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Editorial

Original scientific paper

Profesional paper

Review

Case report

Revistë e Shoqatës së Mjekëve Shqiptarë në Maqedoni
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Medical Journal

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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

Medical Journal

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TOWARD IMPROVING THE QUALITY AND INTEGRITY OF IMJ MEDICUS

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INTRODUCTION

International Medical Journal MEDICUS (IMJ Medicus) is an international peer-review journal in the field of biomedicine established by the Albanian Association of Medical Doctors in Macedonia in 2004. The journal started with publishing two issues per year and from 2013 increased to three editions per year, namely in January, May and September. The Advisory Board and the international Editorial Board members are highly enthusiastic and dedicated team of medical doctors and scientists, coming from 8 countries beside R. Macedonia, including the Nobel Prize Winner in Medicine and Physiology, Mr Ferid Murad, who is a Honorary Member of the Editorial Board of IMJ Medicus. The official web-site of the journal is www.imjm.mk, providing electronic submission of manuscripts and open access to the electronic version of each issue downloadable in pdf. format. In addition, the Journal is also printed and distributed in hard copy version. Papers are predominantly published in English, as well as some in Albanian and Macedonian language but with translated title and abstract in English of all papers either written in Macedonian or Albanian language (1).

IMJ MEDICUS DURING THE YEAR 2016

During the 2016 there were published fifty (50) articles in the IMJ Medicus. The most of them (68%) were prepared by authors from R. Macedonia, then from Albania, Kosovo, Italy, Bulgaria etc.

The acceptance rate of IMJ Medicus in 2016 was 62%. According to the type of articles most of them were original articles (60%), review articles (17%), case reports (13%), professional papers (5%) and short communications (5%).

The total number of reviewers who participated in the review process of manuscripts submitted for publishing in 2016 was 37.

FURTHER STEPS FOR IMPROVING THE JOURNAL QUALITY

IMJ Medicus will continue further development and improving the quality of the journal in 2017 toward indexation in PubMed and Scopus Databases and, later on, to submit application to Thomson Reuters for evaluation and Journal's Impact Factor (IF). The integrity of the journal articles is going to be improved through education of young scientists and potential authors, reviewers and Editorial Board members, strengthening the review process and supportive editing of manuscripts, and updating the instructions for authors and ethical standards of the journal in accordance with the international criteria and conclusions and recommendations from the First Mediterranean Seminar on Science Writing, Editing and Publishing (SWEP 2016), held in Sarajevo on December 2-3, 2016 (2), and adopted Sarajevo Declaration on Integrity and Visibility of Scholarly Publications (3).

Main directions of activities in 2017 and beyond for increasing the awareness about the importance of scientific and publishing ethics and for improving the quality and integrity of manuscripts and visibility of the IMJ Medicus are as follows:

1. Broadening the list of members of the Editorial Board and, beside Editor-in-Chief and Co-Editor-in-Chief, appointing additional section and other editors;

2. Updating the Instructions for authors according to the principles set by Sarajevo Declaration on Integrity and Visibility of Scholarly Publications communication (http://www.cmj.hr/2016/57/6/28051276.htm), (3);
3. Education of young scientists and potential authors in proper writing and tracing the standard template for structure of an article, and to follow the principles of publication ethics and integrity, authorship criteria in accordance with the ICMJE recommendations (4), through the educational activities of Macedonian Association of Medical Editors and newly created Mediterranean Association of Science Editors and Publishers in order to create ethical environment and to prevent scientific and publishing dishonesty, fraud and plagiarism (5);
4. Improving the electronic open access format of the journal in order to meet some additional international criteria for electronic publishing (beside easy identification of the title of the journal, year of publication, volume and number, title of articles, number of pages, the names of authors and their addresses, complete content of each edition and sides of each paper, an individual link to be provided for approaching each separate article);
5. Improving the peer review process by selection of competent reviewers from different fields of biomedicine and to recognize their contribution to the journal quality by presenting a list of reviewers, who contributed in the review process of manuscripts during the year, in the last journal issue of the year;
6. Strengthening the quality and visibility of the journal by establishing the English language as the sole official language of the IMJ Medicus;

CONCLUSION

Publishing and editing a scientific paper is not easy. In our specific conditions and environment and with some modest experience it becomes even harder. With dedication and team work we believe that IMJ Medicus Editors and Editorial Board members will be able to achieve the aims for continuous improvement of quality and visibility of the journal. IMJ Medicus will be a solid platform of biomedical sciences research information and it will serve towards promoting scientific research and the affirmation of professional achievements in medicine.

REFERENCES

1. Pollozhani A. Editorial policies and good practices in editing of the journal 'International Medical Journal MEDICUS'
2. Masic I, Donev D, Sinanovic O, et al. The First Mediterranean Seminar on Science Writing, Editing and Publishing, Sarajevo, December 2-3, 2016. Acta Inform Med. 2016;24(6):424-435. doi:10.5455/aim.2016.24.424-435.
3. Mašić I, Begić E, Donev DM, et al. Sarajevo Declaration on Integrity and Visibility of Scholarly Publications. Croatian Medical Journal. 2016;57(6):527-529. doi:10.3325/cmj.2016.57.527. Available at: http://www.cmj.hr/2016/57/6/28051276.htm
4. ICMJE. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals* - Updated December 2013. Available at: http://www.icmje.org/icmje-recommendations.pdf
5. Donev D. Plagiarism as a problem in scientific publishing. IMJ Medicus 2015; 20(3): 319-24. Available at: http://www.imjm.mk/pubs/IMJMVol_20_%283%29_2015.pdf

Original scientific paper

THE PERFORMANCE OF CLINICAL AND ECG DURING THE PROGRESSION OF AMI IN THE REGION OF ELBASAN

ECURIA E KLINIKËS DHE EKG GJATË DEKURSIT TË IAM NË RAJONIN E ELBASANIT

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ABSTRACT

Introduction. The performance of patients with AMI during the progression of disease is defined based on the clinical and other instrumental examinations as ECG. The recognition of the factors that influence the clinical and ECG changes in patients with AMI is important to determine as soon as possible so individuals will not have a poor prognosis during the progression of the AMI.

Aim. Evaluation of the performance of clinical signs (pain) and ECG during progression of AMI by demographic profiles, clinical signs and treatments in the region of Elbasan.

Methodology. Transversal study time series for the changing clinical signs (pain) and ECG by demographic profile, clinical or treatment and medication status or PCI / CABG at the time of the patient's arrival at the hospital. The study is performed in the Regional Hospital of Elbasan near the Department of Cardiology and were included patients with a new episode of acute myocardial infarction. Data collection was conducted during the period of hospitalization of patients (respectively at the time of hospitalization and after 24 hours). The data are processed in SPPS using chi square test. The value of p<0:05 was considered statistically significant.

Results. The study involved 65 patients with AMI (new episode of AMI). Male patients and in the age group 65-74 years old with a duration of up to six hours of pain at the moment of arriving at the hospital, with wide lesion and treated for 24 hours with medicament therapy have significantly higher percentage of presences of the wave T and Q after 24 hours in ECG (the chi square p <0.05 level). The clinical performance (pain) is closely related to the size of the lesion, duration of pain until arriving at the hospital and the therapy used in 24 hours. Pain after 24 hours is significantly higher in patients of the male sex and age group of 65-74 years, with wide lesions and coming late at the hospital.

Conclusions. Clinical and ECG improvement in patients is affected by the demographic profile of the patient, the time of arriving at the hospital from the moment of occurrence of myocardial infarction and therapy use.

Keywords: performance, clinics, ECG, age, gender, therapy.

INTRODUCTION

AMI Acute Myocardial Infarction (AMI) is one of the main causes of morbidity and mortality in the world (1). The clinical occurrences of AMI have social, psychological, epidemiological and research implications etc (2, 3).

In a typical population of patients who present with acute chest pain in the emergency department, about 20% are diagnosed with acute MI or unstable angina (4).

The outset phase of the MI ischemia is the first step in the development of AMI and stems from the lack of balance in the supply and the metabolic demand for oxygen in the body (5), which is clinically identified by the anamnesis and by the ECG. The latter (ECG) is part of the diagnostic work with the patients who are suspected of MI and is to be applied, and interpreted abruptly (within a maximum of 10 minutes) after the clinical presentation of the patient (6).

The dynamics/changes of ECG waves, during the acute ischemic occurrences of MI, require repeated ECG, especially if the ECG is made in the initial and/or non-diagnosed phase.

The acute alterations or the ones that evolve in the ST-segment, the shapes of the T-wave and Q-wave, when present, potentially allow the clinician to control the incident, to identify the infarct associated with the damaged artery, and assesses the extent of the MI, the prognosis and to establish a therapy treatment.

Approximately one fourth of the patients with MI infarct do not present themselves with the classical chest pain and the incident may pass undiagnosed by the ECG amplitude alterations, are not registered in the Q-waves which are pathological. Undiagnosed ECG, are registered approximately in half of the patients that present themselves with chest pain suspected for a MI infarct patients who are ultimately diagnosed with MI infarct.

Aim: Assessment of the clinical symptoms (pain) and ECG during the onset of AMI according to the demography, time of hospital arrival from the outset of the clinical symptoms, size of the lesion and therapy in patients of Elbasan region.

METHODOLOGY

The study is transversal time series, designed on the clinical symptoms (pain) and ECG alterations observed on a timeline basis, as the demographical profile, time of analysis and the medicine administration treatment or PCI/CABG of the patient presented in hospital.

In this study are included patients who were hospitalized in the hospital of Elbasan and treated for a new AMI. This study has been carried out in the regional hospital of Elbasan in the cardiology department.

The data collection during the hospitalization of the patients (respectively from the moment of hospitalization and after 24 and/or 72 hours) and consists of the ECG characteristics (The ST segment and Q wave) from the first moment and 24 to 72 hours of hospitalization, the hospitalization pain, and the pain after 24 to 72 hours of hospitalization, the lesion size and the moment of hospitalization (as documented) and the time from the outset of the clinical symptoms up to the hospitalization, the used medicine treatment or therapy or surgery methods used.

Data have also been collection on the age and gender of the patients.

In order to analyze the demographic impact in the study, the time of hospitalization and the type of therapy applied with regards to the clinical performance and the ECG is used SPSS 16 and the *chi square*. A $p<0.05$ is considered statistically significant.

THE RESULTS

The study were involved 65 patients with AMI who underwent treatment in the Regional Hospital of Elbasan.

Among which 51 males and 14 females. The age of the patients were 65–74 years old.

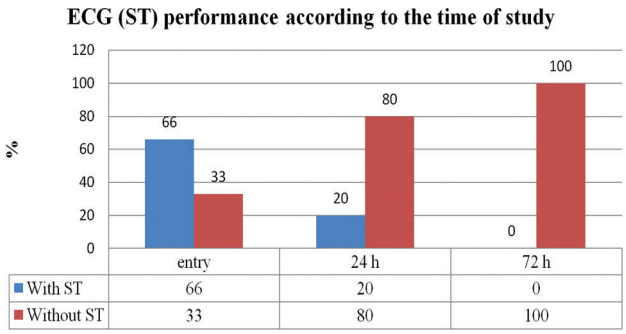
Table 1. Distribution of samples according to age.

	Patient Age			
	45-54	55-64	65-74	>75
N	4	24	27	10

Table 2. The characteristics of patients according to the duration of pain until the admission to hospital, the lesion size and the therapy used.

Clinical characteristics	**N**
Pain duration	
< 6 hours	45
> 6 hours	20
Lesion size	
Small	43
Large	22
Therapy	
PCI/CAGB	16
Medical	49

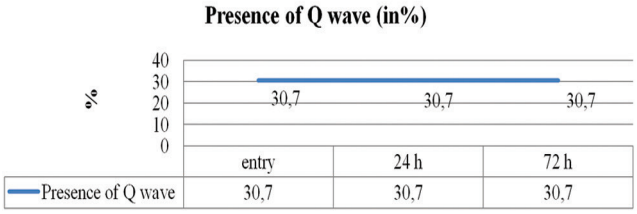
In the majority of cases the time of admission to hospital from the outset of the clinical symptoms is less than 6 hours, the lesion size is estimated to be small and the therapy used is medical treatment (table 2).



Graphic 1. The ongoing of the ST presence according to the time of study.

In graphic 1. is provided the ST segment performance for the first and the third day. In the first day the ST presence is 20% incidence, but in the third day, it is observed a completely weaning ST wave.

In table 2, there is observed a ST segment present after 24 hours, according to the demographic and clinical components.



Graphic 2. Ongoing of Q wave presence (elevation/non-elevation) according to the time of study.

Presence of Q wave in the ECG is observed 24 hours after hospitalization continuing up to 72 hours after the hospitalization of AMI patients.

Table 3. Ongoing of ECG after 24 hours according to patient age.

STEMI		Patient age				P-value*
		45-54	55-64	65-74	>75	
With presence of ST segment	N (%)	1 (7.7)	3 (23)	4 (30.7)	5 (38.4)	0.023
Without presence of ST segment	N (%)	3 (5.7)	21 (40.3)	23 (44.2)	5 (9.6)	0.019

*chi square
p<0.05 is considered significant

Table 4. Ongoing of ECG after 24 hours according to gender.

ST		Male	Female	P value*
With presence of ST segment 24 hours	N (%)	10 (76.9)	3 (23.1)	0.04
Without presence of ST segment 24 hours	N (%)	41 (78.8)	11 (21.2)	0.045

*chi square
p<0.05 is considered significant

The age and gender seem to affect in the presence or without presence (elevation or non-elevation of ST wave after 24 (see *chi square*, p<0.05 table 3 and 4). The males have a higher presence/elevation of ST segment and the >75 year old patients have also a more elevated ST in the ECG.

Table 5. Ongoing of ECG after 24 hours according to the duration of pain, the lesion size and therapy.

	ST elevation 24 hours	**ST non-elevation 24 hours**	**p-value***
Duration of pain			
< 6 hours	5 (11)	40 (89)	0.003
> 6 hours	8 (40)	12 (60)	0.034
Lesion size			
Small	7 (16.2)	36 (83.8)	0.005
Large	6 (26)	17 (74)	0.035
Therapy			
PCI/CAGB	4 (25)	12 (75)	0.029
Medical	9 (18.3)	40 (81.7)	0.05

*chi square
P<0.05 is considered significant

Patients with a pain lasting longer than six hours and with larger lesion size, who underwent medical treatment during the 24 hours, had a significantly higher elevation of the T wave after 24 hours (see chi square p<0.05, table 5).

Table 6. Presence of Q wave according to age.

Patient Age	45-54	55-64	65-74	>75	P value*
Without Q wave	3 (6.6)	19 (42.2)	18 (40)	5 (11.2)	0.036
With Q wave	1 (5)	5 (25)	9 (45)	5 (25)	0.046

*chi square
P <0.05 is considered significant

Table 7. Presence of Q wave according to gender.

	Male	Female	P value *
Without Q wave	35(77.7)	10(22.6)	0.034
With Q wave	16(75)	4(25)	0.021

*chi square
P <0.05 is considered significant

The level of Q wave elevation in the ECG at hospitalization is high, and it is higher in the 65-74 year old male patients with significant alterations with first AMI (in chi square p <0.05; table 6 and 7).

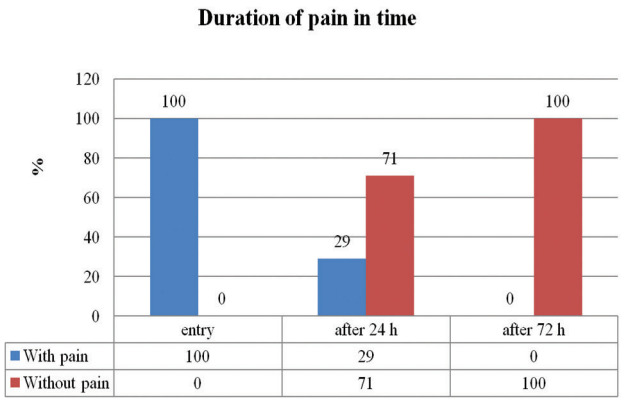
Table 8. Presence of Q wave according to the duration of pain, lesion size.

	Without Q wave	With Q wave	P value*
Duration of pain			
< 6 hours	40 (89)	5 (11)	0.039
> 6 hours	5 (25)	15 (75)	0.03
Lesion size			
Small	39 (93)	3 (7)	0.001
Large	6 (26)	17 (74)	0.003

*chi square
p<0.05 is considered significant

The level of Q wave elevation/presence is significantly higher in patients with a duration of pain for more than 6 hours, with e larger lesion size of AMI (p<0.05 in table 8).

The ongoing of the clinical symptoms in admission to hospital



Graphic 3. The presence of pain according to the time of study.

On hospitalization pain has been present in all the patients, but after 24 hours it persisted only in 29% of the cases and it has been completely weaned after 72 hours.

Table 9. Presence of pain after 24 hours according to patients age.

			Patient age		P value*
	45-54	55-64	65-74	>75	0.04
Without pain	3 (6.6)	19 (41.3)	19 (41.3)	5 (10.8)	
With pain	1 (6)	5 (26)	8 (42)	5 (26)	

*chi square
p<0.05 is considered significant

The pain present after 24 hours has been significantly higher in the 65-74 years old male patients (p<0.05, chart 10 and 11).

Table 10. Presence of pain according to gender.

	Male	Female	P value*
Without pain	37 (80)	9 (20)	0.03
With pain	14 (73)	5 (27)	0.017

*chi square
p<0.05 is considered significant

Table 11. Presence of pain after 24 hours according to the duration, lesion size and therapy.

	Without pain	With pain	p value*
Duration of pain			
< 6 hours	40 (87)	5 (26.3)	0.001
> 6 hours	6 (13)	14 (73.7)	0.029
Lesion size			
Small	42 (91)	0 (0)	0.001
Large	4 (9)	19 (100)	0.001
Therapy			
PCI/CAGB	13 (28.2)	3 (15.7)	0.003
Medical	33 (71.8)	16 (84.3)	0.02

*chi square
p <0.05 is considered significant

The pain after 24 hours has been frequently present in patients with a duration of pain of >6 orë, with a large lesion size and who underwent medical therapy during the first 24 hours (in chi square p<0.05).

DISCUSSION

The clinical (pain) situation, is strictly associated with the lesion size, duration of pain until the admission to hospital and the therapy used during the first 24 hours. The larger the lesion and the later the patient is admitted to hospital, the higher is the probability to feel pain during after 24 hours. The findings of this study emphasize the

correlation that exists between the duration of the pain and the results after AMI (7, 8).

The Q wave is present/elevated during the hospitalization period for AMI patients and this can be explained with the fact that the presence of Q wave elevation, is a transmural lesion, in the meantime the elevation of the ST segment is present until the third day and afterwards is weaned in all patients.

This phenomenon is explained with the physiopathology of AMI incidence and the ECG presentation of an AMI (9, 10). The Q wave presence/elevation has a non-positive prognosis in patients with AMI, as a conclusion derived from the findings in the literature of the field (11, 12).

In the majority of cases the patients that have had a repeated AMI, have had a more frequent Q wave presence during a 3 years period, a result which is supported in the work findings of Berger (13). The therapy used affects in the long-term results of AMI. The patients who have had a CABG or PCI have had a better prognosis in comparison with those who have not had this type of treatment. This confirms the study carried out by Erme at al, where emphasis that patients who have had such interventions have had lower mortality rates during the post AMI period (14, 15).

However other studies have to be carried on this topic, during which other implicating factors may be taken into account.

CONCLUSION

A good knowledge of the AMI patients is helpful in defining a prognosis of the patients and in the same time in defining the group of patients with a disadvantaged prognosis after they leave hospital. Patients who are old, overweight, and who show up late in the hospital with an affected/damaged cardiac muscle and with atypical pain, are at a disadvantaged prognosis. Therefore, taking note of the anamnesis in the right time, is helpful in identifying the patients at risk. Familiarization with this group of patients is helpful in designing a more personalized treatment of patients, as well as in reducing the chances of AMI recurrence or preventing a re-occurrence of AMI. In conclusion the ongoing of patients with AMI is a process defined by a variety of demographic, clinical and biochemical factors. The assessment of such factors in time, the cross-reference interpretation of which helps in providing the right prognosis in the right time.

