropia was defined as more than +0,75D spherical equivalent. Astigmatism was defined as refractive error more than +/-0,75D of cylinder [1].

RESULTS

Ocular findings in our patients were the following:

- epicanthal folds (2patients),
- blepharitis (1 patient),
- blepharoconjunctivitis (1 patient),
- cataract (1 patient),
- hypermetropia (2 patients),
- strabismus (2 patients),
- astigmatism (1 patient),
- myopiaalta (1 patient).

Some of the patients with trisomy 21 had more than one ocular disorder.

We have performed conjunctivitis swab with antibiogram on the patient with blepharoconjunctivitis, through which a Streptococcuspneumoniaewas isolated and a local antibiotic therapy was ordinated after the antibiogram. (photo.

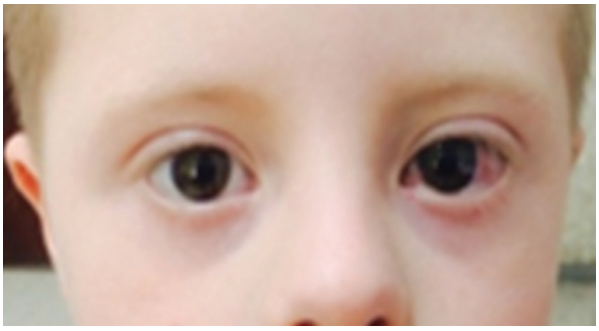

Photo 1. Blepharoconjunctivitisacuta on the left eye

The patient with chronicalblepharitis was advised for a treatment of eyelid hygiene and topical antibiotics.

An operation of phacoemulsification of the lens with implantation of IOL was performed on the patient with age of 39 years, suffering from presenile cataract on the both eyes as well as myopia alta (according to the preoperational performed biometry, IOL in PC of +15,0D on both eye was implanted). (Photo2) Post operationally, his visual acuity was 6/9 cum IOL on both eyes.

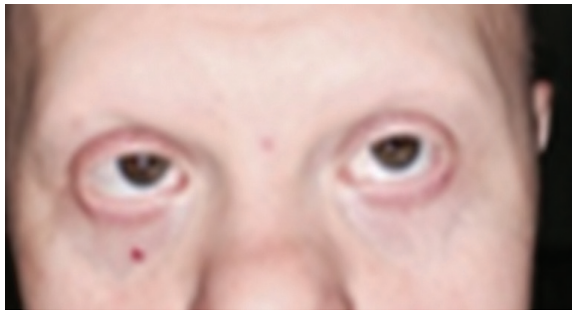

Photo 2. Patient with Down syndrome after cataract surgery on both eyes

After the performed cycloplegicretinoscopy and auto refractometry on the patients with hypermetropiaand astigmatismushypermetropicus, eyeglasses were ordinated to them.

The patients with strabismus, after glasses prescription, have been given an advice for patching for the treatment of amblyopia. (Photo 3)

Photo 3. Patient with strabismus and astigmatismushypermetropicus

DISCUSSION

About 60% of patients with Down syndrome have ophthalmicdisorders.(9) A number of conducted studies so far for analysis of eye and visual disorders on patients with trisomy 21, in which a larger number of patients were included over a longer period, aside for the previously stated ocular changes and refractive anomalies, the following was additionally diagnosed:keratoconus,

retinal anomalies, congenital nasolacrimal duct obstruction,congenital glaucoma,iris anomalies (Brushfield spots, stromal hypoplasia) and nystagmus [(1, 5,10-12].

Patients with Down syndrome may develop amblyopia due to strabismus, refractive errors, or media opacities associated to corneal hydrops or cataracts.

As more patients with Down syndrome live into adulthood, the ophthalmologist plays an increasing role in allowing them to lead productive and meaningful lives [13].

Some authorities recommend an ophthalmic evaluation in infants with Down's syndrome within the first 6 months of life, with subsequent follow up examinations to be performed every 1-2 years during childhood and adolescence [5,14]. The aim of this is early detection and therapy of high ametropia, strabismus, amblyopia, nystagmus and cataractand achievement of best possible visual results [5].

For adults with Down syndrome, it is advised that they should perform ophthalmological examinations, at least on every two years and even more frequent in case of already diagnosed specific ophthalmological disorder [9]. By doing so, the possible complications will be diagnosed on time, which will enable their treatment and a reduction of visual acuity will be prevented.