REFERENCAT

1. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular disease: Part II:variations in cardiovascular disease by specific ethnic groups and geographic regions and prevention strategies. Circulation 2001;**104**:2855-2864.
2. The joint European Society of Cardiology/American College of Cardiology Committee. Myocardial infarction redefined- A consensus document of the Joint ESC/ACC Committee for the redefinition of myocardial infarction. Eur Heart J 2000;**21**:1502-1513.
3. Thygesen Alpert JS, White H, on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. Eur Heart 2007; **28**: 2525-2538.
4. Pope JH, Aufderheide TP, Ruthazer R, et al: Missed diagnoses of acute cardiac ischemia in the emergency department. N Engl J Med 342: 1163, 2000.
5. Lee Th, Rouan GW, Weisberg MC, et al: Clinical characteristics and natural history of patients with acute myocardial infarction sent home from the emergency room. Am J Cardiol 60: 219, 1987.
6. Thygesen K, Alpert JS, White HD, Joint ESC/ACCF/AHA/WHF Task Force the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. Eur Heart J 2007; **28**: 2525-2538; circulation 2007: **116**: 2634-2653; J Am Coll Cardiol 2007; **50**: 2173-2195.
7. Ledwich, J.R. Wong, C.J. Duration of chest pain associated with acute myocardial infarction: a predictor of long-term prognosisCan Med Assoc J, 1985; vol. 132.
8. Canto.J.G at al. Prevalence, clinical characteristic and mortality among patients with myocardial infarction presenting without chest pain. *JAMA*.2000;Vol 283, N0 24
9. Kamberi A, Kondili A, Goda A, Lezha M, Çina P, Qirko S.Infarkti akut i miokardit Sëmundjet kardiovaskulare. Tiranë 2001; 199-236.
10. Berisha S. Infarkti akut i miokardit. Tiranë 1986.
11. Horan LG, Flowers NC, Johnson JC. Significance of the diagnostic Q waves of myocardial infarction: Circulation 1971; **43**: 428-436.
12. Ridker MP, Libby. Risk factor for atherothrombotik disease. 36: 939-954.
13. Ren G, Dewald O, FrangogiannisG N Inflammatory mechanisms in myocardial infarction.*Curr Drug Targets Inflamm Allergy*. 2003 September; 2(3): 242–256

14. Jernberg T, Hasvold P, Henriksson M, Hjelm H, Thuresson M, Janzon M. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. Eur Heart J. 2015; 36: 1163- 1170.

15. Erne P, Radovanovic D, Urban P, Stauffer JC, Berteal O, Gutzwiller F. Early drug therapy and in-hospital mortality following acute myocardial infarction. *Heart Drug* 2003;3:134–40.

ECURIA E KLINIKËS DHE EKG GJATË DEKURSIT TË IAM NË RAJONIN E ELBASANIT

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ABSTRAKT

Hyrje. Ecuria e pacientëve me IAM përgjatë dekursit të sëmundjes përcaktohet në bazë të klinikës dhe të ekzaminimeve të tjera instrumentale si EKG. Njohja e faktorëve që ndikojnë në ndryshimet klinike dhe EKG në pacientë me IAM ka rëndësi për të përcaktuar sa më herët individë që mund të kenë një prognoze jo të mirë gjatë dekursit të IAM.

Qëllimi: Vlerësimi i ecurisë së shenjave klinike (dhimbja) dhe EKG gjatë dekursit të IAM sipas profilit demografik, shenjave klinike dhe terapisë në rajonin e Elbasanit.

Metodologjia. Studimi transversal time seri për ndryshimit të shenjave klinike (dhimbja) dhe EKG sipas profilit demografik, klinikës në momentin e paraqitjes në spital dhe statusit të trajtimit medikamentoz apo PCI/CABG të pacientit në momentin e paraqitjes në spital. Studimi është kryer në spitalin rajonal të Elbasanit pranë pavionit të kardiologjisë dhe janë përfshirë pacientë me një episode të ri të infarktit akut. Mbledhja e të dhënave është kryer gjatë periudhës së qëndrimit në spital të pacientëve (respektivisht në momentin e shtrimit dhe pas 24 orë). Të dhënat janë përpunuar në SPPS duke përdorur chi square test.Vlera e $p<0.05$ është konsideruar sinjifikante nga ana statistikore.

Rezultatet. Në studim u përfshinë 65 pacientë me IAM (epidod i ri i IAM). Pacientë të seksit mashkull dhe të grupmoshës 65-74 vjeç me kohëzgjatje më shumë se gjashtë orë të dhimbjes në momentin e ardhjes në spital, me përmasa të gjera të lezionit dhe që janë trajtuar gjatë 24 orëve të para me terapi medikamentoze kanë në mënyrë sinjifikative një përqindje më të lartë të presencës së dhëmbit T dhe Q pas 24 orëve në EKG (ne chi square $p<0.05$). Ecuria e klinikës (dhimbjes) është e lidhur ngushtësisht me përmasat e lezionit, kohëzgjatjes së dhimbjes deri në paraqitjen në spital si dhe me terapinë e përdorur gjatë 24 orëve të para. Dhimbja pas 24 orëve është në mënyrë sinjifikante më e lartë në pacientë të seksit mashkull dhe të grupmoshës 65-74 vjeç, me lezion të gjerë dhe me ardhje me vonesë (> 6 orë) në spital

Konkluzione. Përmirësimi nga ana klinike dhe në EKG i pacientëve ndikohet nga profile demografik të pacientit, të kohës së ardhjes në spital nga momenti i ndodhjes së infarktit të miokardit , permasat e lezionit si dhe terapisë së përdorur.

Fjalë kyçe: ecuria, klinika, EKG, mosha, terapia.

Original scientific paper

THE ROLE OF PRESERVING THE INNER SPHINCTER MECHANISM AND THE BLADDER NECK IN THE EARLY ACHIEVING URINE CONTINENCE WHEN PERFORMING RADICAL RETROPUBIC PROSTATECTOMY

УЛОГАТА НА ЗАЧУВУВАЊЕТО НА ВНАТРЕШНИОТ СФИНКТЕРЕН МЕХАНИЗАМ И ВРАТОТ НА МОЧНИОТ МЕУР ВО РАНОТО ВРАЌАЊЕ НА УРИНАРНАТА КОНТИНЕНТНОСТ ПРИ ИЗВЕДУВАЊЕ НА РАДИКАЛНА РЕТРОПУБИЧНА ПРОСТАТЕКТОМИЈА

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ABSTRACT

Objective: To assess the effect of preserving the internal sphincter on urine continence in patients who have gone through radical prostatectomy due to prostate cancer.

Materials and methods: Open retropubic prostatectomy has been performed on 69 patients in our Urology department, of whom 44 patients were treated with careful preservation of the internal sphincter mechanism on the bladder neck, and a control group of 25 patients who didn't have preserved internal sphincter. Retrospectively, we used the standardized international questionnaires, ICIQ-UI-SF and IIEF-5, which were translated and adapted. All of the patients were operated in the period 2014-2015.

Results: Patients who had preserved inner sphincter mechanism and bladder neck during their radical prostatectomy, achieved continence much sooner, but the rate of continence in both groups after 12 months remained unchanged. The grade of incontinence till the 9-th month postoperatively was evidently lower in the examined group. The rate of anastomotic stricture and erectile dysfunction remained unchanged.

Conclusion: The remains of the internal sphincter makes passive closing mechanism that helps the continence in the patients till the distal sphincter takes over the control which happens much later in the postoperative period.

Key words: Incontinence, radical prostatectomy, inner sphincter.

INTRODUCTION

The prostate cancer is one of the most common cancer in men. As a cause of death prostate cancer is second only to lung cancer. It is estimated that in Western countries lifetime risk of developing microscopic prostate cancer is 3% (1). In biopsy results, the prevalence of microscopically discovered prostate cancer is approximately 80% of men over 80 years. However, although this is a slow-growing cancer, the risk of developing clinically detectable disease is 8% (2).

Nowadays, most commonly applied method for the treatment of prostate cancer is radical prostatectomy (RP). There are various different procedures that are at our disposal: classic retropubic (open) access, laparoscopic and robotic radical prostatectomy.

Retropubic radical prostatectomy is a method of choice for many decades. It is still considered as a gold standard in the surgical treatment of localized prostate cancer (3). Among the major clinical problems associated with surgical treatment of the prostate carcinoma are the complications that arise immediately after the surgery. Despite improvements in surgical techniques, which allow precise dissection and termino-terminal vesico-urethral anastomosis, urinary incontinence (UI) and erectile dysfunction remains a serious problem for many men and they affect the quality of the lives of more than 50% of the patients (4,5,6). The incidence of post-prostatectomy

urinary incontinence depends a lot on the scaling and grading of the incontinence and length of the post-operative care. Urinary incontinence has a spontaneous recovery in most men, but it can take up to one year after RP. In more than 10% it lasts more than one year after the surgery. The quality of life is quite impaired in these patients, particularly those who had "constantly leakage" and therefore had to use pads or diapers. This is one of the measures for scaling the severity of incontinence. In 6-9% of the patients with incontinence, surgery is necessary to solve this problem (7).

Shortcomings in the radical prostatectomy in terms of urinary incontinence has been subject of intensive research, mainly with urgent task of improving operational technique in order to maintain continence in majority of the patients. A group of technical methods, which can potentially improve continence, are associated with preservation of the neck of the bladder and the nerve pedicle lateral and posterior to the prostate.

Different preoperative risk factors and postoperative factors could affect the restoration of continence after RP. Preoperative evaluation of the individual risk will provide counseling to patients in order to achieve realistic expectations based on the status of the patient. Several predictions are under investigation, such as: age, prostate volume, stage of disease, body weight, comorbidities, history of previous dysfunctions of the lower urinary tract, but in most published studies, conservation of postoperative urinary continence is most credited to the surgical method which was applied. Hence, in this study, we focused on surgical technique as the main cause that can lead to loss or preservation of UI after RP.

In terms of anatomical and physiological division of sphincter mechanism, it is important to distinguish the role of the urethra in the retention of the urine. The urethra has two main roles:

1. To provide adequate continence mechanism (storage phase) and
2. To provide adequate bladder emptying with minimal resistance (voiding phase).

Male urethra has two main sphincter mechanisms:

a) Proximal sphincter, which is composed of the bladder neck, prostate, prostatic urethra to the verumontanum (this part is removed when a radical prostatectomy is performed),
b) Distal urethral mechanism, covering the apex of the prostate, distal urethra and the periurethral muscle structures comprised by the cylindrical rabdosphincter and smooth muscle fibers of the proximal urethra. This mechanism is very strong and provides continence after radical prostatectomy (8, 9).

According to the EUA Guidelines, Gleason score higher than 7 is not eligible for surgery and if there are distant metastases associated with local invasion, the patient is not suitable for radical prostatectomy and such patients are dismissed from this study (10).

In cases where the patient has undergone a radical prostatectomy (no matter of the surgical technique) the key role in maintaining continence switches from proximal to distal mechanism. The cause of postoperative incontinence is very different. It is even possible occurrence of "de novo" pathological process resulting with dysfunction of the bladder, but the most common reason is the loss of sphincter role of distal and proximal mechanism because of the surgical technique. In an attempt to find the most useful technique studies have showed the role of the passive continence which is especially reinforced with conservation of the neck of the bladder. Therefore numerous newly designed techniques had been used to preserve the proximal sphincter, to provide faster recuperation of the patients' continence (11, 12, 13, 14).

The aim of this study is to assess the effect of the preservation of the internal sphincter and the bladder neck on the urine continence in patients who had gone through radical prostatectomy due to prostate cancer.

MATERIALS AND METHODS

This is a non-randomized study with retrospectively collected data from 69 patients. All patients underwent open (retropubic) radical prostatectomy because of the presence of histologically confirmed, localized prostate cancer in any of the listed clinical Stage (cT1-cT3N0M0). Determining factor, in which patients we will make preservation of the internal sphincter of the bladder neck and in which not, is the intra-operative finding, i.e. the presence of fibrous tissue periprostaticaly that changes the quality of the bladder wall. Of a total 69 patients, in 44 we did precise resection of the bladder neck with preservation of the internal sphincter, with the ultimate aim of improving the functional results (urinary continence) after radical prostatectomy. In 25 patients, the resection of the bladder neck was done without extensive conservation of the sphincter; this group of patients is used as a control group. All patients were operated in the period of 2014-2016 in the Department of Urology of the City General Hospital "September 8-th" Skopje by the surgical team with more than 10 years of experience in this field of surgery. Both groups of

patients included in this study are operated in the same time frame, only the control group patients were the prior operations and the examined ones were mostly in the later years of this time period. In all these patients there has been made an attempt to do nerve spearing, i.e. preservation of the is neuro-vascular bundle.

Preoperative staging and evaluation were performed according to the guidelines of the European Association of Urology. All patients included in the study were continent before surgery. Variables that are being examined are urinary continence after removing the catheter and erectile function in patients after the surgery.

The rates of complications after reconstruction of the bladder neck (strictures on the vesico-urethral anastomosis) were also analyzed. Because all the cases, the examined and the control group, have about the same incidence of the stricture and it usually occurs more than 1 year after the operation, we do not expect its impact on the final outcome of this study. There were no cases of acute and chronic urinary retention.

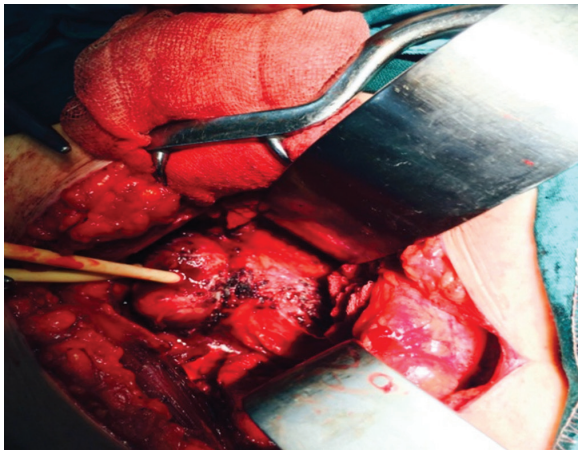
In the postoperative period the patients were examined, every 3 months: the 3th, 6th , 9th and 12th month. For the purposes of this study, patients were asked to answer to questionnaire ICIQ-UI-SF (15), which is standardized and translated in Macedonian language and is a shortened version of the long form for incontinence and disturbance of quality of life. We chose the shortened version because often patients complain and do not want to participate in studyes if it requires too much engagement from their side.

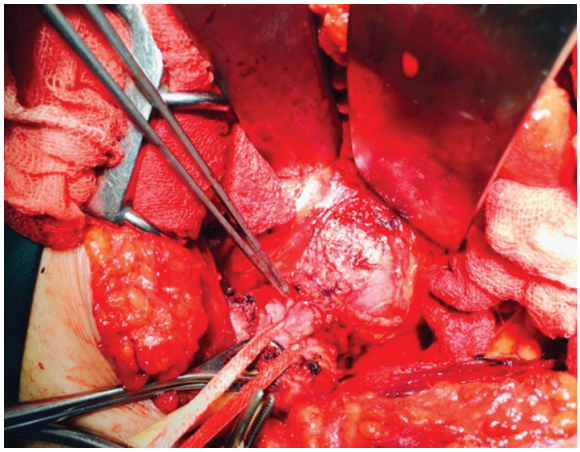
This questionnaire has a scoring system that ranges from 0-21 marks and is quite easy to use in everyday practice at the secondary and tertiary level, because it provides a quick and accurate assessment of how patients experience urinary incontinence and to what extent it is happening. Apart the ICIQ-UI questionnaire, patients answer to the IIEF-5 questionnaire for erectile dysfunction as well. Moreover, in each patient the standard postoperative care has been done. In the statistical analysis of these data is used Chi square test and the results showed significant difference (for $p < 0.05$) regarding the continence in the patients. As for the erectile function, the test showed no significance between the examined group and the control group ($p > 0.05$).

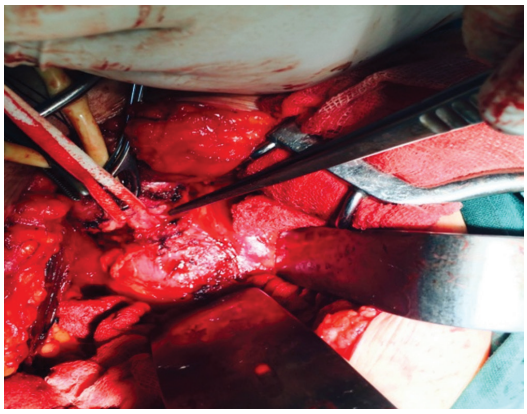
Description of the surgical method used in the study:

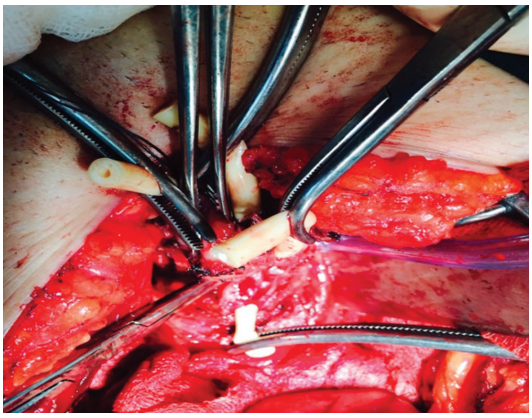
After liberating the prostate in a retrograde manner (apex release, dissection of the urethra, and retrograde dissection of the vascular loops) we continue to the prostate dissection near the bladder. This is the most important part of the procedure for the postoperative continence. The dissection has to be performed in such manner that the rabdosphincter will not be detached of the bladder wall. This will allow the muscle fiber to heal in a more natural manner and the electrophysiology of the muscle will not be damaged. After this, eversion of the lining of the bladder is performed. Additional individual sutures, using Vicryl 2/0, can be set if there is need for reinforcement of the serosa of the bladder. This is the procedure which was performed in the experimental group. In the control group, however, because of the local finding, the neck of the bladder was very stratified and had to be reconstructed in a so-called “tennis racket” manner. This is done to ensure the realignment of the muscle fibers and the bladder neck. In all patients dull and sharp dissection was done to the neuro-vascular budles without using electrocautery devices in order to leave the nerve endings intact. Vesico-urethral anastomosis is created with 6 individual sutures Vycril 2/0 (picture 1).

Picture 1. Ivchev et al. Dissection of the bladder neck with preservation of the inner sphincter. A) top left- removal of the prostate, B) top right- preserved bladder neck with urethra C) bottom left- resection of the urethra and D) bottom right - preparing for the anastomotic stitches.









RESULTS:

Patients that had preserved inner sphincter mechanism and bladder neck during their radical prostatectomy, achieved continence much sooner, but the rate of continence in the examined and the control group both after 12 months remained unchanged (showen in figure 1 and 2).