CONCLUSION

Appearance of different ocular disorder findings has caused the necessity for an ophthalmic screening program for the persons with Down syndrome.

The early recognition, diagnosis and treatmentof ocular disorders in patients with Down syndromeimprove the quality of life they live and minimize their handicaps.

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ОКУЛАРНИ ПОРЕМЕТУВАЊА КАЈ ДАУН СИНДРОМ

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АБСТРАКТ

Вовед: Даун синдром е најчестата хромозомска аномалија. Пациентите со Даун синдром имаат зголемен ризик од појава на голем број здравствени проблеми, вклучувајќи ги и окуларните пореметувања.

Цел: Да се идентификуваат окуларните пореметувања кај пациентите со Даун-ов синдром.

Материјал и методи: Седум пациенти со Даун синдром се лекувани на Универзитетската клиниката за очни болести во Скопје, во период од 18 месеци. Пациентите беа на возраст од 3 до 39 години.

Резултати: Кај овие пациенти беа дијагностицирани следните окуларни пореметувања:epicatus, cataracta, hypermetropia, strabismus, astigmatismus, myopia alta, blepharitisиblepharoconjunctivitis.

Заклучок: Навременото дијагностицирање и лекување на окуларни пореметувања на пациентите со Даун синдром им овозможи поквалитетен живот и го минимизира нивниот хендикеп.

Клучни зборови: Даун синдром, окуларни пореметувања.

MILITIRY HOSPITALS IN THE VARDAR REGION OF MACEDONIAN FROM THE OTTOMAN PERIOD

ВОЕНИ БОЛНИЦИ ВО ВАРДАРСКИОТ РЕГИОН НА МАКЕДОНИЈА ВО ОТОМАНСКИОТ ПЕРИОД

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Abstract

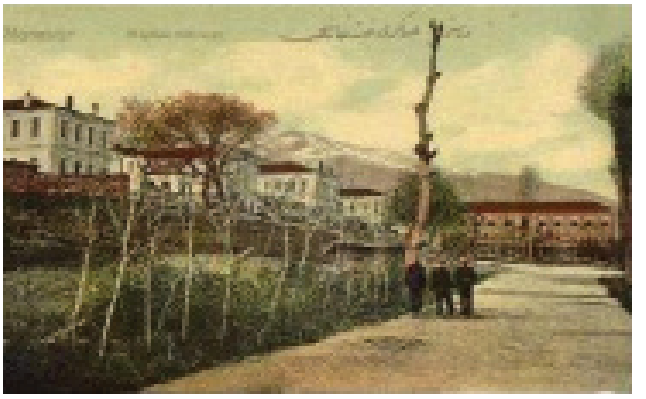
In the paper are processed beginning of construction of hospital facilities in Vardar Macedonia in the 19th century during the Ottoman rule. The need for medical treatment of soldiers and their officers felt due to frequent wars they fought the Empire and the huge number of infectious diseases that reigned in the region. Syphilis as severe infectious disease that quickly spread among the troops was good reason for the reduced number of soldiers of war. Therefore the Turkish army began construction of military hospitals in Skopje, Bitola, Stip, Veles, Debar and Strumica. All these hospitals are individually displayed data for their location, year of construction, hospital facilities and structure of hospital staff.

Key words: Turkish army, infectious diseases, hospital facilities XIX century.

The need of building of hospitals and healing of the civil population was imposed not just of the conquering wars that Ottoman Empire led and the appearance of the syphilis and other diseases among the soldiers of the Turkish Army in the European part of the Ottoman Empire. That is why in the second half of the XIX century the medicine concept began to change. Besides the opening of the hospitals another question about prevention from the zymotic disease. Under the pressure of Europe and with an aim to stop the spread of the zymotic diseases quarantine measures were introduced and the travel to the epidemic countries was forbidden.

Several military hospitals in Bitola, Skopje, Stip, Veles, Strumica and Debar were built in the Vardar region of Macedonia since the second half of the XIX century [1].

Bitola was an important economic centre in the Empire but also it was a centre of constant disturbances. A result of that is the founding of the colonel's barracks. A new hospital was opened in 1846 and it was completely finished in 1850.1 The manager of the hospital was dr Fetulah Efendi. Four doctors, five pharmacists and four surgeons were employed in the hospital up to 1867 [2].