Figure 1. The rate of continence in the examined group

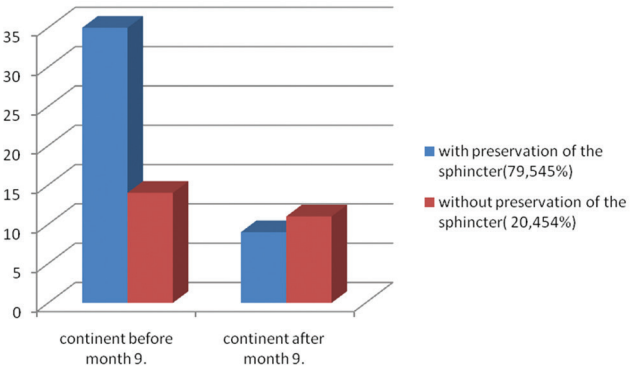
Examined patients (total 44)	ICIQ points	Months of incontinence	ED points
1	10	3 - 6	4
2	0	3 - 6	4
3	0	3 - 6	4
4	0	0 - 3	4
5	6	0 - 3	4
6	15	>12	4
7	11	0 - 3	4
8	13	>12	4
9	4	0 - 3	4
10	0	0 - 3	4
11	0	0 - 3	4
12	0	0 - 3	4
13	0	0 - 3	4
14	0	0 - 3	4
15	9	6 - 9	4
16	8	3 - 6	4
17	16	>12	4
18	0	0 - 3	4
19	16	3 - 6	4
20	13	0 - 3	4
21	7	0 - 3	4
22	8	3 - 6	4
23	0	0 - 3	4
24	0	0 - 3	4
25	0	3 - 6	4
26	9	0 - 3	4
27	13	>12	4
28	15	>12	4
29	12	0 - 3	4
30	9	0 - 3	4
31	11	0 - 3	4
32	15	0 - 3	4
33	7	0 - 3	4
34	7	0 - 3	5
35	7	0 - 3	4
36	0	0 - 3	4
37	9	6 - 9	4
38	11	>12	4
39	9	0 - 3	8
40	4	0 - 3	10
41	6	6 - 9	4
42	0	6 - 9	4
43	8	0 - 3	12
44	4	0 - 3	10

Figure 2. The rate of continence in the control group

Control group (total 25)	ICIQ points	Months of incontinence	ED points
1	0	0 - 3	4
2	10	>12	4
3	15	>12	4
4	14	>12	4
5	6	3 - 6	4
6	13	>12	4
7	0	0 - 3	4
8	0	6 - 9	9
9	0	>12	4
10	0	0 - 3	6
11	5	>12	4
12	6	0 - 3	4
13	14	>12	4
14	9	>12	4
15	0	0 - 3	4
16	7	>12	4
17	10	>12	4
18	5	0 - 3	11
19	5	6 - 9	4
20	0	0 - 3	4
21	5	6 - 9	4
22	14	>12	4
23	10	>12	4
24	6	0 - 3	6
25	9	6 - 9	4

The grade of incontinence till the 9-th month postoperatively was evidently lower in the examined group. Precisely 79.5% of the patients with preserved inner sphincter were continent before month 9, and only 20.4% of those without preservation of the bladder neck (shown in figure 3).

Figure 3. Continency before and after 9 months. Results, Ivchev et al.



The rate of anastomotic stricture and erectile dysfunction remained unchanged. The careful preserving of internal sphincter and bladder neck shows that the remains of the internal sphincter makes passive closing mechanism that helps the continence in the patients till the distal sphincter takes over the control. This happens much later in the postoperative time due to the complexity of the distal sphincter.

DISCUSSION

Investigated in our study was the technique of preservation of the bladder neck during a prostatectomy. Many other techniques for the bladder neck exist, like tunelisation of the bladder neck using a circular stitching, intussusception of the bladder neck and plication of the bladder neck. The effectiveness of these techniques has not been confirmed in large prospective studies, although their use is rational from an anatomical point of view. Published long-term results are limited. Several studies mention the increased risk of complications associated with more aggressive techniques of reconstruction of the bladder neck. Possible explanation for the rapid restoration of continence is the presence of so-called proximal passive mechanism for closing the opening in the neck of the bladder.

In these limited follow-up period in some patients occurred strictures on the vesico-urethral anastomosis, but the rate is low. In addition, it can be said that the greatest risk of anastomotic stricture is present in the first postoperative year. In the opinion of some urologists, the area of the bladder neck after prostatectomy did not play a significant role in urinary continence. Proponents of this theory suggest that achieving continence is only a matter of time necessary for the distal sphincters that are quite complex to take the leading role. We believe that early after the surgery (up to 6 months) the mechanism of the passive proximal closure may be beneficial to the urinary control and can compensate at least partly from changes in abdominal pressure. Later, structural and functional correction of the distal sphincter is important in all patients because it can cause a significant difference in the rate of continence among the subjects examined after the 12th month of operation. The obvious limitation of our study may come only by the fact that although we are trying to do preservation of the neuro-vascular pedicle, objective way to prove how much of it is damaged or not, does not exist. Since we know that nerves play a big role in the quick functional reconstruction of the sphincter mechanism, the preservation of the nerv bundle can be a reason for bias in the study.

CONCLUSION

Continence recuperates much faster in patients with preserved inner sphincter mechanism and bladder neck after radical prostatectomy. There is also evident reduction in the grade of remaining incontinence .The effect is insignificant after the 12-th postoperative month.

REFERENCES

1. Schaeffer EM, Partin AW, Lepor H, Walsh PC. Cambbell-Walsh Urology. Tenth edition. Chapter 102. 2012. Radical retropubic and radical prostatectomy; pp. 2801–2829.
2. Roger SK, Manish IP. Fast facts : Prostate cancer, 8th ed. Abingdon; Health Press Ltd., 2014.
3. Brunocilla E, Schiavina R, Pultrone CV, Borghesi M, Rossi M, Cevenini M, Martorana G. Preservation of the smooth muscular internal (vesical) sphincter and of the proximal urethra for the early recovery of urinary continence after retropubic radical prostatectomy: a prospective case-control study. Int J Urol. 2014 Feb;21(2):157-62.
4. Poon M, Ruckle H, Bamshad BR, Tsai C, Webster R, Lui P. Radical retropubic prostatectomy:Bladder neck preservation versus reconstruction. J Urol. 2000;163:1948.
5. Srougi M, Nesrallah LJ, Kauffmann JR, Nesrallah A, Leite KR. Urinary continence and pathological outcome after bladder neck preservation during radical retropubic prostatectomy: A randomized prospective trial. J Urol. 2001;165:815–8.
6. Klein EA. Early continence after radical prostatectomy. J Urol. 1992;148:92–5.
7. Latiff A. Preservation of bladder neck fibers in radical prostatectomy. Urology. 1993; 41:566–7.
8. Gaker DL, Steel BL. Radical prostatectomy with preservation of urinary continence: Pathology and long-term results. J Urol. 2004;172:2549–52.
9. Nyarangi-Dix JN, Radtke JP, Hadaschik B, Pahernik S, Hohenfellner M. Impact of complete bladder neck preservation on urinary continence, quality of life and surgical margins after radical prostatectomy: A randomized, controlled, single blind trial. J Urol. 2013;189:891–8.
10. European Association of Urology Guidelines 2015, https://uroweb.org/guidelines/.

11. Koraitim MM. The male urethral sphincter complex revisited: An anatomical concept and its physiological correlate. J Urol. 2008;179:1683–9.
12. Gomez CA, Soloway MS, Civantos F, Hachiya T. Bladder neck preservation and its impact on positive surgical margins during radical prostatectomy. Urology. 1993;42:689–93.
13. Gudziak MR, McGuire EJ, Gormley EA. Urodynamic assessment of urethral sphincter function in post-prostatectomy incontinence. J Urol. 1996;156:1131–4.
14. Braslis KG, Petsch M, Lim A, Civantos F, Soloway MS. Bladder neck preservation following radical prostatectomy: Continence and margins. Eur Urol. 1995;28:202–8.
15. International Consultation on Incontinence Modular Questionnaire (ICIQ), http://www.iciq.net/ICIQ.FLUTSsex.html.

УЛОГАТА НА ЗАЧУВУВАЊЕТО НА ВНАТРЕШНИОТ СФИНКТЕРЕН МЕХАНИЗАМ И ВРАТОТ НА МОЧНИОТ МЕУР ВО РАНОТО ВРАЌАЊЕ НА УРИНАРНАТА КОНТИНЕНТНОСТ ПРИ ИЗВЕДУВАЊЕ НА РАДИКАЛНА РЕТРОПУБИЧНА ПРОСТАТЕКТОМИЈА

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Градска општа болница “8ми Септември” Скопје, уролошко одделение

АБСТРАКТ

Цел: Да се процени улогата на зачувувањето на внатрешниот сфинктер на уринарната континентност кај пациенти кај кои е направена радикална простатектомија поради карцином на простатичната жлезда.

Материјал и методи: Отворена ретропубична простатектомија направена е кај 69 пациенти на уролошкото одделение, од кои кај 44 пациенти направено е внимателно зачувување на внатрешниот сфинктерен мехамизам на вратот на мочниот меур, а кај контролната група од 25 пациенти направена е операција без зачувување на внатрешниот сфинктер. Ретроспективно, го употребивме стандардниот меѓународен прашалник ICIQ-UI-SF и IIEF-5, кои беа преведени и адаптирани на наши услови. Сите пациенти беа оперирани во периодот од 2014 до 2015 година.

Резултати: Пациентите кои имаа зачуван внатрешен сфинктерен механизам и врат на мочниот меур за време на нивната радикална простатектомија, добија континентност многу порано, но стапката на континентност кај двете групи после 12 месеци остана непроменета. Степенот на инконтиненција се до 9-тиот месец постоперативно, беше евидентно понизок кај испитуваната група. Стапката на стриктури на местото на анастомозата и на еректилната дисфункција останаа непроменети.

Заклучок: Зачуваниот внатрешен сфинктер овозможува пасивен механизам на затворање кој ја помага континетноста кај пациентите се додека дисталниот сфинктер ја превземе контролата, што се случува многу покасно во постоперативниот период.

Клучни зборови: Инконтинентност, радикална простатектомија, внатрешен сфинктер.

Original scientific paper

PERSONAL ASSESSMENT OF HOSPITALIZATION AND THE POSSIBILITIES FOR COMPLAINT - COMPARATIVE ANALYSIS OF THE SITUATION IN PUBLIC AND PRIVATE HOSPITALS IN KOSOVO

VLERËSIMI PERSONAL I HOSPITALIZIMIT DHE MUNDËSITË PËR ANKESË - ANALIZË KRAHASUESE E GJENDJES NË SPITALE PUBLIKE DHE PRIVATE NË KOSOVË

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ABSTRACT

Patients and their relatives are the only source of data for information on the dignity and respect with which they treated and the best source of information on patients' needs. A health service that does not listen to complaints is unlikely to reflect its patients' needs.

The purpose of this study was to assess the patient complaints and patient satisfaction with healthcare services as a measure of the quality of hospital care.

Material and methods: This is a cross sectional study. Data collection was conducted through a standardized questionnaire. The study included 2605 patients aged 15+, who were randomly selected and who have been hospitalized in clinics of the University Clinical Center of Kosovo and other public and private hospitals in Kosovo. Analysis of data is made using statistical programs (Statistica for Windows 7,0 and SPSS 17.0). Chi square test and Fisher exact test, were used to determine the difference between attributive variables in two groups. To determine the statistical significance we used a significance level for $p < 0.05$ and $p < 0.01$.

Results and discussion: A total of 1054 (51.3%) of patients in public hospitals and 357 (71%) of private hospitals reported they have information about right for formal complaint. For $p < 0,0001$, we found a significant difference between level of awarenes of patients in public and private hospitals for the opportunity to a formal complaint in the hospital (Chi-square: 80,935, df = 2, p = 0,0001). The reason for the complaint of the patients hospitalized in the public hospital is about 2,619 times greater than patients in private hospitals [OR = 2,619 (1.955-3508) 99% CI].

Conclusion: Rigorous analysis of the patient complaints will help to identify and solve problems in patient safety and better quality of care.

Keywords: Assessment, complaints of patients, public and private hospitals, Kosovo

INTRODUCTION

Quantitative measurement of patient complaints is a comparative measure of service quality, (1-3) and several authorities believe that quality-assurance measures should include patient satisfaction and an analysis of

patient complaints.(3-5). "A health service that does not listen to complaints is unlikely to reflect its patients' needs. One that does will be more likely to detect the early warning signs that something requires correction, to address such issues and to protect others from harmful treatment." "A complaints system that does not respond flexibly, promptly and effectively to the justifiable concerns of complainants not only allows unacceptable practice to persist, it aggravates the grievance and suffering of the patient and those associated with the complaint, and undermines the public's trust in the service" (8). The need for continuous improvement of quality and safety in the provision of patient care has become axiomatic. Patients and their relatives are the only source of data for information on the dignity and respect with which they are treated and the best source of information on patient education and pain-management (9).

Assessment, monitoring and exploration of patient complaints and patient satisfaction data provide one indicator of quality of care (10), that can contribute to clinical care improvement strategies (11) and provide health care consumers input into improvement of health care services and delivery (12). Patient complaint and satisfaction data is used for two purposes. Firstly to evaluate patient care and secondly to predict patient 'consumer' behaviour (ie will they recommend a health care service or return for care in the future) (13). Ware et al proposed characteristics of the health care providers and services that influence patient satisfaction. The dimensions of patient satisfaction include: art of care (caring attitude); technical quality of care; accessibility and convenience; finances (ability to pay for services); physical environment; availability; continuity of care; efficacy and outcome of care (13). The first study published by Ooi identifed standard of care and communication issues as the major sources of complaints (14). Although there was no standard categorisation system across different studies, the main reasons for complaints revolved around standard of care, communication and waiting time issues (15, 16, 17). It has been reported that female patients generate more complaints than male patients (18, 19) but the reason is not known. Likewise, the higher complaint rate in public patients has not been explained.

The purpose of this study was to assess the patient complaints and patient satisfaction with healthcare services as a measure of the quality of hospital care in public and private hospitals in the territory of Kosovo.

MATERIAL AND METHODS

This is a quantitative analytical study - cross sectional study. Data collection was achieved through a survey using a standardized questionnaire. Quality is measured based on selected and defined key performance indicators (KPIs) for the process and results of the process. Survey questions related to perceptions of hospital care by measuring service conditions, organization of hospital care, and patient communication - health personnel. The questions were grouped and measured seven aspects of patient care: 1. Admission to the hospital; 2. Condition of the patient before hospital admission; 3. Stay in the hospital; 4. Treatment and opinion on the conditions in the hospital; 5. The way how the hospital meets the needs of the patient; 6. Discharge from the hospital; 7. The overall experiences and impressions of their stay in hospital. To ensure a fully representative of the population in this study were surveyed a total of 2605 respondents with 95% level of significance (CI) and confidence interval 2. Target group were respondents who were admitted to hospital in 2015 and early 2016, within 12 months before the time of the survey. The survey included 2605 respondents 15+, who were selected randomly and who have been in hospital or clinics of University Clinical Center of Kosovo and other public and private hospitals in Kosovo. Processing of data obtained from the survey is made using appropriate statistical programs (Statistica for Windows 7,0 and SPSS 17.0). Pearson Chi square test and Fisher exact test, are used to determine the difference between certain attribute dichotomous variables in two groups of subjects. The risk factors were quantified using terms of probabilities (Odd ratio - OR). Spearman rank correlation coefficient was used to determine the association between non-homogenite numerical statistical series. To test the significance of the differences between certain independent parameters with an irregular distribution of frequencies used are non-parametric tests for independent samples and consequently Mann Whitney U test and Kruskal Wallis test. Multiple linear regression analysis was used for identifying and quantifying the significant independent predictors. To determine the statistical significance we used a significance level for $p < 0.05$ and $p < 0.001$.

RESULTS

To evaluate the possibilities of complaint that patients in public and private hospitals, within the survey asked three questions with possible answers: a) Yes b) No c) Not sure.

To the question "Are you informed that you are eligible for a formal complaint to the hospital" a total of 1054 (51.3%) patients in public hospitals and 357 (71%) in private hospitals reported that they have information. Statement "not sure" gave 149 (7.2%) patients from the public and 50 (9.9%) patients in private hospitals. For p <0.05, found a significant difference between patients in public and private hospitals in the awareness of the opportunity for a formal complaint to the hospital (Pearson Chi-square: 80,935, df = 2, p = 0,0001). Further analysis to answer yes / no, indicated no significant difference between patients in two groups (Pearson Chi-square: 84,353; df = 1; p = 0,0001). The probability of patients hospitalized in public hospitals, to be informed of the appeal is 66.8% lower compared with patients in private hospitals with real population effect between 73,9% and 57,6% [OR = 0,332 (0,261 - 0,424) 99 % CI] (table 1, chart 1).

Table. 1. Descriptive analysis of the sample in a hospital and reporting to a formal complaint

Notice of the right to formal complaint to the hospital Public		Hospitals		Total
		Private		
Yes	N	1054	357	1411
	%	51,26%	70,97%	
No	N	853	96	949
	%	41,49%	19,09%	
I'm not sure	N	149	50	199
	%	7,25%	9,94%	
Total	N	2056	503	2559
	%	80,34%	19,66%	100%

Pearson Chi-square: 80,935, df=2, p=0,0001* * significant for p<0,05
Pearson Chi-square: 84,353, df=1, p=0,0001* yes/no

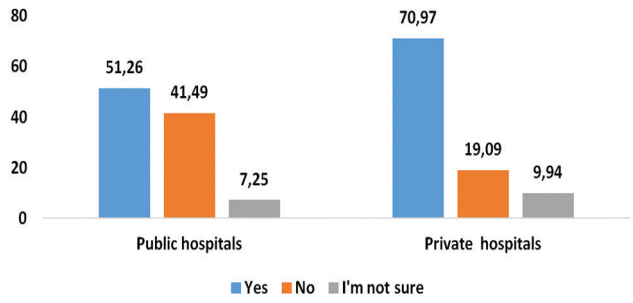

Chart 1. Descriptive analysis of the sample in a hospital and reporting to a formal complaint

An analysis of the interrelation between the notification of the right to formal complaints and the overall satisfaction of patients from public or private hospitals. In public hospitals, consequently determined the existence of linear positive weak correlation (Spearman Rank Order Corellation: R = 0,213) ie with increasing awareness of complaint grows and patient satisfaction. In private hospitals, consequently determined the existence of a strong positive linear correlation (Spearman Rank Order Corellation: R = 0,435) ie with increasing awareness of complaint grows and patient satisfaction.

The question "Did you have any reason to complain during your stay?" A total of 521 (25.5%) of patients in public hospitals and 58 (11.5%) patients in private hospitals said they had cause for complaint. Statement "not sure" gave 94 (4.6%) patients from public and 29 (5.8%) patients from private hospitals. For p <0,05, found a significant difference between patients in public and private hospitals in terms of having a reason for complaint (Pearson Chi-square: 44,976; df = 2; p = 0,0001). Further analysis to answer yes / no indicated significant difference between patients in the two groups (Pearson Chi-square: 44,118; df = 1; p = 0,0001). The probability of patients hospitalized in public hospitals have cause for complaint is about 2,619 times greater than patients in private hospitals [OR = 2,619 (1,955 - 3,508) 99% CI]. Analysis by type of hospital and having the reason for appeal is given in Table 2.

Table 2. Descriptive analysis of the sample in a hospital and having a reason for complaint

Having a reason for complaint Public		Hospitals		Total
		Private		
Yes	N	521	58	579
	%	25,51%	11,53%	
No	N	1427	416	1843
	%	69,88%	82,70%	
I'm not sure	N	94	29	123
	%	4,60%	5,77%	
Total	N	2042	503	2545
	%	80,24%	19,76%	100%

Pearson Chi-square: 44,976, df=2, p=0,0001** significant for p<0,05
Pearson Chi-square: 44,118, df=1, p=0,0001* yes/no

The question "Have you submitted a complaint?" 94 (4.7%) of patients in public hospitals and 10 (2.1%) patients in private hospitals said that they submitted a complaint. For p <0,05, we found a significant difference between patients in public and private hospitals in terms of having a reason for complaint (Pearson Chi-square: 6,269; df = 2; p = 0,012). The probability of patients hospitalized in public hospitals to appeal is 2,272 times greater than patients in private hospitals [OR = 2,272 (1,174 - 4,394) 99% CI]. Despite the fact that patients in public hospitals have

reason for complaint, they do not present complaint, this can be explained by the fact that may be fear of punishment during treatment (Table 3).

Table 3. Descriptive analysis of the sample in a hospital and complaint

Complaint Public		Hospitals		Total
		Private		
Yes	N	94	10	104
	%	4,66%	2,11%	
No	N	1924	465	2389
	%	95,34%	97,89%	
Total	N	2018	475	2493
	%	80,95%	19,05%	100%

Pearson Chi-square: 6,269, df=2, p=0,012* * significant for p<0,05

The respondents were asked two questions of which the first relates to their personal assessment of the impact of hospitalization on improving the health condition and the second relates to the assessment of length of stay in hospital. Regarding the question "How much you have been helped during hospitalization?", Patients were able to choose one of five possible answers: a) much; b) partially; c) slightly; d) not at all; e) I'm not sure / on.