The first turkish hospital Bitola from 1850 (old postcard)

In the period of Serbian – Turkish and Russian – Turkish war from 1877 to 1878 the manager of the hospital was colonel dr Andon Bej, his assistant was dr Mehmed who at the same time was the mayor of Bitola. Beside these two doctors, the colonel Mustafa Arif, three surgeons and several pharmacists worked at the hospital. This hospital team was increasing permanently. Dr Hasan, colonel Mehmed Galip, six doctors, 12 surgeons and others were employed in 1878. The cavalry units were

stationed in Bitola in this period and because of that the need for bigger hospital increased. Pasha Fazli and Pasa Jemal started the building of the new hospital in 1885. The building of the hospital was finished by Ahmet Ejup Pasha in 1893. Doctors Ali Riza, Konstantin, Kond Rijetis, Rajt, Bdul Halim, captains Behiri and Selim, and four pharmacists worked in the hospital at that time.

Doctors Xemal, Salih, Mehmed, Haki, five pharmacists, four surgeons and others started to work in 1899. The manager of the hospital was dr Husein Remzi. During the Turkish – Greek war in 1897 the army and the population suffered massive smallpox. Dr Xemal, bacteriologist Vasfi Ethem, Mustafa Hajrulah and others made massive vaccination and stopped the spreading of the epidemic. The manager of the Bitola's hospital was the surgeon dr Rifki Osman Bej. During the Ilinden Uprising in 1903 the manager of the hospital was dr Ibrahim Pasha from Egypt, and the doctors that worked then were Arif, captains Faik Fikret and Vasif. During the Young Turk Revolution the manager of the hospital was the dr Mehmed Arif, and as doctors worked the captain Refik Sajdam who became a minister of health later and the prime minister of the Republic Turkey.

In 1910 the manager of the hospital was the doctor Miralaj Mustafa Ali, and vice manager and mayor of Bitola was the surgeon doctor Fuat Ali.Before the first Balkan war and during the war at the hospital worked the dermatologist dr Saban, the surgeon dr Rexep, majors Hajrula and Hulisi and captains Tefik, Fazli and Zekli Hamdi. After conquering Bitola in 1912 the Serbian Army took the hospital and the barracks.

Accoriding to the records of the mayor of Skopje Hivzi Pasa, Skopje's military hospital was built in 1844 [3].

The first Turkish military hospital at Skopje's fortress from 1844 (old postcard)

Hivsi Pasha took this duty by the order of the Belgrade Pasha region. Skopje's military hospital was named as Bey's and in the middle of the XIX century the doctor Albaj Konstantin and major Jani Mihal worked in it. According the records of Sejud

Mehmed Tahir pasha, since 30 March 1883, found in the Istanbul library, fortress with warehouse was built for the hospitals' need. Beside the fortress other war buildings and granges were built.

According to the material prepared by the local general hospital in Ankara and „Annals" from 1889, 1892, 1894, 1896, this hospital was formed in the Skopje's fortress barracks county.

On 23 October 1884, according to the same sources, the soldiers of Sahane helped by the Skopje's citizens built a new modern military hospital with two floor and 17 rooms with a capacity of 350 beds on the Skopje's fortress. In both army hospitals on the Fortress during the period between 1844 and 1905 worked many doctors Constantin, Jani Mihail, (1844); doctors Aleksandar, Constantin, Jani Mihail (1866); dr Hasan, dr Matkovik (1867); dr Mustafa, dr Ali (1877); dr Jemal (1883); dr Hadi, dr Harun Bey (1887); dr Niko, dr Ahmet Ferhat (1888); Primarius dr Sulejman Fahri, dr Rasid, head dr primarius dr Jusuf Azis, dr Refik (1889).

Head surgeon at that time was dr Mehmed, second surgeon dr Hasif Mustafa, and third surgeon dr Ali Mustafa. Head pharmacist was Avram, second Zekiria, third Karambeg. In 1892 the director of the hospital was Alaj Kjatibi, dr Ahmed, secretary dr Bezat, head doctor dr Rasid, prim. dr Jusuf Azis and dr Galib. Responsible of the surgery department was dr Osman, head surgeon dr Edem, second surgeon dr Jakub, third surgeon dr Mehmed and fourth surgeon dr Isak.

Another Turkish military hospital at Skopje's fortress from 1884 (old postcard)

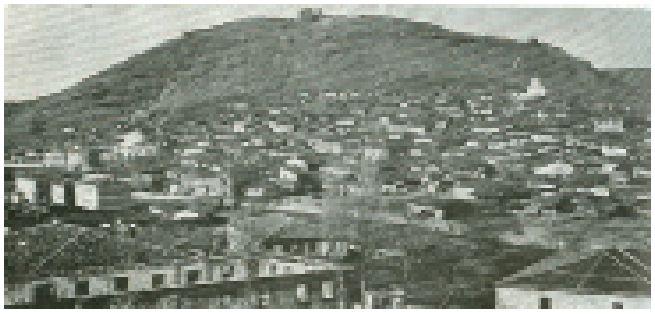
In 1905, from Skopje to the road of Kumanovo a new military hospital of the Red Cross

was built, but because of the Islamic character of the country the hospital got the name “Red Half Moon” later called only Half Moon.

Turkish Military Hospital “ Red Crescent “ from 1905 (old postcard)

The military hospital in Stip was built in the second half of the XIX century.

The manager of the hospital was captain doctor Haxi Nuri. From 1905 to 1911 in the military



The ruins of the Turkish military hospital in Stip

hospital in Stip worked captain Mehmet Nuri (urologist) captain Haxi Faik Fikret, captain Remzi, captain Rifki (surgeon), captain Hilmi, region captain Mehmet Zekirija, captain Mustafa Hulusi and captaion Galip Basri. Just before the Balkan wars the team was increased by colonel Hilmi Izet, surgeon, lieutenant-colonel Abdul Kabir, region colonel Hasan Jamil, captain Mahmut Mustafa and others. This hospital also became part of the Serbian army after the Balkan wars.

In the absence of relevant data for a Turkish military hospital in Veles1 that exists on postcards from that time I decided that I display as well.

Turkish military hospital on the hill above Veles

The military hospital in Debar1 was built in 1847. The manager of the hospital from 1873 to 1891 was colonel doctor Sakir Ibrahim Bey. His assistant was major dr Mustafa Bey, and also the colonels dr Ahmet and dr Kirkor. During the Greek-Turkish war in 1897 the hospital in Debar had a lot of work. The manager of the hospital from 1908 to 1910 was dr Husein Dora. This hospital also became part of the Serbian army after the Balkan wars in 1912.

There was also a military hospital in Strumica1. According the records during the period from 1909 to 1911 the manager of the hospital was dr Fehmi Mehmet Bey. After the FWW was finished Strumica was under Bulgarian reign. Strumica went under the reign of Bulgaria and its hospital was converted into a war medical school.

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Апстракт

Во Трудот се обработуваат почетоците на изградба на болнички установи, во Вардарскиот дел од Македонија во 19 век, во време на Османлиското владеење. Потребата од болнички третман на војниците и нивните старешини се чувствувала поради честите војни што ги водела Империјата и огромниот број на заразни болести кој царувал на овие простори. Сифилисот како тешка заразна болест, која бргу се ширела меѓу војниците, бил сериозна причина за намалениот број на војници способни за војна. Поради тоа Турската армија започнала со изградба на воени болници во Скопје, Битола, Штип, Велес , Дебар и Струмица.Сите овие болници поединечно се прикажани со податоци за нивната местоположба, година на изградба, болнички капацитети и структура на болничкиот персонал.

Клучни зборови: Турска армија, заразни болести, болнички установи, XIX век

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Additional Information for Authors

I. First page - *front page*: It should contain: (a) title of paper, a short, but informative; (b) the first name, initials of middle name and last name of each author; (c) the institution; (d) the name of the department that is attributable to the scientific work; (e) the name and address of the author with whom to correspond about the manuscript (f) source/support in the form of grants, equipment, drugs, or all.

II. Second page - *abstract and keywords*: The abstract should be written with a maximum of 150 words for unstructured abstracts and 250 words for structured abstracts (containing parts: objective(s) of study or research, basic procedures, such as selection of subjects or laboratory animals, observational and analytical methods, then, the main findings/results (data and their statistical significance, if possible), and the main conclusions. Emphasize the new and important aspects of the study or observation.

Below the abstract identify and write the keywords: 35 words or short phrases that will assist in indexing the paper and publication of the abstract.

Use terms from the list of Index Medicus for Medical Sub-Headings (MeSH); if there is no appropriate MeSH term for some newly introduced terms, we can use the given terms.

III. Third and further pages – *full text of the article*: The full text of research or observational articles should normally be, but not necessarily, divided into sections with the following headings: introduction, material and methods, results and discussion.