Table 4. Descriptive analysis of the sample by type of hospital and post how much help hospitalization

"How much did you been helped during hospitalization? Public		Hospitals		Total
		Private		
Much	N	410	224	634
	%	19,71%	44,27%	
Partially	N	1502	281	1783
	%	72,21%	55,53%	
Slightly	N	126	1	127
	%	6,06%	0,20%	
Not at all	N	25	0	25
	%	1,20%	0%	
I'm not sure / a	N	17	0	17
	%	0,82%	0%	
Total	N	2080	506	2586
	%	80,43%	19,57%	100%

Pearson Chi-square: 91,85, df=4, p=0,00001* * significant for p<0,05
Pearson Chi-square: 108,39, df=1, p=0,00001* a lot / partially

410 (19.7%) of patients in public hospitals and 224 (44.3%) in private hospitals have been helped by the staff «much», «moderate» from 1502 (72.2%) patients from a public hospital and 281 (55.5%) in the private sector. Only 1 (0.2%) patients in private and 126 (6.1%) than those in public hospitals declared the assistance of personnel during hospitalization as «minor». For p <0.05, we found a significant difference between patients in public and private hospitals in the comments what was assistance during hospitalization (Pearson Chi-square: 91.85; df = 4, p = 0.00001) in addition to opinion positive patients from private hospitals. Further analysis of the respondents / part noted that for p <0.05, there is a significant difference between patients in public and private hospitals (Pearson Chi-square: 108.39, df = 4, p = 0.00001) in addition to patients from private hospitals (Table 4).

The survey was analyzed in relation to the question "How would you rate the length of time you have spent in the hospital?". They were given four possible answers: a) it should; b) very short; c) very long and d) I'm not sure / on. Total 1273 (61.8%) of patients in public and 401 (79.2%) than those in private hospitals consider the length of stay was "Adequate time". Patients in public or private hospitals assessed the length of hospitalization as "very short" of consequently 368 (17,9%) v.s. 67 (13.2%); "Very long" for the consequent 240 (11,7%) v.s. 2 (0.4%) and "not sure / 'for the consequent 178 (8,6%) v.s. 36 (7.1%).

Table 5:. Descriptive analysis of the sample in a hospital and opinion on the length of hospitalization

Opinion on the length of hospitalization Public		Hospitals		Total
		Private		
Adequate time	N	1273	401	1674
	%	61,83%	79,25%	
A lot short	N	368	67	435
	%	17,87%	13,24%	
Very long	N	240	2	242
	%	11,66%	0,40%	
I'm not sure	N	178	36	214
	%	8,64%	7,11%	
Total	N	2059	506	2565
	%	80,27%	19,73%	100%

Pearson Chi-square: 76,764, df=3, p=0,00001* * significant for p<0,05
Pearson Chi-square: 14,626, df=1, p=0,0001* Adequate time/ A lot short
Pearson Chi-square: 68,093, df=1, p=0,0001* Adequate time/ very long
Pearson Chi-square: 36,092, df=1, p=0,0001* very long / A lot short

For p <0,05, found a significant difference between patients in public and private hospitals on the comments for the length of hospitalization (Pearson Chi-square: 76,764; df=3; p=0,00001). Further analysis indicated that, for p<0,05, there is a significant difference between the two patient groups with regard to each of the combinations of possible answers (Table 5, chart 2).

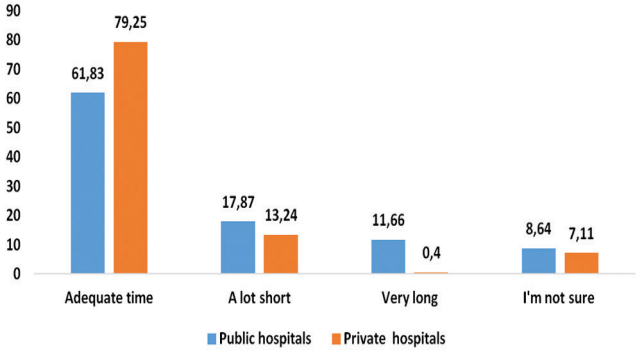

Chart 2. Descriptive analysis of the sample in a hospital and opinion on the length of hospitalization

DISCUSSION

A range of clinical, management and relationship issues underlie patient complaints. The systematic collation of data on patient complaints potentially provides a mechanism through which the standard of healthcare can be monitored and system-level interventions developed (20). In the final report (6) the impression that this sense of confusion caused by lack of information made people fear that they or their relative had not received the right care. As a result, they were more likely to question the treatment or make a formal complaint.

Complaints analyses, though not without limitations, help to highlight service gaps that need to be bridged, and procedures and policies that need to be changed. Findings could also be translated into staff training goals. Although it is unlikely that patients' complaints can ever be totally eliminated because it is impossible to "please all of the people all the time", particularly where it hinges on standard of medical care, communication and systems that could be improved. On the other hand, there must also be appropriate checks and balances, to ensure that doctors can continue to practise good medicine in the wider interests of all patients with the confidence that the hospital will stand up for them if the complaints are not valid. Only with such actions doctors can feel safe to practise cost-effective medicine. Staff-patient communication and organisation/logistics must be continually improved to reduce complaints, while upholding a good standard of care. (21) Patient complaints provide a valuable source of insight into safety-related problems within healthcare organisations (22) thus, patient complaints can provide important and additional information to healthcare organisations on how to improve patient safety (23). Studies of patient complaints do not have comparison data on complaint rates. Some studies found that female patients generate more complaints than male patients (18,19) but the reason is not known. Overall complaint rate in Australian hospital is 1.12 complaints/1000 patients, but a higher rate was reported in a US hospital (5 complaints/ 1000). Complaints relating to communication were common, as also reported in other studies (4). Studies evaluated in this systematic review do not support the claim that the private sector is usually more efficient, accountable, or medically effective than the public sector (7).

This indicates a fundamental failure of staff to interact appropriately with patients (24). Lack of clear communication and not updating the patient or family members if the patient's condition changes is one item from most 10 items compiled (25) which they note should be used as a conversation starter in healthcare.

CONCLUSION

Information on the possibility of complaints, had a slightly higher percentage in private hospitals. Reasons for complaints were higher in public hospitals, but not declared enough, perhaps for fear of punishment receiving health services. Rigorous analyses of patient complaints will help to identify and solve problems in patient safety. To achieve this, it is necessary to standardise how patient complaints are analysed and interpreted. Furthermore explanation, information provision, and resolution of misunderstandings contributed to a successful outcome for many patients, suggesting that communication problems may underpin most complaints lodged.

REFERENCES

1. Schwartz LR, Overton DT. Emergency department complaints: a one-year analysis. Ann Emerg Med 1987; 16: 857-861.

2. Burstin HR, Conn A, Setnik G, et al. Benchmarking and quality improvement: the Harvard Emergency Department Quality Study. Am J Med 1999; 107: 437-449.
3. Schwartz LR, Overton DT. The management of patient complaints and dissatisfaction. Emerg Med Clin North Am 1992; 10: 557-572.
4. Anderson K, Allan D, Finucane P. A 30-month study of patient complaints at a major Australian teaching hospital. J Qual Clin Practice 2001; 21: 109-111.
5. Javetz R, Stern Z. Patients' complaints as a management tool for continuous quality improvement. J Manag Med 1996; 10: 39-48.
6. Putting Patients back in the Picture – final Report, A Review of the NHS Hospitals Complaints System, Ann Clwyd MP and Professor Tricia Hart, 2013 https://www.gov.uk/government/publications/nhs-hospitals-complaints-system-review
7. Basu S, Andrews J, Kishore S, Panjabi R, Stuckler D. Comparative Performance of Private and Public Healthcare Systems in Low- and Middle- Income Countries: A Systematic Review. PLoS Med, 2012, 9(6)
8. Robert Francis QC. Public Inquiry into the Mid Staffordshire NHS Foundation Trust 2013, Volume 1, Chapter 3 pp 245-287 Mid Staffordshire Inquiry Report https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/255615/NHS_complaints_accessible.pdf
9. Cleary PD. A hospitalization from hell: a patient's perspective on quality. *Annals of Internal Medicine* 2003;138(1):33-9.
10. Leino-Kilpi H, Vuorenheimo J. Patient satisfaction as an indicator of the quality of nursing care. *Nordic Journal of Nursing Research & Clinical Studies / VÃ¥rd i Norden* 1992;12(3/4):22.
11. Bendall-Lyon D, Powers TL. The role of complaint management in the service recovery process. *Joint Commission Journal on Quality Improvement* 2001;27(5):278-86.
12. Vuori H. Patient satisfaction--does it matter? *Quality Assurance in Health Care* 1991;3(3):183-9.
13. Ware J, Davies-Avery A, Stewart A. The Measurement and Management of Patient Satisfaction: A Review of the Literature, 1977.
14. Miró O, Sánchez M, Espinosa G, Millá J. Quality and effectiveness of an emergency department during weekends. Emerg Med J 2004; 21:573-4.
15. Taylor DM, Wolfe R, Cameron PA. Complaints from emergency department patients largely result from treatment and communication problems. Emerg Med (Fremantle) 2002; 14:43-9.
16. Schwartz LR, Overton DT. Emergency department complaints: a one- year analysis. Ann Emerg Med 1987; 16:857-61.
17. Salazar A, Ortiga B, Escarrabill J, Corbella X. Emergency department complaints: a 12 year study in a university hospital. Ann Emerg Med 2004; 44: Supp1 ACEP Research Forum.
18. Schwartz LR, Overton DT. Emergency department complaints: a one-year analysis. Ann Emerg Med 1987; 16: 857-861
19. Daniel AE, Burn RJ, Horarik S. Patients' complaints about medical practice. Med J Aust 1999; 170: 598-602.
20. Reader TW, Gillespie A, Roberts J. Patient complaints in healthcare systems: a systematic review and coding taxonomy . BMJ Qual Saf 2014;0:1–12. doi:10.1136/bmjqs-2013-002437
21. Wong L L, Ooi S B S, Goh L G. Patients' complaints in a hospital emergency department in Singapore. Singapore Med J 2007; 48 (11) : 990
22. Donaldson L. An organisation with a memory: Learning from adverse events in the NHS. London: Department of Health, 2000.
23. Weingart SN, Pagovich O, Sands DZ, et al. What can hospitalized patients tell us about adverse events? Learning from patient-reported incidents. J Gen Intern Med 2005;20:830–6.
24. David McD Taylor, Rory S Wolfe and Peter A Cameron. Analysis of complaints lodged by patients attending Victorian hospitals, 1997–2001. MJA 2004; 181: 31–35
25. http://health.usnews.com/health-news/patient-advice/slideshows/the-most-common-patient-complaints.

VLERËSIMI PERSONAL I HOSPITALIZIMIT DHE MUNDËSITË PËR ANKESË - ANALIZË KRAHASUESE E GJENDJES NË SPITALE PUBLIKE DHE PRIVATE NË KOSOVË

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ABSTRAKTI

Pacientët dhe të afërmit e tyre janë burimi i vetëm i të dhënave për informacion mbi dinjitetin dhe respektin me të cilin ata trajtohen dhe burimi më i mirë i informacionit mbi nevojat e pacientëve. Një shërbim shëndetësor që nuk e dëgjon ankesat nuk ka gjasa për të reflektuar nevojat e pacientëve të saj.

Qëllimi i këtij studimi ishte për të vlerësuar ankesat e pacientit dhe kënaqësinë e pacientit me shërbimet e kujdesit shëndetësor, si një masë e cilësisë së kujdesit spitalor.

Materiali dhe metoda: Ky studim është një studim transversal - cross sectional. Mbledhja e të dhënave është realizuar përmes pyetësorit të standardizuar. Studimi përfshiu 2605 pacientë të moshës 15+, të cilët janë zgjedhur në mënyrë të rastësishme dhe të cilët kanë qenë të hospitalizuar në klinikat e Qendrës Klinike Universitare të Kosovës dhe spitalet e tjera publike dhe private në Kosovë. Analiza e të dhënave është bërë duke përdorur programet statistikore (Statistica for Windows 7,0 dhe SPSS 17.0). Chi square dhe testi Fisher janë përdorur për të përcaktuar dallimin në mes të variablave atributive në dy grupe. Për të përcaktuar rëndësinë statistikore kemi përdorur nevelet e besueshmerisë për $p < 0.05$ dhe $p < 0.01$.

Rezultatet dhe diskutimi: Një total prej 1054 (51.3%) të pacientëve në spitalet publike dhe 357 (71%) të spitaleve private kanë raportuar që kanë informacion. Për $p<0,0001$, gjetëm një ndryshim të rëndësishëm midis pacientëve në spitale publike dhe private në vetëdijen e mundësive për një ankesë formale në spital (Chi-testi: 80,935, df = 2, p = 0,0001. Arsyea për ankesa e pacientëve të hospitalizuar në spitalet publike është rreth 2,619 herë më e madhe se sa pacientët në spitalet private [OR = 2,619 (1,955-3.508) 99% CI].

Përfundimi: Analiza rigoroze e ankesave të pacientëve do të ndihmojë për të identifikuar problemet dhe zgjidhjet në sigurinë e pacientit dhe kujdesin cilësor.

Fjalët bosht: Vlerësimi, ankesat e pacientëve në spitalet publike dhe private, Kosova

Original scientific paper

THE NEPHRON SPARING SURGERY IN LOCALIZED RENAL TUMOR

KIRURGJIA E RUAJTJËS SË VESHKËS TE TUMORI I LOKALIZUAR NË VESHKË

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ABSTRACT

Purpose: Conservative renal surgery has become the gold standard treatment for small and peripheral malignant kidney lesions or in cases of reduced renal function or bilateral lesions.(1)

The first nephron-sparing surgery (NSS) for a renal tumor was done by Czerny in 1887.(2)

Aim: Our objectice is to analyze the importance of renal tumor size and his localization in kidney in success rate of NSS in our operated patients.

Material and methods: We retrospectively analyzed our database relating to the use of NSS in 33 ptts from 216 ptts. operated for renal tumor in the cohort study January 2000 through December 2015. All patients included in analysis were with a single renal mean tumor size 3,6 cm (range 3,2 - 4,3cm) and with a normal contralateral kidney.

Results: We have performed 33 nephron sparing surgeries in a total of 216 patients, 16 were female and 17 were male. The patients mean age was 49 ± 9.5 years and in all patients the indication was elective. In 19 patients lesions were located in the upper pole, 13 in the lower pole. One case was with meso-renal location. In our study, NSS corresponds to 26 % of the operated tumors, but in other series reaches from 20 - 32% of the performed partial nephrectomies.(5)

Conclusiones: In patients with solitary, small localized, unilateral renal tumors with normal contralateral kidney, elective open NSS is safe and provides excellent long-term local control.

Keywords: NSS, open surgery.

INTRODUCTION

Conservative renal surgery has become the gold standard treatment for small and peripheral malignant kidney lesions or in cases of reduced renal function or bilateral lesions.(1)

The first nephron-sparing surgery (NSS) for a renal tumor was done by Czerny in 1887. (2)

Nephron sparing surgery provides effective therapy in patients with a solitary sporadic renal tumor 4 cm. or less and in presence of normal contralateral kidney or in presence of an anatomic or functional solitary kidney. (3)

In 1950, Vermooten first suggested that localized RCC could successfully be excised while leaving a surrounding area of normal renal parenchyma.(4) Nephron sparing surgery provides effective therapy in patients with a solitary sporadic renal tumor 4 cm or less and in presence of normal contralateral kidney or in presence of an anatomic or functional solitary kidney.(4)

However, the optimal selection criteria for NSS have not yet been defined.

Recent studies have suggested that nephron sparing

surgery and radical nephrectomy provide equally effective therapy for patients with small (less than 4 cm), solitary, unilateral renal cell carcinoma and a normal contralateral kidney . (5,6)

The indications for nephron-sparing surgery in patients with unilateral renal tumor and a completely normal opposite kidney are not established, and radical nephrectomy should still be considered the treatment of choice in this setting. (7)

Partial nephrectomy in patients with a normal contralateral kidney is still under discussion. However, the optimal selection criteria for NSS have not yet been defined.

Partial nephrectomy in solitary kidneys carries the risk of tumor progression as well as loss of renal function but more and more surgeons perform nephron sparing surgery in these patients with good results . (8,9)

The risk of local recurrence depends primarily on the initial local pathological tumor stage.

By some studies the risk of multifocal disease is low at less than 5% when the maximal diameter of the primary tumor is 4 cm or less. The reported incidence of multifocal renal cell carcinoma (RCC) is approximately 15% and it also depends on tumor size, histology and stage. (10)

For renal cell carcinoma long-term cancer-free survival is comparable to that after radical nephrectomy, particularly for low stage disease.

The various series have proved that NSS technical success rate is safe, cost-effective and results in low morbidity. (11,12)

AIM

Our aim is to analyze the importance of renal tumor size and his localization in kidney in success rate of NSS in our operated patients.

MATERIAL & METHODS:

We retrospectively analyzed our database relating to the use of NSS in 33 ptts from 126 ptts operated for renal tumoral mass in the cohort study January 2000 through December 2015.

The majority of tumors lesions were incidental findings by ultrasound abdomen (US), contrast enhanced computed tomography (CECT) or magnetic resonant imaging (MRI) abdomen scan in 26 cases for various medical indications and symptomatic (with flank pain) only in 7 cases.

Radiographic data was used to exclude locally advanced or metastatic disease.

The relevant data of 33 patients were analyzed, with special focus in the size of the renal tumor obtained from radiological investigations, the operative details (the need for clamping the renal pedicle, the marking out the limits of the visible lesion about 5 mm), pathology results (sending tumor and perirenal fat), intra- and postoperative complications and follow up by radiological investigations.

RESULTS

We have performed 33 nephron sparing surgeries in a total of 216 patients, 16 were female and 17 were male. All patients included in analysis were with a single renal mean tumor size 3,6 cm (range 3,2 - 4,3) and with a normal contralateral kidney.

The patients mean age was 49 ± 9.5 years and in all patients the indication was elective. In 19 patients lesions were located in the upper pole, 13 in the lower pole.

One case was with meso-renal location. There were no patients with bilateral tumors and no patients with tumors in a solitary kidney. The open approach was used in all cases.

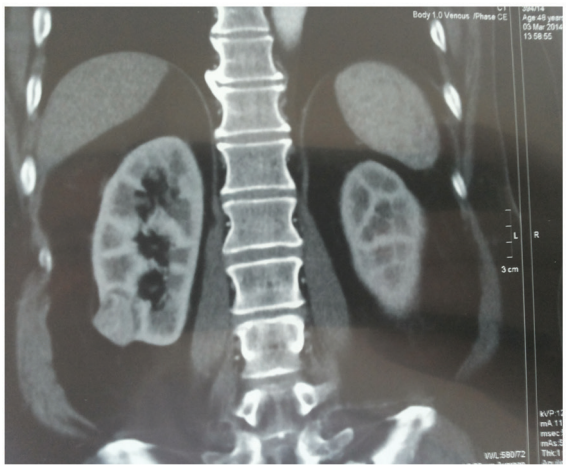

Fig. 1 Preoperative CECT scan

The general approach involves an extraperitoneal flank incision through the 11th and 12th ribs.

The kidney is mobilized within Gerota's fascia while leaving the perirenal fat around the tumor intact.

Intraoperatively afterwards we delimiting perfectly the tumor mass in the kidney, we clamp the pedicle (vascular tape) in selected cases before performing the tumor excision in their border. Arterial occlusion was less than 20 min to minimize ischemic injury to the kidney.

Tumors confined to the upper or lower poles of the kidney are generally excised by means of a partial polar nephrectomy only in one case performed segmental resection. The mean tumor size was 3,6 cm (range 3,2-4,3).