1. Introduction: Provide a context or background for the study (that is, the nature of the problem and its significance). To do this you must complete a literature review – searching for, finding and reading relevant papers, which must be referenced in your manuscript. Explain your hypotheses and the plan to test them, and describe your aims. Clearly state what you expect to find and the reasoning that led you to the hypotheses that you have made. The research objective is often more sharply focused when stated as a question. Do not include data or conclusions from the work being reported.

2. Methods & Material: This section should include only information that was available at the time the plan or protocol for the study was being written. All information obtained during the study belongs in the Results section.

Describe your selection of the observational or experimental participants (patients or laboratory animals, including controls) clearly, including eligibility and exclusion criteria.The guiding principle should be clarity about how and why a study was done in a particular way.

Give sufficient details of the methods, apparatus and materials (give the manufacturer's name and address in parentheses), and procedures to allow others to understand and reproduce your results.

If a particular method used is well known then there is no need to give a complete description. You can reference the paper in

përmendni ndonjë modifikim/ndryshim që keni bërë. Jepni arsyet për përdorimin e tyre dhe vlerësoni kufizimet e tyre. Në fund, përshkruani se si i keni analizuar të dhënat tuaja, duke përfshirë metodat statistikore dhe pakon programore që keni përdorur.

Autorët e doreshkrimeve të rishqyrtuara duhet të përfshijnë një paragraf që përshkruajnë metodat që kanë përdorur për lokalizimin, përzgjedhjen, ekstrahimin dhe sintetizimin e të dhënave. Përdorni formën joveprore të foljes, në vetën e tretë, kur dokumentoni metodat, gjë që do të fokusonte vëmendjen e lexuesit tek puna që është bërë e jo tek hulumtuesi (P.sh. Janë marrë, janë realizuar, janë prezantuar etj.)

2. a) Statistikat: Përshkruani metodat statistikore me detaje të mjaftueshme për t'ia mundësuar një lexuesi me njohje në atë fushë t'i qaset të dhënave origjinale për të verifikuar rezultatet e raportuara. Kur është e mundur, përcaktoni sasinë e zbulimeve dhe prezantoni ato me indikatorë përkatës të gabimeve në matje apo pasiguri (siç janë inter-valet e besueshmërisë). Evitoni mbështetjen vetëm në testet statistikore të hipotezave, siç janë vlerat p, që dështojnë të transmetojnë informacion të rëndësishëm mbi madhësinë e efektit. Jepni detaje rreth përzgjedhjes së rasteve (randomizimi) dhe përshkruani metodat dhe sukseset e vro¬jtimit gjatë realizimit të studimeve të verbuara. Definoni termet statis¬tikore, shkurtesat dhe më së shumti simbolet. Specifikoni programin kompjuterik që është përdorur.

3. Rezultatet: Ky paragraf duhet t'i bëjë gjetjet tuaja të qarta. Prezantoni rezultatet tuaja në rend logjik në tekst, tabela dhe ilustrime, duke dhënë së pari rezultatet kryesore ose më të rëndësishme. Mos i përsërisni të gjitha të dhënat në tabela apo ilustrime, në tekst. Nënvizoni ose përm-bledhni shkurtimisht vetëm vrojtimet më të rëndësishme.

Kur të dhënat përmblidhen në paragrafin e Rezultateve, jepni rezultate numerike jo vetëm si derivate (për shembull, përqindja) por gjithashtu si numra absolut nga të cilët derivatet janë llogaritur, dhe specifikoni metodat statistikore që janë përdorur për t'i analizuar ato.

Kufizoni tabelat dhe figurat në aq sa janë të nevojshme për të sqaruar argumentin e punimit dhe për të vlerësuar të dhënat ndihmëse. Duke përdorur grafikonet për të reprezentuar të dhënat tuaja si alternativë e tabelave, do të rrisë kuptueshmërinë e lexuesit. Mos i dyfishoni të dhënat në grafikone dhe tabela. Duhet të jeni të qartë se cili lloj i grafikoneve është i përshtatshëm për informacionet tuaja. Për shembull, për të reprezentuar korelimin mes dy ndryshoreve, preferohet grafiku vijëzor, krahasuar me grafikun rrethor apo në formë shtyllash.

Sa i përket të gjitha paragrafeve, qartësia dhe të qënit i thuktë është kyçe. Mos prezantoni të njëjtat të dhëna më shumë se një herë. Kufizojeni veten në të dhënat që ndihmojnë në adresimin e hipotezave tuaja. Kjo është e rëndësishme edhe nëse të dhënat i aprovojnë ose nuk i pranojnë ato. Nëse keni bërë analiza statistikore, duhet të jepni vlerën e proba¬bilitetit (p) dhe të tregoni se është shprehës (sinjig në nivelin që ju po testoni. Varësisht nga analizat e përdorura, gjithashtu mund të jetë e rëndësishme të jepni intervalet e besueshmërisë së rezultateve (Confidence Interval –

which it was first described and mentioned any modifications you have made. Give the reasons for using them, and evaluate their limitations. Finally,, describe how you analysed your data, including the statistical methods and software package used.

Authors submitting review manuscripts should include a section describing the methods used for locating, selecting, extracting, and synthesizing data.

Use the third person passive voice when documenting methods which would focus the readers' attention on the work rather than the investigator.(e.g. Were taken, was performed, were presented itd.)

2. a) Statistics: Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as p values, which fail to convey important information about effect size. Give details about the randomization and describe the methods and success of observations while using blinded trials. Define statistical terms, abbreviations, and most symbols. Specify the computer software used.

3. Results: This section should make your findings clear. Present your results in logical sequence in the text, tables, and illustrations, giving the main or most important findings first. Do not repeat all the data in the tables or illustrations in the text. Emphasize or summarize only the most important observations.

When data are summarized in the Results section, give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical methods used to analyze them.

Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Using graphs to represent your data as an alternative to tables will improve the reader's understanding. Do not duplicate data in graphs and tables. You need to be clear what type of graphs is suitable for your information. For example, to represent the correlation between two variables, a line graph is preferred to a pie chart or a bar chart.

As with all sections, clarity and conciseness is vital. Don't present the same data more than once. Restrict yourself to the data that helps to address your hypotheses. This is important whether the data supports or disproves them. If you have carried out a statistical analysis, you should give the probability (P) value and state it is significant at the level you are testing. Depending on the analysis used, it may also be important to give the confidence intervals of the results, or the statistical parameters such as the odds ratios. Provide a caption for each figure making the gen¬eral meaning clear without reference to the main text, but don't discuss the results. Let the readers decide for themselves what they think of the data. Your chance to say what you think comes next, in the discussion.

3. Tables: Each table should be inserted at the point of the text where they have to be placed logically, typed by the same rules

CI), ose parametrat statistikorë si proporcionet e rastit (odds ratio). Bëni përshkrimin tek secila figurë duke bërë të qartë domethënien e përgjithshme pa referencë në tekstin kryesorë, por mos diskutoni rezultatet në të. Lëreni lexuesin të vendosë vetë se çfarë men-don për të dhënat. Mundësia juaj për të thënë se çfarë mendoni, është në vazhdim, tek diskutimi.

3. Tabelat: Secila tabelë duhet të vendoset në vendin e tekstit ku duhet të vihet logjikisht, e plotësuar me të njëjtat rregulla sikur teksti i plotë. Mos i dërgoni tabelat si fotografi. Secila tabelë duhet të citohet në tekst. Tabelat duhet të jenë me numra ashtu që të jenë në koordinim me refer-encat e cituara në tekst. Shkruani një përshkrim të shkurtë të tabelës nën titullin. Çdo sqarim shtesë, legjendë ose sqarim i shkurtesave jostan¬darde, duhet të vendoset menjëherë poshtë tabelës.

4. Diskutimi: Ky paragraf është pjesa ku ju mund të interpretoni të dhë-nat tuaja dhe të diskutoni duke ballafaquar dhe krahasuar gjetjet tuaja me ato të hulumtuesve të mëparshëm. Rishikoni referencat e literaturës dhe shihni nëse mund të përfundoni se si të dhënat tuaja përkojnë me atë që keni gjetur.

Ju gjithashtu duhet të llogarisni rezultatet, duke u fokusuar në mekaniz¬mat në prapavij të vrojtimit. Diskutoni nëse rezultatet tuaja mbështesin hipotezat tuaja origjinale. Gjetjet negative janë aq të rëndësishme në zhvillimin e ideve të ardhshme sikur gjetjet pozitive.

E rëndësishme është se, nuk ka rezultate të këqija. Shkenca nuk të bëjë me të drejtën dhe të gabuarën, por merret me zgjerimin e njohjeve të reja.