In routine we sent for pathologic examination the surgical margins in the rim of normal parenchyma in the visible lesion about 5 mm from the tumor border for pathogy examination based on intraoperative palpation. They were divided especially. Tumor and kidney tissue samples obtained from the surgical specimen, fixed in buffered neutral formalin and embedded in paraffin were investigated. Tissue sections were cut and stained with haematoxylin and eosin (H&E).

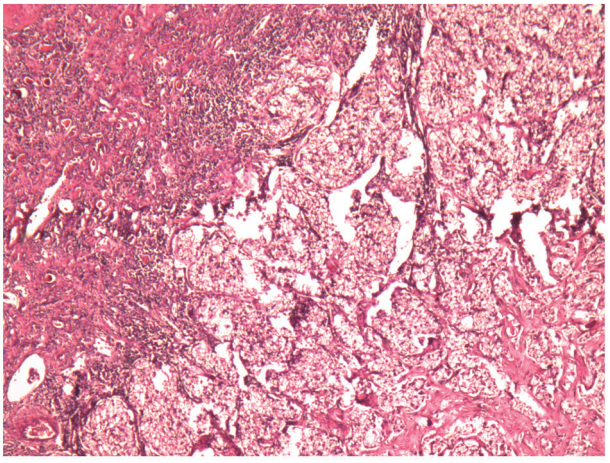

Fig. 2 Tissue sections stained with (H&E).

In all cases we perform a technique of serial encircling (running) haemostatic sutures through the renal parenchyma around the tumoral bed. In some cases where the tumor was in close proximity to the pelvi-calyceal system, based on preoperative imaging study the suspicious area was closed by absorbable sutures. The renal defect was closed using approximating vicryl.

After surgical reconstruction, in the next minutes we observe the renal reperfusion and possible bleeding in operative area. There were no major intraoperative complications.

In all cases we leave a drainage tube for two to three days.

The pathologic findings demonstrate a RCC in 30 cases and benign lesions in 3 patients (9 %).

The histological reports showed in majority of patients RCC (clear cell carcinoma, papillarycarcinoma) $pT_{1a}N_0M0$/, Grade 2 with no positive surgical margins. In three cases it was benign laesions (angiofibrolipoma-1, angiomyolipoma-1, pyelonephtitis xanthogranulomatosa -1). Only one case was with positive surgical margins.

The patient who shows delayed bleeding for two days subsequent nephrectomy was performed. In that case the tumor size was 4,3 cm with meso-renal location. The subsequent nephrectomy was positive for residual tumor (RCC).

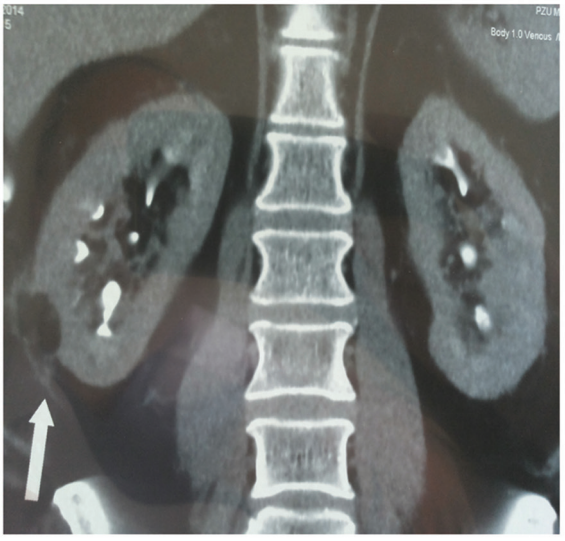

Fig. 3 Postoperative CECT scan

In our study, NSS corresponds to 26 % of the operated tumors, but in other series reaches from 20 - 32% of the performed partial nephrectomies.(5)

The ultrasound was performed at one to three months postoperatively.

CECT / MRI was used subsequently six-monthly for two years and then yearly.

radiological investigations shows no local recurrence, no metastasis.

Also no one of these patients developed a tumor in the contralateral kidney after NSS.

The mean follow-up by laboratory tests and US / CECT / MRI was 42 months (3,5 years).

Patients experienced postoperatively no deterioration in renal function.

DICUSSION

Our data shows that in selected cases where the tumor size was < 4 cm, the implementation of NSS offers long-term benefits in terms of functional results and a good cancer control. Nephron-sparing surgery has been increasingly used in patients with small localized renal tumors as with safety and maximum preservation of renal function. (13) The improved surgical techniques including better methods of hemostasis, preventing ischemic renal damage and meticulous dissection have significantly decreased intraoperative and postoperative complications. For us one of the major concerns during NSS was focused in careful preparation of the tumor area and in adequate hemostasis of the resected surface and this have translated into better long-term outcomes. Earlier various reports have shown intraoperative and delayed bleeding with secondary nephrectomy as its complications. (14)

One other concern with this approach has been the risk of local recurrence due to inadequate tumor excision or tumor multifocality.

Based in our study, after a mean follow-up of 42 months (3,5 years), there was no one local recurrence.

By some authors the local recurrence and five-year cancer-specific survival has been reported to be 0 % - 7.3 % and urinary fistula in 6,5% of cases. (15,16)

Our data shows that in selected cases where the tumor size was < 4 cm, the implementation of NSS offers long-term benefits in terms of postoperative results.

CONCLUSIONS:

Our results suggest that appropriate patient selection criteria and technical surgical improvements are important factors for satisfactory functional long-term outcome.

Open nephron sparing surgery and laparoscopic radical nephrectomy are relatively recent and significant developments for treating patients with renal tumor and they represent accepted standards of care in those with a small renal mass and normal contralateral kidney. (5)

The NSS has become a method of choice in our department in for patients with renal tumor size < 4 cm. These data suggest that nephron sparing surgery (NSS) can be performed with safety and maximum preservation of renal function.

REFERENCES

1. Seveso M[1], Maugeri O, Taverna G, Giusti G, Piccinelli A, Benetti A, Pasini L, Graziotti P.
   Incidence and treatment of complications in nephron sparing surgery. Arch Ital Urol Androl. 2005 Dec; 77 (4): 206-10.
2. Pahernik S, Roos F, Hampel C, Gillitzer R, Melchior SW, Thuroff JW.
   Nephron sparing surgery for renal cell carcinoma with normal contralateral kidney: 25 years of experience. J Urol. 2006;175:2027–31.[PubMed]
3. Matin SF[1], Gill IS, Worley S, Novick AC.
   Outcome of laparoscopic radical and open partial nephrectomy for the sporadic 4 cm. or less renal tumor with a normal contralateral kidney. J Urol. 2002 Oct ; 168 (4 Pt 1) : 1356-9; discussion 1359-60.
4. Vermooten V. Indications for conservative surgery in certain renal tumors: a study based on the growth pattern of the clear cell carcinoma. J Urol. 1950 ; 64 : 200. [PubMed]
5. Krejci KG[1], Leibovich BC
   Should there be a size limit for elective nephron-sparing surgery? Curr Urol Rep. 2003 Feb; 4 (1) :21-9.
6. Hafez KS[1], Novick AC, Butler BP.
   Management of small solitary unilateral renal cell carcinomas: impact of central versus peripheral tumor location. J Urol. 1998 Apr; 159 (4) : 1156-60.
7. Novick AC[1] The role of renal-sparing surgery for renal cell carcinoma. Semin Urol. 1992 Feb; 10 (1) : 12-5.
8. Van Poppel H[1], Dilen K, Baert L.
   Incidental renal cell carcinoma and nephron sparing surgery. Curr Opin Urol. 2001 May; 11 (3) : 281-6.
9. Berdjis N[1], Hakenberg OW, Novotny V, Manseck A, Oehlschläger S, Wirth MP. Nephron-sparing surgery for renal cell carcinoma in the solitary kidney. Scand J Urol Nephrol. 2007 :41 (1) : 10-3.
10. Uzzo RG[1], Novick AC.
    Nephron sparing surgery for renal tumors: indications, techniques and outcomes. J Urol. 2001 Jul; 166 (1) : 6-18.
11. Stephenson AJ, Hakimi AA, Snyder ME, Russo P. Complications of radical and partial nephrectomy in a large contemporary cohort. J Urol. 2004;171:130–4. [PubMed]
12. Poulakis V[1], Witzsch U, de Vries R, Moeckel M, Becht E
    Quality of life after surgery for localized renal cell carcinoma: comparison between radical nephrectomy

and nephron-sparing surgery. Urology. 2003 Nov; 62 (5) : 8144

13. Lee CT, Katz J, Shi W, Thaler HT, Reuter VE, Russo P. Surgical management of renal tumors 4 cm or less in a contemporary cohort. J Urol. 2000;163:730–6. [PubMed]
14. Thompson RH, Leibovich BC, Lohse CM, Zincke H, Blute ML. Complications of contemporary open nephron sparing surgery: A single institution experience. J Urol. 2005; 174:855–8. [PubMed]
15. Zigeuner R, Quehenberger F, Pummer K, Petritsch P, Hubmer G. Long term results of nephron sparing surgery for renal cell carcinoma in 114 patients: Risk factors for progressive disease. BJU Int. 2003;92:567–71. [PubMed]
16. Uzzo RG, Novick AC. Nephron sparing surgery for renal tumors: Indications, techniques and outcomes.J Urol. 2001;166:6–18. [PubMed] (range - 1.4-17.4).[13] In our series, there was no case of urinary fistula

KIRURGJIA E RUAJTJËS SË VESHKËS TE TUMORI I LOKALIZUAR NË VESHKË

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ABSTRAKTI

Qëllimi i punimit: Të analizohet rëndësia e madhësisë së tumorit dhe të lokalizimit të tij në veshkë në nivelin e suksesit te kirurgjisë së ruajtjës së veshkës te pacientet tanë të operuar.

Materiali dhe Metodat: Kemi analizuar në mënyrë retrospektive në bazën tonë të të dhënave aplikimin e kirurgjisë së ruajtjës së veshkës te 33 pacientë të operuar për tumor në veshkë në periodën kohore të studimit Janar 2000 deri në Dhjetor 2015.

Të gjithë pacientët e përfshirë në analizë ishin me një tumor të vetëm në veshkë me madhësi mesatare 3,6 cm (vargu 3,2 - 4,3 cm) dhe me veshkë normale kontralaterale.

Rezultatet: Janë realizuar 33 raste me kirurgji të ruajtjes së veshkës nga totali prej 216 pacientëve të operuar për tumor në veshkë,16 ishin femra dhe 17 ishin meshkuj. Mosha mesatare e pacientëve ishte 49 ± 9.5 vite dhe te të gjitha rastet indikacionet ishin elektive.Te 19 pacientë lezionet tumorale ishin të lokalizuar në polin e sipërm, në 13 raste në polin e poshtëm,Te një rast lokalizimi i tumorit ishte në mes të veshkës. Në studimin tonë, kirurgjia e ruajtjës së veshkës korrespondon me 26% të tumorëve renal të operuar derisa në disa seri ajo hasët 20-32%.

Përfundimi: Të dhënat tona tregojnë se aplikimi i kirurgjisë së ruajtjes të veshkës ofron dobi afatgjate në kuptim të rezultateve funksionale dhe kontrollës të mirë të tumorit.

Te pacientet tanë që iu kanë nënshtruar kirurgjisë së ruajtjes të veshkës nuk kemi hasur në paraqitjen e metastazave dhe as në insuficiencë kronike të veshkave.

Fjale kyçe: Kirurgjia e ruajtjes të veshkës, kirurgjia e hapur.

Original scientific paper

CORRELATION BETWEEN CYTOPATHOLOGY AND HISTOPATHOLOGY IN WOMEN WITH SQUAMOUS CELL ABNORMALITIES OF THE UTERINE CERVIX

КОРЕЛАЦИЈА ПОМЕЃУ ЦИТОПАТОЛОШКИТЕ И ХИСТОПАТОЛОШКИТЕ НАОДИ КАЈ ЖЕНИ СО СКВАМОЗНИ КЛЕТОЧНИ АБНОРМАЛНОСТИ НА ГРЛОТО НА МАТКАТА

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ABSTRACT

Objective: The aim of the study was to correlate the results of cervical cytology and cervical biopsy in women with squamous cell abnormalities of the uterine cervix.

Materials and Methods: This comparative retrospective study was conducted in a series of 184 sexually active women, aged 20 to 60, who came to their annual gynecological exam at the University Clinic for Gynecology and Obstetrics in Skopje between September 2015 and March 2016. In all 184 patients with cytologically diagnosed squamous cell abnormalities of the uterine cervix, a colposcopic cervical biopsy with endocervical curettage for histopathological analysis was taken, with was analyzed at the University Clinic for Radiotherapy and Oncology in Skopje. The results of the liquid-based cytology smears and cervical biopsies were compared to evaluate the diagnostic agreement between the cytology findings and the biopsies.

Results: Cytopathologically, there were 118 (64.13%) ASC-US, 22 (11.96%) LSIL, 38 (20.65%) HSIL and 6 (3.26%) invasive carcinoma cases. Histopathologically, there were 108 (58.70%) non-neoplastic lesions, 24 (13.04%) LGSIL cases, 42 (22.83%) HGSIL cases and 10 (5.43%) invasive squamous cell carcinomas. Including all squamous cell abnormalities, the sensitivity of the smear test in low-grade and higher grade lesions was 58.70% (108/184) and the false positivity was 41.30% (76/184). Excluding ASC-US lesions, the sensitivity of the smear test was 78.80% (52/66) and the false positivity was 21.21% (14/66). After evaluating cervical cytopathological correlation the positive predictive value was found to be 100% (6/6) in invasive carcinoma, 68.42% (26/38) in HGSIL and 31.82% (7/22) in LGSIL.

Conclusions: The high sensitivity of the cervical smear test for high-grade squamous lesions shows that it is an effective screening test for cervical cancer and precursor lesions.

Key words: cytopathology, histopathology, squamous cell abnormalities, liquid-based cytology, cervical biopsies

INTRODUCTION

Cervical cancer is the third most common malignancy in women worldwide, annually with 500.000 newly diagnosed cases and almost 250.000 deaths [1]. About 90% of cervical cancer cases are squamous cell carcinomas, 10% are adenocarcinomas and a small number are other types [2]. Various forms of squamous cell abnormalities precede the appearance of the cervical cancer, which include a lot of progressive morphological changes, from

productive human papillomavirus (HPV) infection-mild dysplasia to carcinoma in situ [3].

A significant decrease in the incidence and mortality of cervical cancer can be realized with effective cervical cytology screening programs [4].The aim of the Papanicolaou (PAP) smear test is to detect precancerous cervix lesions before they become invasive cancer. The accuracy of the PAP smear test is evaluated using: sensitivity, specificity and predictive value. Evaluating the correlation between cervical cytology and biopsy is the best method of the determining the PAP smear test accuracy. However, it is not a perfect methods due to the potential sampling and interpretation errors [5].

The aim of the study was to correlate the results of cervical cytology and cervical biopsy in women with squamous cell abnormalities of the uterine cervix.

MATERIAL AND METHODS

This comparative retrospective study was conducted in a series of 184 sexually active women, aged 20 to 60, who came to their annual gynecological exam at the University Clinic for Gynecology and Obstetrics in Skopje between September 2015 and March 2016. In all 184 patients with cytologically diagnosed squamous cell abnormalities of the uterine cervix, a colposcopic cervical biopsy with endocervical curettage for histopathological analysis was taken, with was analyzed at the University Clinic for Radiotherapy and Oncology in Skopje. The results of the liquid-based cytology smears and cervical biopsies were compared to evaluate the diagnostic agreement between the cytology findings and the biopsies.

Criteria of inclusion

This study included 184 sexually active women with squamous cell abnormalities of the uterine cervix of the PAP smear.

Criteria of exclusion

This study did not include: pregnant women, women with previous surgery on the uterine cervix (cervical conization, carbon dioxide laser vaporization and total hysterectomy) and also previous abnormal cytological and histopathological findings of the uterine cervix.

Methods of examination

All samples for cytology were taken using Thin Prep PAP smear cytology and were analized in the Cytology laboratory of the University Clinic for Gynecology and Obstetrics in Skopje by a doctor-cytopathologist. Cytological results were classified according to the revised Bethesda classification [6,7], such as: Atypical Squamous Cells of Undetermined Significance-ASC-US; Low-grade Squamous Intraepithelial Lesion-LSIL (productive HPV infection, Cervical Intraepithelial Neoplasia grade 1-CIN1); High-grade Squamous Intraepithelial Lesion-HSIL (CIN2, CIN3, CIS) and invasive squamous cell carcinoma.

Samples for histopathological analysis were taken at the University Clinic for Gynecology and Obstetrics in Skopje and were analyzed at the University Clinic for Radiotherapy and Oncology in Skopje, at the Department of Histopathology and Clinical Cytology by an experienced expert in histopathology. According to the morphology determined in biopticsamples , cervical findings were characterized as: normal finding (non-specific cervicitis); Low-Grade Squamous Intraepithelial Lesion-LGSIL (Flat condyloma, cervicitis chronicavirosa, mild dysplasia); High-Grade Squamous Intraepithelial Lesion-HGSIL (moderate dysplasia, severe dysplasia, carcinoma in situ) and invasive squamous cell carcinoma.

Statistical analysis

Data were analyzed by a specific software for databases (Excel). Statistical analysis of the established statistical series was made with the statistical program SPSS (Statistical Package for the Social Sciences), version 22.0.

The structure of numerical signs was analyzed by determining the measures of central tendency (arithmetical mean) and measures of dispersion (standard deviation).

The Spearman correlation test, ANOVA test, one-way variance analysis and the Tamhane test were used for statistical evaluations. Two-way comparisons were used to create 2x2 tables and calculate the positive predictive values.

A p value <0.05 was considered significant for statistical evaluation.

RESULTS

The study included 184 women, aged 20 to 60 years (39.81±9.26). The cases aged of the cytopathological diagnostic groups were compared and the difference was found to be significant ($p=0.001$). A significant difference was found between the age of ASC-US and invasive cancer cases ($p<0.03$). There was also a significant difference between the age of LSIL and HSIL women ($p<0.03$) (Table 1).

Table 1. Distribution of mean age of cytopathological diagnostic groups

Cytopathological diagnosis	n	%	mean	sd
ASC-US	118	64.13	37.30	8.00
LSIL	22	11.96	34.63	8.53
HSIL	38	20.65	41.75	9.68
Invasive carcinoma	6	3.26	45.56	10.26
Total	184	100	39.81	9.26

Legend: ASC-US-atypical squamous cells of undetermined significance; LSIL-low grade squamous intraepithelial lesion; HSIL-high grade squamous intraepithelial lesion; n-number; sd-standard deviation

Table 2. Distribution of mean age of histopathological diagnostic group

Histopathological diagnosis	n	%	mean	sd
Nonneoplastic	108	58.70	38.73	7.21
LGSIL	24	13.04	33.11	8.51
HGSIL	42	22.83	43.22	11.00
Invasive carcinoma	10	5.43	44.16	10.30
Total	184	100	39.81	9.26

Legend: LGSIL-low grade squamous intraepithelial lesion; HGSIL-high grade squamous intraepithelial lesion, n-number; sd-standard deviation

Cytopathologicaly, there were: 118 (64.13%) ASC-US, 22 (11.96%) LSIL, 38 (20.65%) HGSIL and 6 (3.26%) invasive carcinoma cases.

We found a significant difference between the age of the nonneoplastic group and LGSIL women (p=0.001). There was also a significant difference between the age of LGSIL and squamous cell carcinoma women (p=0.002) (Table 2).

Histopathologicaly, there were108 (58.70%) nonneoplastic lesions, 24 (13.04%) LGSIL

cases, 42 (22.83%) HGSIL cases and 10 (5.43%) invasive squamous cell carcinomas (Table 3).

Table 3. Correlation between results of cervical cytology and cervical biopsy

Cytopathological diagnosis	Histopathological diagnosis									
	Nonneoplastic		LGSIL		HGSIL		Invasive carcinoma		Total	
	n	%	n	%	n	%	n	%	n	%
ASC-US	94	51.08	12	6.52	12	6.53	0	0	118	64.13
LSIL	11	5.99	7	3.80	4	2.17	0	0	22	11.96
HSIL	3	1.63	5	2.72	26	14.13	4	2.17	38	20.65
Invasive carcinoma	0	0	0	0	0	0	6	3.26	6	3.26
Total	108	58.70	24	13.04	42	22.83	10	5.43	184	100

Legend: ASC-US-atypical squamous cell of undetermined significance; LGSIL-low grade squamous intraepithelial lesion; HGSIL-high grade squamous intraepithelial lesion; n-number; %-percent

The relationship between cytopathological and histopathologicalresukts was significant (r=0.9992, p<0.00001, p<0.05).

When all the squamous cell abnormalities in the cervical cytology was included, the sensitivity of the PAP test for LSIL and higher grade lesions was 58.70% (108/184) while false positivity was 41.30% (76/184). When ASC-US were excluded, the sensitivity was 78.80% (52/66) and false positivity 21.21% (14/66).

We were unable to calculate sensitivity, specificity and negative predictive value for the women groups as there were no real negative or false negative groups. The correlation was calculated using the positive predictive value (PPV) according to our study data.

The cyto-histopathological correlation increased in parallel to the grade of PPV and was 100% for invasive squamous cell carcinoma, 68% for HSIL and 32% for LSIL (Table 4).

Table 4. Positive predictive value of cyto-histopathological diagnosis

Cytopathological diagnosis	Histopathological diagnosis	PPV
LSIL	LGSIL	0.32
HSIL	HGSIL	0.68
Invasive carcinoma	Invasive carcinoma	1

Legend: PPV-positive predictive value; LGSIL-low grade squamous intraepithelial lesion; HGSIL-high grade squamous intraepithelial lesion

The cyto-histopathological comparison for cervical intraepithelial lesions and invasive carcinoma revealed that the PAP test predictive value increased as the epithelial abnormality of the lesion increased and was 20% for ASC-US, 50% for LSIL, 92% for HSIL and 76% for LSIL+HSIL (Table 5).

Table 5. Positive predictive value of cytology groups

Cytopathological diagnosis	PPV
ASC-US	0.20
LSIL	0.50
HSIL	0.92
LSIL+HSIL	0.76

Legend: PPV-positive predictive value; ASC-US-atypical squamous cell of undetermined significant; LSIL-low squamous intraepithelial lesion; HSIL-high squamous intraepithelial lesion

DISCUSSION

The aim of using the cervical smear test is screening sexually active women to enable early detection and treatment of precancerous lesions and prevent mortality due to cervical cancer. There is a relationship between the widespread use of the cervical smear test and decreased mortality due to invasive squamous cancer. Screening programs have therefore been developed all over the world. Cases where a cytological abnormality has been detected undergo biopsy from the suspect lesions under colposcopy for a definite diagnosis [8].

It is difficult to definitely establish PPV of the PAP smear test preinvasive lesions. The literature figures are 50-90% for sensitivity and 31-90% for specificity [9]. The PPV is 17-89% for preinvasive or microinvasive lesions and almost 100% for squamous cell carcinoma [10,11].

A study where the cyto-histopathological correlation of 374 cases was analyzed showed full match between the cytology and biopsy in 43.10% of the cases while this rate was48.38% and 62.50% for low-grade and high-grade lesions, respectively. Cervical cytology sensitivity was 77.31% [12].

We found increased cyto-histopathological correlation with the cervical intraepithelial lesion as the degree of epithelial cell abnormality increased. The PPV was 20% for ASC-US, 50% for LSIL, 92% for HSIL and 76% for LSIL+HSIL. We evaluated the cervical cytology and cervical biopsy correlation again after matching the Bethesda terminology counterpart of the smear results with the SIL terminology results of the biopsy results. The PPV again showed an increase with the lesion degree and was 32%, 68% and 100% for LSIL, HSIL and invasive carcinoma cases, respectively.

Cervical precancerous lesions can be detected approximately 10 years before they become cancerous with the PAP smear screening. Comparison of the age of our patients revealed a significant difference between LGSIL and invasive carcinoma. The mean age for LGSIL group was 33.11 while the squamous cell carcinoma group had a mean age of 44.16 with a difference of over 10 years. This indicates that a period where lesions can be detected and treated before they become cancerous exists.

The clinical results of patients diagnosed as ASC-US by cervical smear can show great variety, from clearly bening lesions to potentially serious lesions and it is therefore not possible to provide a definite classification. In our study the total rate of cervical intraepithelial lesions among cases with an ASC-US smear result was 20.34%. According to a study by Massad et al., on the basis of histological results of cytological finding, 22.3% of ASC-US finding really are histologically positive [13]. Various laboratories report a SIL rate of 15-30% among ASC-US cases [14,15].

In our study , women with LSIL cytology results had a dominant histological LGSIL results (50%), whereas the HGSIL results was confirmed in 18.18%. Our results corresponding with results in study byMilenkovicet al. [16].

Studies show that, with a cytological HSIL result, more than 50% of the women will have HGSIL and 2% will have invasive carcinomas [17].In our study 68.42% of cytological

HSIL results had a histological HGSIL results and 10.55% had a invasive cervical carcinomas. Data also show that between 20% and 30% of HSIL results are not diagnosed by cervical cytology [18].

In our study the sensitivity of the PAP smear test in LGSIL and higher grade lesions was 58.70% and the false positivity was 41.30%. Excluding ASC-US lesions, the sensitivity of the PAP smear test was 78.80% and the false positivity was 21.21%. Another study on cyto-histopathological correlation found a false positivity rate of 3.5% and a false negativity rate of 5.3%. The most common cause of false negativity was sampling error [19].

CONCLUSION

Increased degree of neoplasia in cervical lesions increases the correlation between PAP smear and biopsy. The high sensitivity of the PAP smear test for high-grade lesions shows that it is an effective screening test for cervical cancer and precursor lesions.

REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011; 61:69-90.
2. American Cancer Society: Cancer Facts and Figures 2016. Atlanta, GA: American Cancer Society, 2016.
3. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No.99: Management of abnormal cervical cytology and histology. ObstetGynecol 2008; 112(6): 1419-1444.
4. Sankaranarayanan R, Gaffikin L, Jacob M, Sellors J, Robles S: A critical assessment of screening methods for cervical neoplasia. Int J GynaecolObstet 2005; 89:4-12.
5. Rohr LR. Quality assurance in gynecologic cytology. What is practical? Am J ClinPathol 1990; 94:754-758.
6. Zerat L. La nouvelle terminologie de Bethesda: quells-chan-gements? Rev PratGynecolObstetNumero Special. 2002; 3-10.
7. Solomon D, Davey D, Kurman R. The 2001 Bethesda System. Terminology for reporting results of cervical cytology. JAMA 2002; 287:2114-2119.
8. Wright TC, Cox JT, Massad LS, Twiggs LB, Wilkinson EJ. ASCCP-Sponsored Consensus 2001 Consensus Guideline for the management of women with cervical cytological abnormalities. JAMA 2002; 287:2120-2129.
9. Uyar DS, Eltabbakh GH, Mount SL. Positive predictive value of liquid-based and conventional cervical Papanicolaou smears reported as malignant. GynecolOncol 2003; 89:227-232.
10. Johnson SJ, Wadehra V. How predictive is a cervical smear suggesting invasive squamous cell carcinoma? Cytopathology 2001; 12:144-150.
11. Clark SB, Dawson AE. Invasive squamous-cell carcinoma in Thin Prep speciments: diagnostic clues in the cellular pattern. DiagnCytopathol 2002; 26:1-4.
12. Abali R, Bacanskgil BH, Celik S, Aras O, Koca P, Boran B, Dursun N. Histopathological correlation of squamous cell abnormalities detected on cervical cytology. Turk PatolojiDerg 2011; 27(2):144-8.
13. Massad LS, Collins YC, Mayer PM. Biopsy correlates of abnormal cervical cytology classified using the Bethesda system. GynecolOncol 2001; 82(3):516-22.
14. Eltabbakh GH, Lipman JN, Mount SL, Morgan A. Significance of atypical squamous cells of undetermined significance on Thin Prep Papanicolaou smears. GynecolOncol 2000; 79:44-49.
15. Barcelos ACM, Antoniazi MM, Adad SJ, Candido EF. Atypical squamous cells of undetermined significance: Bethesda classification and association with human papillomavirus. Infect Dis GynecolObstet 2011; 904674:9.
16. Milenkovic V, Sparic R, Dotlic J, Tulic L, Mirkovic L, Milenkovic S, Atanackovic J. Reliability and relationship of colposcopical, cytological and histopathological findings in the diagnostic process. VojnosanitetskiPregled 2012; 69(10):869-873.
17. Koss LG, Melamed MR. Koss diagnostic cytology and its histopathologic bases, 5th ed. USA: Lippincott Williams & Wilkins. 2006.
18. Cibas ES, Ducatman BS. Cytology: Diagnostic principles and clinical correlates, 3rd ed. Philadelphia: Saunders. 2009.
19. Mete O, Yavuz E, Tuzlali S, Ilhan R, Ozluk Y, Topuz S, Iyibozkurt C, Iplikci A. Retrospective study of 112 patients who had colposcopy-guided biopsy: Comparison of the cytology results with histology. Turk PatolojiDerg 2007; 23:33-

КОРЕЛАЦИЈА ПОМЕЃУ ЦИТОПАТОЛОШКИТЕ И ХИСТОПАТОЛОШКИТЕ НАОДИ КАЈ ЖЕНИ СО СКВАМОЗНИ КЛЕТОЧНИ АБНОРМАЛНОСТИ НА ГРЛОТО НА МАТКАТА

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АБСТАРКТ

Вовед: Целта на студијата беше да направиме корелација помеѓу цервикалните цитолошки наоди и цервикалните биоптични наоди кај жени со сквамозни клеточни абнормалности на грлото на матката.

Материјал и методи: Оваа компаративна ретроспективна студија беше направена на серија од 184 сексуално активни жени, на возраст од 20 до 60 години, кои дојдоа на редовен годишен гинеколошки преглед на Универзитетска Клиника за Гинекологија и Акушерство во Скопје, во периодот од Септември 2015 година до Март 2016 година. Кај сите 184 жени со цитолошки наод на сквамозни клеточни абнормалност на грлото на матката, беше направена цервикална биопсија со ендоцервикална киретажа за хистопатолошка анализа, која беше направена на Универзитетска Клиника за Радиотерапија и Онкологија во Скопје. Резултатите од liquid-based ПАП размаските и од цервикалните биопсии беа споредени и евалуирани за дијагностичка точност помеѓу цитопатолошките и хистопатолошките наоди.

Резултати: Цитопатолошки беа: 118 (64.13%) случаи на ASC-US, 22 (11.96%) случаи на LSIL, 38 (20.65%) случаи на HSIL и 6 (3.26%) случаи на инвазивен сквамозен карцином на грлото на матката. Хистопатолошки беа 108 (58.70%) случаи на нормален наод, 24 (13.04%) случаи на LGSIL, 42 (22.83%) случаи на HGSIL и 10 (5.43%) случаи на инвазивен сквамозен карцином на грлото на матката. Вклучувајќи ги сите сквамозни клеточни абнормалности, сензитивноста на ПАП тесот за лезиите од низок степен и за повисоките степени беше 58.70% (108/184) и лажно позитивноста беше 41.30% (76/184). Исклучувајќи ги ASC-US лезиите, сензитивноста на ПАП тестот беше 78.80% (52/66) и лажно позитивноста беше 21.21% (14/66). После направената цервикална цитопатолошка корелација, позитивната предиктивна вредност беше 100% (6/6) за случаите со инвазивен карцином, 68.42% (26/38) за HGSIL случаите и 31.82% (7/22) за LGSIL случаите.

Заклучок: Високата сензитивност на ПАП тестот за сквамозните интраепителни лезии од висок степен, кажува дака ПАП тестот е ефективен скрининг тест за цервикалниот карцином и неговите преканцерозни лезии.

Клучни зборови: цитопатологија, хистопатологија, сквамозни клеточни абнормалности, liquid-based размаска, цервикални биопсии

Original scientific paper

КАРАКТЕРИСТИКИ НА ДОНОРИТЕ И АФЕРЕЗНАТА ПОСТАПКАКОИ ВЛИЈААТ НА ЕФИКАСНОСТА НА КОЛЕКЦИОНИРАЊЕТО НА ХЕМАТОПОЕТСКИТЕ МАТИЧНИ КЛЕТКИ ОД ПЕРИФЕРНА КРВ

DONORS AND APHERESIS CHARACTERISTICS THAT INFLUENCE COLLECTION EFFICIENCY OF PERIPHERAL BLOOD HEMATOPOIETIC STEM CELLS

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АБСТРАКТ

Вовед: За успешно колекционирање на мононуклеарни клетки (МНК) и ЦД34+ клетки од периферна крв потребна е идентификација на предиктивните фактори. Целта на нашата студија е да ги истражи потенцијалните предиктивни фактори кои би можеле да влијаат на бројот на колекционирани хематопоетски матични клетки (ХМК).

Материјал и метод: Испитуваната група ја чинат 120 автологни и алогени аферезни донори на ХМК од периферна крв. Влијанието на потенцијалните предиктивни фактори (демографски, лабораториски, карактеристиките на аферезното колекционирање во двете групи, и мобилизациионата стратегијаи карактеристиките поврзани со болеста кај автологните донори) на ефикасноста на колекционирањето, односно вкупниот број на колекционираните МНК и ЦД34+ клетки,беа определувани со мултипла регресиона анализа.

Резултати: Направени се 226 аферезни процедури, 182 кај 90 автологни и 44 кај 30 алогени донори, средно 2 аферези (опсег 1-3) кај автологните и 1.5 аферези (опсег 1-2) кај алогените донори. Нашата студија покажа дека на вкупниот број на колекционираните МНК клетки сигнификантно влијаеле пред-аферезниот број на тромбоцитите(p=0.045576), мобилизирачката стратегија(p=0.044071), видот на сет за харвестрација(p=0.042254), бројот на аферзни циклуси во една процедура(p=0.037069) и бројот на циклуси на примена хемотерапија (p=0.033519), додека на вкупниот број на колекционирани ЦД34+ клетки кај автологните донори сигнификантно влијаел бројот на аферезни циклуси во една процедура (p=0.014608). Мултипла регресиона анализа не покажа сигнификантна поврзаност меѓу вкупниот колекциониран број на МНК и ЦД34+ клетки и испитуваните предиктивни фактори од интерес кај алогените донори.

Заклучок: Потребно е да се направат универзални водичи за употребата на лабораториски параметри во иницијацијата на аферезната процедура за оптимизацијата на колекционирањето на ХМК.

Клучни зборови: хематопоетски матични клетки, трансплантација на хематопоетски матични клетки, мононуклеарни клетки, ЦД34+ клетки, аферезно колекционирање

ВОВЕД

Трансплантирањето на хематопоетски матични клетки е потврден третман за многу малигни и немалигни болести на крвта, како и некои генетски заболувања (1-3). Аферезните постапки за добивање

на хематопоетски матични клетки од периферна крв (ХМК) го имаат приматот во изборот на постапка за добивање на матични клетки добиени од коскена срцевина и умбиликална крв. Неинвазивноста на самата процедура за прибирање на матични клетки, ниската контаминација со еритроцити и тромбоцити, побрзиот енграфтмент, помалата употреба на трансфузии и антибиотици и пократкиот болнички престој се само дел од работите кои ја фаворизираат оваа постапка во однос на другите (4,5).

Во светот 99% од автологните трансплантации на ХМК и 75% од алогените трансплантации се изведуваат со хематопоетски матични клетки од периферна крв и нивната употреба се повеќе се зголемува и од ден на ден се шират нивните индикациони подрачја (6,7).

Колекционирањето на хематопоетските матични клетки од периферна крв се врши со харвестрирање на делот од крвта богат со buffy coat, со специјално екстрахирање на делот богат со мононуклеарни клетки (МНК), кој содржи CD34+матични клетки(8,9). Прогениторските матични клетки се ретки и се наоѓаат примарно во коскената срцевина, со екстремно мали количини (0.01-0.5% од клетките со јадро) во периферната крв (10,11). Но, мобилизирањето на овие клетки во периферната крв со фактори на раст и/или хемотерапија резултира со зголемен број на циркулирачки хематопоетски матични клетки, олеснувајќи го нивното харвестрирање од периферна крв (11,12). Сеуште нема консензус за количеството на ХМК кои треба да се трансплантираат и постигнат адекватно хематопоетско опоравување. Успешен енграфтмент е забележан при трансплантирање на минимум $2x10^6$/kgCD34+ клетки, односно $2x10^8$/kgМНК(13,14). Тајмингот на колекционирањето на ХМК по мобилизацијата е клучен за максимизација на харвестот на ХМК. Неколку различни параметри се испитувани како можни предиктивни фактори за аферезниот харвест, како што се апсолутниот број на лимфоцити (15), бројот на тромбоцити (16) и проценти на циркулирачки незрели гранулоцити (17). Во медицинската пракса, бројот на CD34+ клетки во периферната крв е прифатен како најдобар индикатор за започнување на харвестрирањето (3,5,18-23).Но и покрај тоа штосе високо специјализирани и имаат висока цена на чинење, техниките кои се користат за пресметување на бројот на CD34+ клетки не се универзално достапни за сите и потребно е подолго време за да бидат изведени (24). Заради тоа, параметрите кои се подостапни се евалуирани како потенцијални предиктивни фактори. Сеуште е нејасно кој протокол е оптимален во однос на максималното харвестрирање на матични клетки. Целта на ова истражување е да се идентификуваат лабораториските параметри од крвната слики на донорите, аферезната техника и параметрите кај автологните и алогените донори, како и мобилизрачката стратегија и карактеристиките на болеста кај автологните донори кои би можеле да бидат потенцијални предиктивни фактори за успешно и ефикасно колекционирање на ХМК, на тој начин овозможувајќи да се редуцираат трошоците и непотребното изложување на донорите на факторите на раст и поголемиот број на аферезни процедури.

МАТЕРИЈАЛ И МЕТОД

Ова истражување е ретроспективно-проспективна студија изведена во ЈЗУ Институт за трансфузиона медицина на РМ и ЈЗУ Универзитетска клиника за хематологија во Скопје во период од 2008 до 2016 година. Испитуваната група ја чинат 120 донори – 90 автологни и 30 алогени, на возраст од 18 до 65 години. Од сите учесници во студијата е добиена писмена информативна согласност за реализација на мобилизацијата и харвестрацијата (аферезното колекционирање) на ХМК, како и за примената на крвни компоненти (според препораките на Ревизијата на Женевската декларација за биомедицински истражувања). Мобилизацијата на ХМК е вршено со гранулоцито-колоно стимулирачки фактор (G-CSF) 10 μcg/kg/ден (кај здрави донори) и G-CSF 10 μcg/kg/ден (како самостојна мобилизирачка стратегија) или во комбинација на G-CSF + хемотерапија во зависност од дијагнозата и моменталната состојба на автологните донори. Харвестрацијата на ХМК е реализирана со аферезна процедура користејќи клеточен сепаратор COBE SpectraVersion 6.1 (CaridianBCT) во Институтот за трансфузиона медицина по однапред утврдени протоколи. Минимален посакуван број на колекционирани МНК и/или CD34+ клетки во нашето истражување е ≥ 2.0 $x10^8$/kg МНК и/или ≥ 2.0 $x10^6$/kg CD34+ клетки. Броењето на мононуклеарните клетки (МНК) и CD34+ клетките е вршено на Универзитетската клиника за хематологија по однапред утвдени протоколи (24,25). Вршена е анализа на следниве параметри: карактеристики на донори (пол, возраст, телесна тежина, телесна висина, крвна група,

лабораториски параметри – на приемен ден – леукоцити (WBC), хемоглобин (Hgb), тромбоцити (Plt), предаферезни на прв ден харвестрација – WBC, Hgb, Plt, еритроцити (RBC), хематокрит (Htc), моноцити (Mono), лимфоцити (Lympho), лимфомоноцити (LymMon); аферезни карактерестики – број на аферезни процедури, број на аферезни циклуси во една процедура, тотален волумен на крв (TBV), процесирана крв, времетраење на харвестрација, искористен аденозин цитрат декстроза-А (АЦД-А), количина на графт, вид на сет за харвестрација и несакани реакции од истата. Кај автологните донори се анализирани и основното заболување, стадиум на болест, мобилизирачка стратегија, видови применета терапија, број на циклуси на хемотерапија, примена на зрачна терапија и/или претходна трансплантација на ХМК (ТХМК), време од откривање на болест до харвестрација, трансфузиска подршка пред харвестрација со еритроцити, тромбоцити и тромбоцитен концентрат.