Diskutoni si janë paraqitur gabimet në studimin tuaj dhe çfarë hapa keni ndërmarrë për të minimizuar ato, kështu duke treguar se ju çmoni ku¬fizimet e punës tuaj dhe fuqinë e përfundimeve tuaja. Duhet gjithashtu të merrni në konsideratë ndërlikimet e gjetjeve për hulumtimet në të ardhmen dhe për praktikën klinike. Lidhni përfundimet me qëllimet e studimit, por evitoni qëndrimet dhe përfundimet e pakualifikuara, që nuk mbështeten në mënyrë adekuate nga të dhënat. Shmangni prioritetet deklarative apo të aludoni në punën që nuk është krahasuar.

5. Referencimi: Referencat janë baza mbi të cilën është ndërtuar raporti juaj. Shqyrtimi i literaturës dhe leximi i referencave gjithmonë duhet të jetë pikë fillestare e projektit tuaj. Ky paragraf duhet të jetë i saktë dhe të përfshijë të gjitha burimet e informacionit që keni përdorur.

Në formatin " Vancouver" , referencat numërohen një nga një, sikur që shfaqen në tekst dhe identifikohen me numra në bibliografi..

Shënoni të gjithë autorët kur janë gjashtë e më pak; kur janë shtatë ose më tepër, shënoni tre të parët, pastaj shtoni "et.al." Pas emrave të autorëve shkruhet titulli i artikullit; emri i revistës i shkurtuar sipas mënyrës së Index Medicus; viti i botimit; numri i vëllimit; dhe numri i faqes së parë dhe të fundit.

Referencat e librave duhet të jepen sipas emrit të autorit, titulli i librit (mund të citohet edhe titulli i kapitullit para titullit), vendi i botimit, botuesi dhe viti.

as for the full text. Do not send tables as photographs. Each table should be cited in the text.Tables should be numbered so that they will be in sequence with references cited in the text. Provide a brief explanation of the table below the title. Any additional explanations, legends or explanations of non¬standard abbreviations, should be placed immediately below the table.

4. Discussion: This section is where you interpret your data and discuss how your findings compare with those of previous researchers. Go over the references of your literature review and see if you can determine how your data fits with what you have found.

You also need to account for the results, focusing on the mechanisms be¬hind the observation. Discuss whether or not your results support your original hypotheses. Negative findings are just as important to the de¬velopment of future ideas as the positive ones.

Importantly, there are not bad results. Science is not about right or wrong but about the continuing development of knowledge.

Discuss how errors may have been introduced into your study and what steps you took to minimise them, thus showing that you appreciate the limitations of your work and the strength of your conclusions. You should also consider the implications of the findings for future research and for clinical practice. Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. Avoid claiming priority or alluding to work that has not been compared.

5. Referencing: The references are the foundation on which your report is built. Literature searches and reading of references should always be the starting point of your project. This section must be accurate and in¬clude all the sources of information you used.

In the Vancouver format, references are numbered consecutively as they appear in the text and are identified in the bibliography by numerals.

List all authors when there are six or fewer; when there are seven or more, list the first three, then add "et al." The authors' namer are fol-lowed by the title of the article; the title of the journal abbreviated ac-cording to the style of Index Medicus; the year of publication; the volume number; and the first and last page numbers.

References to books should give the names of any editors, place of publication, editor, and year.

In the text, reference numbers are given in superscript. Notice that issue number is omitted if there is continuous pagination through¬out a volume, there is space between volume number and page numbers, page numbers are in elided form (51-4 rather than 51-54) and the name of journal or book is in italics.The following is a sample reference:

Në tekst, numrat e referencave jepen me indeks të sipërm. Vëreni se çështja e numrave neglizhohet nëse ka numërtim të vazhdueshëm përg¬jatë gjithë vëllimit, ka hapësirë mes numrit të vëllimit dhe numrit të faqes, numrat e faqeve janë në këtë formë: 51-4 në vend të 51-54, dhe emri i revistës ose librit është në italic. Në vazhdim është një shembull i referencës:

Artikujt e revistave:

1. Lahita R, Kluger J, Drayer DE, Koffler D, Reidenberg MM. Antibodies to nuclear antigens in patients treated with procainamide or acetylpro¬cainamide. *N Engl J Med* 1979;301:1382-5.
2. Nantulya V, Reich M. The neglected epidemic: road traffic injuries in developing countries. *BMJ* 2002;324: 1139.
3. Murray C, Lopez A. Alternative projections of mortality and disability by cause 1990-2020: global burden of disease study. *Lancet* 1997;349: 1498-504.