Статистичка обработка на податоците

Статистичката обработка на податоците е вршена во статистичка програма STATISTICA 7.1 и SPSS 13.0. Во истражувањето се користени следните методи: кај сериите соо атрибутивни белези се одредувани проценти на структура (%); кај сериите со нумерички белези употребена е дескриптивна статистика - Descriptive statistics (Mean±Std.Dev., Min., Max., Median); разликите меѓу автологните и алогените донори/пациенти кај параметрите со атрибутивни и нумерички белези (во зависност од дистрибуцијата на податоците) се тестирани со t-test за независни примероци (t), Mann-Whitney U тест (U/Z), AnalysisofVariance тест – (F);влијанието на одредените анализирани параметриво однос на колекционираните МНК, односно CD34+ клетки е одредувано со мултипла регресиона анализа. Користен е ниво на сигнификатност $p < 0.05$.

РЕЗУЛТАТИ

Карактеристики на донори

Табела 1. Карактеристики на донори

Карактеристики на донори	**Автологни**	**Алогени**	**p < 0.05**
Пол			
Мажи	56 (62.2%)	21 (70.0%)	
Жени	34 (37.8%)	9 (30.0%)	
Возраст(години)			
(просек, ранг)	45±13.0 (18-65)	34.3±12.2 (19-63)	
< 20	3 (3.4%)	2 (6.7%)	
20-29	11 (12.2%)	12 (40.0%)	
30-39	15 (16.7%)	4 (13.3%)	
40-49	21 (23.3%)	7 (23.3%)	
50-59	31 (34.4%)	5 (16.7%)	
>=60	9 (10.0%)	/	
Телесна тежина(кг) (просек, ранг)	78.5±15.5 (51-136)	75.9±14.1 (56-105)	
Телесна висина(см) (просек, ранг)	170.8±9.6 (150-190)	173.8±7.1 (160-190)	
Крвна група			
O+	33 (36.7%)	13 (43.3%)	
O-	4 (4.4%)	/	
A+	25 (27.8%)	8 (26.7%)	
A-	3 (3.3%)	/	
B+	18 (20%)	3 (10.0%)	
B-	2 (2.2%)	3 (10.0%)	
AB+	5 (5.6%)	1 (3.3%)	
AB-	1 (1.1%)	1 (3.3%)	

продолжува

Параметри пред започнување на мобилизација (просек, ранг)			
WBC (x10^9/l)	5.6±2.3 (1.9-14.1)	8.1±5.6 (3.9-29.1)	p=0.001198
Hgb (g/dl)	12.1±1.7 (8-15.5)	14.7±1.5(11.8-18)	p=0.000000
Plt (x10^9/l)	254±117.0(78-649)	216±46.0(130-306)	NS
Параметри пред започнување на харвестрација (просек, ранг)			
WBC (x10^9/l)	21.5±12.6(2.95-61.8)	29.6±8.2 (13.3-42.8)	p=0.000170
Hgb (g/dl)	12.0±1.3(9.7-16)	14.4±1.5(11.1-17.5)	p=0.000000
Plt (x10^9/l)	167.9±95.0(40-381)	201.2±61.2(140-305)	p=0.032651
Hct (%)	36.0±4.3 (15.6-48)	43.6±3.9(36.1-49.7)	p=0.000000
RBC (x10^9/l)	3.9±0.5 (3.1-7.73)	4.8±0.4 (3.98-5.7)	p=0.000000
Monocytes (%)	9.7±4.9 (1.3-25.1)	5.4±2.4 (1.4-10.5)	p=0.000001
Lymphocytes (%)	12.2±6.1 (3.2-28.8)	11.8±3.5 (6.6-20.6)	NS
LymMon (%)	21.8±9.4 (7-53)	17.5±4.5 (10-26)	p=0.027808
Примена трансфузија пред харвестација			
Пациенти кои примиле RBC единици (број,%, просек, ранг)	21 (23.3%) 3.8±2.8 (1-11)	/	
Пациенти кои примиле Plt единици (број,%, просек, ранг)	20 (22%) 16.3±17.6 (1-66)	/	
Пациенти кои примиле Plt концентрат –единици (број, %)	7 (7.8%) (1-2)	/	
Мобилизирачка стратегија			
G-CSF	64 (71.1%)	30 (100%)	
G-CSF + хемотерапија	26 (28.9%)	/	
Несакани реакции			
Да	14.4%	43.3%	p=0.0009
Не	85.6%	56.7%	

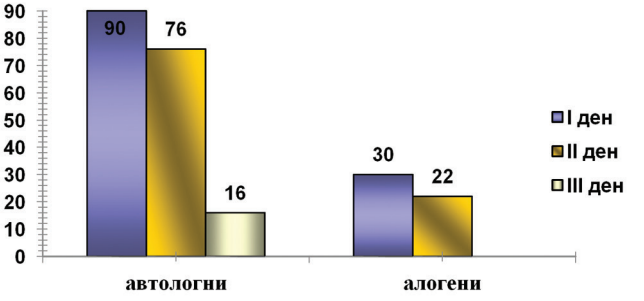
Табела 2. Клинички карактеристики на автологните донори

Клинички карактеристики на автологните донори	**Број** (%)
Дијагноза	
AML	30 (33.3%)
MM	30 (33.3%)
HD	19 (21.1%)
NHL	11 (12.3%)
Стадиум на болест	
CR	46 (51.1%)
PR	23 (25.6%)
Активна болест (релапс)	21 (23.3%)
Циклуси на хемотерапија	
0	/
1-4	45 (50%)
5-8	21 (23.3%)
9-12	13 (14.4%)
13-16	7 (7.8%)
≥ 17	4 (4.4%)
Претходна терапија со зрачење и/или ТХМК	
Терапија со зрачење+ТХМК	2 (2.2%)
Терапија со зрачење	12 (13.3%)
ТХМК	7 (7.8%)
Без терапија со зрачење и/или ТХМК	69 (76.7%)
Период од дијагноза до харвестрација (месеци) – просек,, ранг	16.8±27.8 (1-148)

*AML-акутна миелоидна леукемија, MM-мултипли миелом, HD-хочкинова болест, NHL-нехочкинов лимфом, CR-комплетна ремисија, PR-парцијална ремисија, ТХМС-трансплантација на хематопоетски матични клетки

Карактеристики на аферезна процедура

Во текот на истражувањето направени се вкупно 226 аферезни процедури, од кои 182 се изведени кај автологните донори и 44 кај алогените. Следствено на тоа добиени се вкупно 226 графта, 182 автологни и 52 алогени (графикон 1).



Графикон 1. Графички приказ на бројот на аферезни процедури

Бројот на аферезни процедури-харвестрации во првата група (автологни донори) изнесува 2.0±0.6 (опсег 1-3), а во втората група (алогените донори) е 1.5±0.5 (опсег 1-2), разликата е статистички сигнификантна за p<0.05 (Mann-WhitneyUтестZ= 3.769697 p=0.000163). Во првата група во најголем процент се застапени две постапки (66.7%), 3 постапки - 17.7%, една постапка - 15.6%. Во втората група во

најголем процент е застапена една постапка (53.3%), а 2 постапки имале 46.7% донори.Просечниот бројна аферезни циклуси во една процедура во првата група (автологни донори) при првата харвестрација изнесува 8.6±2.5 (ранг 4-15), при втората 8.6±2.7 (ранг 3-15) и при третата харвестрација 8.9 ± 2.1 (4-12). Разликата која се регистрира помеѓу просечните вредности е статистички несигнификантна за p>0.05 (AnalysisofV ariancetestF=0.117701p=0.889031). Просечниот бројна аферезни циклуси во една процедура во втората група (алогени донори) при првата харвестрација изнесува 9.6±1.6 (ранг 7-13), и при втората 7.9±1.9 (5-11). Разликата која се регистрира помеѓу просечните вредности е статистички несигнификантна за p>0.05(Mann-WhitneyZtestU=-0.352767 p=0.724263). Разликата која се регистрира помеѓу просечните вредности на првата и втората група при првата харвестрација е статистички сигнификантна за p<0.05 (Mann-WhitneyUtestZ=-2.32727 p=0.019951),при втората харвестрација статистички е несигнификантна за p>0.05 (Z=-0.901756p=0.367193). Во двете групи (автологни и алогени донори) при харвестрација во поголем процент (65.9%, 77.3%) е користен AutoPBSC сет, а WBC сет е користен при –34.1% и 22.7% харвестрации.

Табела 3. Приказ на процесирана крв (ml) при харвестацијата (волумен на крв користен во аферезната постапка) кај автологни и алогени донори

Процесирана крв (ml) 1 група (автологни донори)	Бр.	Просек	Медиана	Миним.	Максимум	Стд.Дев.
1 харвестрација	90	9475.6	9042.5	6918.0	14194.0	1219.045
2 харвестрација	76	9536.6	9049.0	7434.0	14192.0	1387.846
3 харвестрација	16	9419.9	9065.0	7505.0	11562.0	1117.849
2 група (алогени донори)						
1 харвестрација	30	9502.3	9042.0	8252.0	11507.0	887.143
2 харвестрација	14	8775.9	9026.5	6553.0	11422.0	1138.989
3 харвестрација	/					

Разликата која се регистрира помеѓу просечните вредности на процесираната крв при првата, втората и третата харвестрација кај автологните донори е статистички несигнификантна за p>0.05 (Analysis of Variancetest F=0.077339 p=0.925607). Разликата која се регистрира помеѓу просечните вредности на процесираната крв при првата и втора харвестрација кај алогените донори е статистички несигнификантна за p>0.05 (Mann-WhitneyUtest Z=1.776433 p=0.075662). Разликата која се регистрира помеѓу просечните вредности на процесираната крв меѓу автологните и алогени донори при првата харвестрација статистички е несигнификантна за p>0.05 (Mann-WhitneyUtest Z=0.215152 p=0.829649),а при втората харвестрација статистички е сигнификантна за p<0.05 (Z=2.115206 p=0.034413).

Табела 4. Приказ на вкупен број на колекционирани МНК и ЦД34+ клетки

Вкупен број MNK($x10^8$/kg)						
	Просек	Медиана	Стд.Дев.	Минимум	Максим.	p<0.05
Автологни донори	3.09	3.05	1.135517	0.8	6.2	NS
Алогени донори	3.23	3.15	1.028669	2.0	7.3	
Вкупен број CD34+($x10^6$/kg)						
	Просек	Медиана	Стд.Дев.	Минимум	Максим.	p< 0.05
Автологни донори	2.85	2.75	1.056728	0.7	5.9	NS
Алогени донори	3.20	3.10	1.004473	2.0	7.3	

Просечната вредност на колекционираните МНК (x10^8/kg) кај автологните донори изнесува 3.09±1.1, а кај алогените донори изнесува 3.23±1.03, разликата помеѓу двете групи е статистички несигнификантна зар>0.05 (Mann-WhitneyU тест Z=-0.46364 p=0.642909). Просечната вредност на колекционираните CD34+ клетки (x10^6kg) кај автологните донори изнесува 2.85±1.1, а кај алогените изнесува 3.20±1.01, разликата помеѓу двете групи е статистички несигнификантна зар>0.05 (Mann-WhitneyU тест Z=-1.53091 p=0.111631) (таб 4).Сите алогени донори во нашето истражување го дадоа посакуваниот број на МНК и ЦД34+ клетки и 85.6% од автологните донори.

Несаканите реакции во помал процент се регистрираат во првата група (автологни донори) при првата харвестрција - 14.4%, при втората - 14.5% и при третата харвестрација - 12.5% . Од несаканите реакции се регистрираат трнење на прсти, нозе, јазик, уста, лице, мачнина-гадење, болки во грб и јаки болки во кичма.Несаканите реакции во поголем процент се регистрираат во втората група (алогени донори) при првата харвестрција - 43.3%, и при втората - 35.7 %. Од несаканите реакции се регистрираат трнење на прсти, нозе, кожа, раце, болки во грб, промашена вена и погодена a.femoralis. Процентуалната разлика која се регистрира во однос на регистрација на несаканите реакции при првата харвестрација помеѓу двете групи е статистички сигнификантна за p=0.0009, како и таа што се регистрира при втората харвестрација помеѓу двете групиза p=0.0159.

Мултипла регресиона анализа

Со мултиплата регресиона анализа е утврдена поврзаност помеѓу вкупниот број на МНК x10^8/kg tt кај автологни донори (зависна-критериумска варијабла) и системот на предикторски варијабли од интерес пол, возраст, крвна група,телесна тежина и висина, мобилизирачка стратегија, ден на мобилизација/ започнување на харвестрација, предаферезен број на WBC, Hgb, Plt, вид на сет, тотален волумен на крв, број на аферзни циклуси во една процедура, времетраење на харвестрација, процесирана крв, употреба на АЦД-А, количина на колекциониран графт, трансфузиска подршка пред харвестрација со тромбоцити, еритроцити и тромбоцитен концентрат, дијагноза, терапија, терапија со зрачење и/или трансплантација на ХМК (ТХМК), број на циклуси на хемотерапија, стадиум на болест, коморбидитети, време од откривање на долест до харвестрација (независни варијабли), при што, коефициентот на мултипла корелација (R) изнесува 0,659. Коефициентот на детерминација (R^2) изнесува 0,661 и покажува дека сите независни варијабли заедно влијаат на варијабилитетот на вкупниот број на МНКкај автологните донори со 43.5%, додека 56.5% отпаѓа на влијание на други фактори.Значајноста на коефициентот на мултипла корелација тестиран врз основа на F – дистрибуција покажува дека влијанието на предикаторскиот систем на варијабли врз вкупниот број МНКкај автологните донори (зависна варијабла), статистички е значајно за p = 0,033670. Со анализа на поединечните варијабли, се заклучи дека значајно влијание има мобилизирачката стратегија, предаферезниот број на тромбоцитите, вид на користен сет за харвестрација, број нааферзни циклуси во една процедура и број нациклуси на хемотерапија. За мобилизирачката стратегија коефициентот на парцијална регресиона анализа изнесува 0.574, а тестиран со t-тест покажува дека влијанието врз вкупниот број на МНК кај автологните донори е статистички значајно за p = 0.044071. За бројот на тромбоцитите коефициентот на парцијална регресиона анализа изнесува 0.301, а тестиран со t-тест покажува дека влијанието врз вкупниот број на МНК кај автологните донори е статистички значајно за p = 0.045576. За вид на сетот коефициентот на парцијална регресиона анализа изнесува 0.525, а тестиран со t-тест покажува дека влијанието врз вкупниот број на МНК кај автологните донори е статистички значајно за p = 0.042234. За број нааферзни циклуси во една процедура коефициентот на парцијална регресиона анализа изнесува 0.354, а тестиран со t-тест покажува дека влијанието врз вкупниот број МНК кај автологните донори е статистички значајно за p = 0.037069. За број нациклуси на хемотерапија коефициентот на парцијална регресиона анализа изнесува -0.353, а тестиран со t-тест покажува дека влијанието врз вкупниот број на МНК кај автологните донори е статистички значајно за p = 0.033519. Со анализа на останатите поединечните варијабли, се заклучи дека значајно влијанието на предикторски варијабли од интерес врз вкупниот број на МНК кај автологните донори не е статистички значајно за оваа група на испитаници.

Табела 5. Мултипла регресиона анализа за вкупен број на МНКкај автологните донори

независни варијабли	**R = 0,659 R² = 0,435 F = 1.764 p = 0,033670**		
	Beta	**t – test**	**p – level**
Возраст	0.057760	0.44102	0.660731
Пол	0.009668	0.03974	0.968427
Крвна група	-0.104392	-0.86658	0.389516
Телесна тежина	-0.912433	-1.82651	0.072588
Телесна висина	-0.509431	-1.77004	0.081637
Мобилизирачка стратегија	0.574883	2.05528	0.044071*
Ден на мобилизација/ започнување на харвестрација	-0.610477	-1.79029	0.078290
WBC (10^9/л)	0.095491	0.58015	0.563916
Hgb (г/дл)	-0.034238	-0.28794	0.774350
Plt (10^9/л)	0.301735	2.04039	0.045576*
Вид на сет	0.525177	2.07384	0.042254*
Тотален волумен на крв	1.303972	1.38199	0.171934
Број на аферзни циклуси во една процедура	0.354353	2.13091	0.037069*
Времетраење на прва харвестрација	0.077261	0.17697	0.860107
Процесирана крв	-0.342519	-0.50662	0.614218
Употребен АЦД-А	0.180851	0.24273	0.809016
Количина на колекциониран графт (мл)	-0.239522	-1.17112	0.246032
Тромбоцитни трансфузии пред почеток на харвестрација	-0.068293	-0.45068	0.653793
Еритроцитни трансфузии пред почеток на харвестрација	0.036450	0.25031	0.803174
Тромбоцитен концентрат	0.185017	1.08897	0.280381
Дијагноза	0.062599	0.56677	0.572919
Терапија	-0.040225	-0.29101	0.772016
Терапија со зрачење и/или ТХМК	-0.178745	-1.39021	0.169435
Број на циклуси хемотерапија	-0.353527	-2.17415	0.033519*
Стадиум на болест	-0.090471	-0.56119	0.576688
Коморбидитет	0.021322	0.15732	0.875503
Време од откривање на болеста до харвестрација	0.082010	0.58289	0.562079

*статистичка сигнификантност (значајност)

Со мултиплата регресиона анализа е утврдена поврзаност помеѓу вкупниот број на CD34+клетките x10^6/kg ttкај автологни донори (зависна-критериумска варијабла) и погоре наведениотсистем на предикторски варијабли од интерес (независни варијабли), при што, коефициентот на мултипла корелација (R) изнесува 0,624. Коефициентот на детерминација (R^2) изнесува 0,390 и покажува дека сите независни варијабли заедно влијаат на варијабилитетот на вкупниот број на CD34+ kletkikај автологните донори со 39.0%, додека 61.0% отпаѓа на влијание на други фактори.Значајноста на коефициентот на мултипла корелација тестиран врз основа на F – дистрибуција покажува дека влијанието на предикаторскиот систем на варијабли врз вкупниот број на CD34+кај автологните донори (зависна варијабла), статистички е незначајно за p = 0,107046.Со анализа на поединечните варијабли, се заклучи дека значајно влијание има бројот на аферезни циклуси во една процедура.За број нааферзни циклуси во една процедура коефициентот на парцијална регресиона анализа изнесува 0.433, а тестиран со t-тест (2.512) покажува дека влијанието врз вкупниот број на CD34+ клеткитекај автологните донори е статистички значајно за p = 0.014608. Со анализа на останатите поединечните варијабли, се заклучи дека значајно влијанието на предикторски варијабли од интерес врз вкупниот број на CD34+ клеткикај автологните донори не е статистички значајно за оваа група на испитаници.