Librat dhe tekste tjera:

4. Colson JH, Tamour NJJ. Sports in juries and their treatment. 2nd ed. London: S. Paul, 2006.
5. Department of Health. *National service framework for coronary heart disease*. London: DoH, 2000.

   www.doh.gov.uk/nsf/coronary.htm (accessed 6 Jun 2003).
6. Kamberi A, Kondili A, Goda A, dhe bp; *Udhërrëfyes i shkurtër i Shoqatës Shqiptare të Kardiologjisë për parandalimin e Sëmundjes Aterosklerotike Kardiovaskulare në praktikën klinike*, Tiranë, 2006
7. Azemi M, Shala M, dhe bp. *Pediatria sociale dhe mbrojtja shëndetësore e fëmijëve dhe nënave*. Pediatria, Prishtinë 2010; 9-25

Shmangni përdorimin e abstrakteve si referenca; "të dhëna të papub-likuara" dhe "komunikime personale". Referencat e pranueshme, por ende të papublikuara lejohet të merren, vetëm nëse shënoni se janë "në shtyp".

6. Mirënjohjet: Ju mund të keni dëshirë të falënderoni njerëzit që ju kanë ndihmuar. Këto mund të rangohen prej atyre që ju kanë përkrahur me teknika eksperimentale deri tek ata që ju kanë këshilluar deri në bër¬jen e dorëshkrimit final.

7. Formati i fajllit të të dhënave për **ilustrimet** (**figurat**): JPG

Nëse përdoren fotografitë e pacientëve, qoftë subjekti, qoftë fotografitë e tyre nuk duhet të jenë të identifikuara, ato duhet të shoqërohen me lejen e shkruar nga ta për përdorimin e figurës. Format e lejuara janë në dispozicion nga redaksia.

Nëse fajllet e të dhënave janë shumë të mëdha për t'u dërguar me e-mail, rekomandohet dërgimi me CD në adresën tonë.

8. Legjendat për Ilustrimet (Figurat)

Legjenda e tabelës duhet të vendoset mbi tabelë. Referenca e një tabeleje, e cila është marrë nga ndonjë publikim tjetër, duhet të vendoset poshtë tabelës. (Është përgjegjësi e autorit të sigurojë lejen e ribotimit nga botuesit e atij botimi) Legjenda e figurës duhet të vendoset në fund të faqes. Referenca e figurës e marrë nga ndonjë tjetër publikim vendoset në fund të legjendës. (Leja e ribotimit duhet të sigurohet nga botuesi i këtij botimi).

Journal articles:

1. Lahita R, Kluger J, Drayer DE, Koffler D, Reidenberg MM. Antibodies to nuclear antigens in patients treated with procainamide or acetylpro¬cainamide. *N Engl J Med* 1979;301:1382-5.
2. Nantulya V, Reich M. The neglected epidemic: road traffic injuries in developing countries. *BMJ* 2002;324: 1139.
3. Murray C, Lopez A. Alternative projections of mortality and disability by cause 1990-2020: global burden of disease study. Lancet 1997;349: 1498-504.

Books and other monographs:

4. Colson JH, Tamour NJJ. Sports in juries and their treatment. 2nd ed. London: S. Paul, 2006.
5. Department of Health. *National service framework for coronary heart disease*. London: DoH, 2000.

   www.doh.gov.uk/nsf/coronary.htm (accessed 6 Jun 2003).
6. Osler AG. *Complement: mechanisms and functions*. Englewood Cliffs: Prentice-Hall, 1976.

Avoid using as references abstracts; "unpublished data" and "personal communications". References to accepted but yet unpublished articles are allowed to be made, only if you note "in press".

6. Acknowledgements: You may wish to acknowledge people who have helped you. These can range from those who supported you with exper¬imental techniques to those who read or offered advice on your final manuscript.

7. Data file format for **illustrations** (**figures**): JPG

If photographs of patients are used, either the subjects should not be identifiable or their pictures must be accompanied by written permis-sion to use the figure. Permission forms are available from the Editor.

If data files are too big for transmission as an Email attachment submis¬sion of a CD to our address is recommended.

8. Legends for Illustrations (Figures)

The legend of a table has to be placed above the table. The reference of a table, which has been taken from another publication, must be placed below the table. (It is the author's responsibility to obtain the permission of reproduction from the publishers of the publication.) Figure legends are to be placed at the end of the paper. The reference of a figure taken from another publication stands at the end of the legend. (Permission of reproduction must be obtained from the publishers of this publication).