Со мултиплата регресиона анализа е утврдена поврзаност помеѓу вкупниот број на МНК кај алогени донори (зависна-критериумска варијабла) и

системот на предикторски варијабли од интереспол, возраст, крвна група, телесна тежина и висина, мобилизирачка стратегија, ден на мобилизација/ започнување на харвестрација, број на WBC, Hgb, Plt пред харвестрација, вид на сет, тотален волумен на крв, број на аферзни циклуси во една процедура, времетраење на харвестрација, процесирана крв, употреба на АЦД-А, количина колекциониран графт - (независни варијабли), при што, коефициентот на мултипла корелација (R) изнесува 0,737. Коефициентот на детерминација (R^2) изнесува 0,537 и покажува дека сите независни варијабли заедно влијаат на варијабилитетот на вкупниот број на МНК со 53.7%, додека 46.3% отпаѓа на влијание на други фактори. Значајноста на коефициентот на мултипла корелација тестиран врз основа на F – дистрибуција покажува дека влијанието на предикаторскиот систем на варијабли врз вкупниот број на МНКкај алогени донори (зависна варијабла), статистички е незначајна за p = 0,655111.Со анализа на поединечните варијабли, се заклучи дека влијанието на предикторски варијабли од интерес врз вкупниот број на МНКкај алогените донори не е статистички значајно за оваа група на испитаници.

Со мултиплата регресиона анализа е утврдена поврзаност помеѓу вкупниот број наCD34+клетки кај алогени донори и системот на предикторски варијабли од интерес наведени погоре, при што, коефициентот на мултипла корелација (R) изнесува 0,772. Коефициентот на детерминација (R^2) изнесува 0,596 и покажува дека сите независни варијабли заедно влијаат на варијабилитетот на вкупниот број на CD34 со 59.6%, додека 40.4% отпаѓа на влијание на други фактори. Значајноста на коефициентот на мултипла корелација тестиран врз основа на F – дистрибуција покажува дека влијанието на предикаторскиот систем на варијабли врз вкупниот број на CD34+ клеткикај алогени донори, статистички е незначајно за p = 0,481447. Со анализа на поединечните варијабли, се заклучи дека влијанието напредикторски варијабли од интерес врз вкупниот број на CD34+ клеткикај алогените донори не е статистички значајно за оваа група на испитаници.

ДИСКУСИЈА

Факторите кои можат да влијаат на мобилизацијата и колекционирање на ХМК од периферна крв се многукратно истражувани со цел да се подобри ефикасноста и сигурноста на мобилизацијата и харвестрација (15-23). Сеуште постојат големи контрадикторности во различните студии кои ја истражувале оваа тематика, и не можат да се извлечат дефинитивни заклучоци, пред се заради хетерогеноста на пациентите односно донорите. Возраста на донорите и телесната тежина (23,26) не биле сигнификантен фактор кој влијаел на бројот на МНК и CD34+ клетките во нашата и во студијата на Fordetal. (26).Вкупниот број на леукоцитите бил идентификуван како независен фактор кој инверзно влијаел на ефикасноста на колекцијата (26-28), додека студијата на Sarkodee-Adooetal. (23) не покажала сигнификантна корелација со бројот на МНК и CD34+ клетките. Слично како во нашата студија, некои студии (23,29) сугерираат дека нема корелација помеѓу хематокритот и посакуваниот број на ХМК, додека друга студија покажува инверзна корелација помеѓу двата параметри (26). Студијата на Mehta et al. (29) иако не покажала корелација помеѓу посакуваниот број на ХМК и хематокритот кај автологните донори, сепак укажува дека е добро харвестрацијата да започне кога хематокритот е меѓу 25-30%, бидејќи автологните донори, односно пациенти се најчесто анемични и потребни се трансфузии со крвни компоненти за да се започне харвестрацијата, што е случај и со тромбоцитите доколку нивниот број е помал од $30x10^9$/L (5). Предаферезниот број на тромбоцити во нашата студија сигнификантно влијаел на бројот на колекционирани МНК клетки кај автологните донори, што не било случај во некои други студии (23).Повеќе студии (23,26,30) покажале дека мобилизирачката стратегија и бројот на циклуси на примени хемотерапии (26,31) сигнификантно влијаеле на бројот на колекционирани МНК и CD34+ клетки кај автологните донори, што корелира со наодите во нашата студија, а леукоцитите биле најдобар предиктор за ефикасноста на колекционирањето на CD34+ клетките (26,32,33).Многу други фактори се исто така проучувани и добиени се различни резултати. Тие истражувања го вклучувале полот (23,26), стадиум на болест (26), режимот на хемотерапија(26), инвазија на болеста во коскената срцевина (26,30), употреба на алкилирачки агенси (31)и друго. Ефикасноста на колекцијата е испитувана и во однос на клеточниот сепаратор, рефлектирана во неговата моќ да ги екстрахира и концентрира клетките од интерес, како и карактеристиките на аферезната процедура (9,33-35). Во нашето истражување на вкупниот број на колекционираните МНК и CD34+ клетки сигнификантно влијаел бројот на аферезни циклуси во една процедура кај автологните донори и алогени

донори, како и видот на користен сет при аферезните процедури кај автологните донори. Студијата на Zengatal. (33) покажаладека бројотнаколекционира ниМНКбилпозитивнокорелирансокористењето на AutoPBSC сет, а бројот на CD34+ клетки бил корелиран сокористење на WBCсет кај алогените донори.Во друга студија WBC сетот се покажал како посупериорен од AutoPBSC сетот за колекционирање на ХМК кај пациенти со мутипен миелом мобилизирани со G-CSF+хемотерапија.Еден од факторите кој не покажал асоцираност со ефикасноста на колекцијата во нашата студија, но е презентиран во други студии како сигнификантен е процесираниот волумен на крв при афереза (3,23,32). Студијата на Ikeda et al.(30) покажала дека мобилизирачките цитокини, тајмингот на аферезата, карактеристиките на клеточниот сепаратор и оперативниот софтвер влијаеле на колекционирањето на ХМК кај автологните и алогени донори, додека возраста на донорите и полот влијаеле на бројот на колекционирани ХМК кај алогените донори. Во нашата студија не најдовме сигнификантна поврзаност на вкупниот број на колекционирани МНКи CD34+ клетки со испитуваните предиктивни фактори од интерес кај алогените донори со мултипла регресиона анализа. Тоа е можеби поради малиот примерок или заради тоа што сите алогени донори го дадоа посакуваниот број на МНК и CD34+ клетки.

ЗАКЛУЧОК

Ефикасноста на колекционирањето на ХМК е под влијание од голем број на фактори поврзани со карактеристиките на донорите, лабораториските параметри и процедуралните карактеристики и покажува голема варијабилност во клиничките наоди кај автологните донори. Податоците од различните студии покажуваат голема разновидност во клиничката пракса. Определувањето на точното ниво на предаферезните лабораториски параметри за започнување на аферезната постапка која би била безбедна за донорите и со голема ефикаснот на колекционирање на ХМК, би го намалил проблемот на помалку успешни и/или повеќекратни харвестрации. Потребно е да се направат универзални водичи за употребата на лабораториски параметри во иницијацијата на аферезната процедура за оптимизацијата на колекционирањето на ХМК.

РЕФЕРЕНЦИ

1. Majhail NS, Farnia SH, Carpenter PA, Champlin RE, Crawford S, Marks DI et al. Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2015;21(11):1863-9.
2. Ramakrishna LR. Mobilization and collection of peripheral blood progenitor cells for transplantation. Transfus Apher Sci. 2005; 32(1):63–72.
3. Sakashita AM, Kondo AT, Ribeiro AAF, Cipolletta ANF, Colesanti MV, Hamerschlak N et al. Factors affecting autologous peripheral blood hematopoietic stem cell collections by large-volume leukapheresis: a single center experience. Einstein (São Paulo). 2011;9(2):196-200.
4. Anasetti C, Logan BR, Lee SJ, et al. Peripheral-blood stem cells versus bone marrow from unrelated donors. N Engl J Med. 2012; 367(16): 1487-96.
5. Mijovic A, Pamphilon D. Harvesting, processing and inventory management of peripheral blood stem cells. Asian J Transfus Sci. 2007;1(1):16–23.
6. EBMT - European Group fot Blood and Bone Marrow Transplantation, www.ebmt.org, податоци превземени на 21.10.2016.
7. Pasquini MC, Wang Z. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR Summary Slides, 2015. CIBMTR-Center for International Bone Marrow Transplantation Research, available at: http://www.cibmtr.org
8. Moog R. Apheresis techniques for collection of peripheral blood progenitor cells. Transfus Apher Sci. 2004; 31(3):207-20.
9. Brauninger S, Bialleck H, Thorausch K, Seifried E, Bonig H. Mobilized allogeneic peripheral stem/progenitor cell apheresis with Spectra Optia v.5.0, a novel, automatic interface-controlled apheresis system: results from the first feasibility trial. Vox Sang. 2011;101(3):237-46.
10. Schulz C, von Andrian UH, Massberg S. Hematopoietic stem and progenitor cells: their mobilization and homing to bone marrow and peripheral tissue.Immunol Res.2009;44(1-3):160-8.
11. Reddy RL. Mobilization and collection of peripheral blood progenitor cells for transplantation. Transfus Apher Sci. 2005;32(1):63-72.
12. Moog R. Mobilization and harvesting of peripheral blood stem cells. Curr Stem Cell Res Ther. 2006;1(2):189-201.
13. Takeyama K, Ohto H. PBSC mobilization. Transfus Apher Sci. 2004;31(3):233-43.

14. Pusic I, Jiang SY, Landua S, Uy GL, Rettig MP, Cashen AF, et al. Impact of mobilization and remobilization strategies on achieving sufficient stem cell yields for autologous transplantation. Biol Blood Marrow Transplant. 2008;14(9):1045-56.
15. Hansson M, Svensson A, Engervall P, Björkholm M, Gruber A, Soderstrom T. Increase of monocytes predicts mobilization of peripheral stem and progenitor cells after chemotherapy followed by G-CSF administration. Eur J Haematol 1995;54:321-8.
16. Zubair AC, Grant R, Wu W, Tun H, Rivera C, Moreno-Aspitia A, et al.Platelet count is a sensitive predictor of autologous peripheral blood progenitor cell collection yield in previously treated plasma cell disease patients. Transfusion 2008;48:1106-14.
17. Kozuka T, Ikeda K, Teshima T, Kojima K, Matsuo K, Bessho A, et al.Predictive value of circulating immature cell counts in peripheral blood for timing of peripheral blood progenitor cell collection after G-CSF plus chemotherapy-induced mobilization. Transfusion 2002;42:1514-22.
18. Sinha S, Gastineau D, Micallef I, Hogan W, Ansell S, Buadi F, et al. Predicting PBSC harvest failure using circulating CD34 levels: Developing target-based cutoff points for early intervention. Bone Marrow Transplant 2011;46:943-9.
19. Ford CD, Chan KJ, Reilly WF, Petersen FB. An evaluation of predictive factors for CD34+ cell harvest yields from patients mobilized with chemotherapy and growth factors. Transfusion.2003;43(5):622-5.
20. Kudo Y, Minegishi M, Saito N, Itoh T, Fushimi J, Takahashi H et al. The absolute number of peripheral blood CD34+ cells predicts a timing for apheresis and progenitor cell yield in patients with hematologic malignancies and solid tumors.Tohoku J Exp Med. 2003;199(2):111-8.
21. Makar RS, Padmanabhan A, Kim HC, Anderson C, Sugrue MW, Linenberger M. Use of laboratory tests to guide initiation of autologous hematopoietic progenitor cell collection by apheresis: results from the multicenter hematopoietic progenitor cell collection by Apheresis Laboratory Trigger Survey.Transfus Med Rev. 2014;28(4):198-204.
22. Lysak D, Koza V, Jindra P. Factors affecting PBSC mobilization and collection in healthy donors. Transfusion and Apheresis Science. 2005;33(3): 275–83.
23. Sarkodee-Adoo C, Taran I, Guo C, Buadi F, Murthy R, Cox E, et al. Influence of preapheresis clinical factors on the efficiency of CD34+ cell collection by large-volume apheresis. Bone Marrow Transplant 2003;31:851-5.
24. Sutherland DR, Anderson L, Keeney M, Nayar R, Chin-Yee I. The ISHAGE guidelines for CD34+ cell determination by flow cytometry. International Society of Hematotherapy and Graft Engineering. J Hematother 1996;5:213-26.
25. Pivkova A. Avtologna transplantacija so krioprezervirani maticni kletki vo lekuvanje na maligni hematoloski zaboluvanja (magisterski trud). Medicinski fakultet - Skopje, 2009.
26. Ford CD, Pace N, Lehman C. Factors affecting the efficiency of collection of CD34-positive peripheral blood cells by a blood cell separator. Transfusion 1998;38:1046-50.
27. Gidron A, Verma A, Doyle M, Boggio L, Evens A, Gordon L, et al. Can the stem cell mobilization technique influence CD34+ cell collection efficiency of leukapheresis procedures in patients with hematologic malignancies? Bone Marrow Transplant 2005;35:243-6.
28. Matic GB, Ullrich H, Barlage S, Rothe G, Schmitz G. Effect of processed blood volume, leukocyte count and concentration of CD34-positive cells in peripheral blood on efficiency of stem cell apheresis. Beitr Infusionsther Transfusionsmed 1997;34:139-43.
29. Mehta J, Oyama Y, Winter J, Williams S, Tallman M, Singhal S, et al. CD34(+) cell collection efficiency does not correlate with the pre-leukapheresis hematocrit. Bone Marrow Transplant 2001;28:597-601.
30. Ikeda K, Kozuka T, Harada M. Factors for PBPC collection efficiency and collection predictors. Transfus Apher Sci. 2004; 31(3):245-59.
31. Wuchter P, Ran D, Bruckner T, Schmitt T, Witzens-Harig M, Neben K et al. Mobilization of Hematopoietic Stem Cells—Definitions, Incidence, Risk Factors, and Impact on Outcome of Autologous Transplantation. Biol Blood Marrow Transplant. 2010;16: 490-99.
32. Verlinden A, Van de Velde A, Verpooten GA, Janssen van Doorn K. Determining factors predictive of CD34+ cell collection efficiency in an effort to avoid extended and repeated apheresis sessions. J Clin Apher. 2013;28(6):404-10.
33. Zeng F, Wei SJ, Huang HB, Huang QH, Lin QY, Fan LP et al. Analysis of the efficiency and influence factors of PBSC collection with AutoPBSC and MNC procedure of cell separator. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2014;22(6):1684-90.
34. Heuft HG, Dubiel M, Kingreen D, Oertel J, De Reys S, Rick O et a.. Automated collection of peripheral blood stem cells with the COBE Spectra for autotransplantation. Vox Sang. 2000;79(2):94-9.

35. Cooling L, Hoffmann S, Herrst M, Muck C, Armelagos H, Davenport R. A prospective randomized trial of two popular mononuclear cell collection sets for autologous peripheral blood stem cell collection in multiple myeloma. Transfusion. 2010;50(1):100-19.

DONORS AND APHERESIS CHARACTERISTICS THAT INFLUENCE COLLECTION EFFICIENCY OF PERIPHERAL BLOOD HEMATOPOIETIC STEM CELLS

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ABSTRACT

Introduction: Succsessful collection efficiency of mononuclear cells(MNC) and CD34+ peripheral blood cells requires identification of predictive factors. The aim of our study was to investigate possible predictive factors that could influencehematopoietic stem cell (HSC) yield.

Material and Methods: The investigation group is concluded of 120 autologous and allogeneic donors undergoing apheresis collections of HSC.The influence of possible predictive factors (demographic characteristics, laboratory parameters, collection characteristics in both groups, and mobilization strategy and the disease characteristics in autologous donors) on the MNC and CD34+ cells collection efficiency was determined by multiple regression analysis.

Results: There were 226 apheresis collections, 182 in 90 autologous and 44 in 30 allogeneic donors, mean 2 apheresis(range 1-3) in autologous and 1.5 apheresis(range 1-2) in allogeneic donors. Collection efficiency of MNC in autologous donors was significantly influenced by preapheresis platelet count (p=0.045576), mobilization strategy (p=0.044071), type of set for apheresis collection (p=0.042254), number of apheresis cycles in one procedure (p=0.037069) and number of cycles of chemotherapy (p=0.033519). Collection efficiency of CD34+ cells in autologous donors was affected by number of apheresis cycles in one procedure (p=0.014608). Statistical relationship was not found,between the investigated predictive variables of interest and collected number of MNC and CD34+ cells in allogeneic donors, by multiple regression analysis.

Conclusion: Development of universal guidelines for iniciation of apheresis procedure based on preapheresis blood count values is needed for optimization of collection efficiency of hematopoietic stem cells.

Kew words: hematopoietic stem cells, transplantation of hematopoietic stem cells, mononucleated cells, CD34+, apheresis collection

Original scientific paper

СПЕКТАР НА МАЛФОРМАЦИИ КАЈ РАНО ДИЈАГНОСТИЦИРАНИ КОНГЕНИТАЛНИ МАЛФОРМАЦИИ НА БУБРЕЗИТЕ И УРИНАРНИОТ ТРАКТ

MALFORMATION SPECTRUM IN EARLY DIAGNOSED CONGENITAL ANOMALIES OF THE KIDNEYS AND URINARY TRACT

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АБСТРАКТ

Конгениталните малформации на бубрезите и уринарниот тракт (Congenital anomalies of the kidney and urinary tract- CAKUT) се чести во детската возраст и сочинуваат помеѓу 20 и 30% од сите конгенитални аномалии кои се детектираат во перинаталниот период. Значењето на конгениталните аномалии на бубрезите и уринарниот тракт е ризикот што тие го носат за влошување на бубрежната функција со развој на прогресивна бубрежна болест и бубрежна инсуфициенција.Не постојат доволно студии за клиничкиот тек, спектарот на малформации, генетските и прогностичките фактори на рано дијагностицираните конгенитални малформации на бубрезите и уринарните патишта.

Целта на оваа студија е да се анализираат демографските карактеристики (пол, возраст, етницитет, фамилијарна пердиспозиција) на новородените со рано дијагностициран CAKUT, типот и тежинатана конгениталните малформации на бубрезите и уринарниот тракт и присуството на екстраренални манифестации.

Студијата беше дизајнирана како ретроспективна обсревациона студија. Студијта отфати 100 испитаници со пренатално поставено сомнение за конгенитална малформација на бубрезите и уринарнот тракт. Пациентите беа прегледани на Клиниката за детски болести, Скопје. Резултатите ги прикажуваат клиничките и демографските карактеристики, како и спектарот на малформации кај пациентите со рана дојагноза на конгенитални аномалии на бубрезите и уринарниот тракт.

Оваа студија дава допринос во разбирање на карактеристиките на рано детектираните конгенитални малформации и поставување на стратегија за рана постнатална потврда на пренатално поставеното сомнение за малформација и ран, оптимизиран третман, со цел редукција или одложување на прогресија на детериорација на бубрежната функција и терминална бубрежна болест.

Клучни зборови: малформации, CAKUT, уринарен тракт, рана дијагноза

ВОВЕД

Конгениталните малформации на бубрезите и уринарниот тракт (Congenital anomalies of the kidney and urinary tract- CAKUT) се чести во детската возраст и сочинуваат помеѓу 20 и 30% од сите конгенитални

аномалии кои се детектираат во перинаталниот период [1]. Структурните малформации од спектарот на CAKUT опфаќаат различи ентитети кои ги афектираат бубрезите (пример ренална агенезија, хипоплазија или дисплазија, мултицистична дисплазија), уринарните патишта (хидронефроза или мегауретер, двоен канален систем, уретеропелвична обструкција), бешиката (везикоуретрален рефлукс, уретероцела), уретра (валвула на задна уретра) или во исто време и бубрезите и уринарните патишта [2].

Најчеста од сите антенатално дијагностицирани ренални аномалии е хидронефрозата. Со подобрување на антенаталната ултрасонографија, феталната хидронефроза се дијагностицира почесто од порано. Антенаталната хидронефроза се дијагностицира кај 1-5% од сите бремености и представува една од најчестите вродени малформации [3, 4, 5].

CAKUT представуваат широк спектар малформации кои се јавуваат со инциденца од 3-6 на 1000 новородени. Глобалната стапка на CAKUT кај живи и мртвородени новороденчиња изнесува 0,3 до 1,6 на 1000 [1, 6, 7]. Се проценува дека овие малформации преставуваат причина за смрт кај 1:2000 раѓања [8]. Се работи за сложени малформации (билатерална ренална агенезија асоцирана со малформација на други системи), кои се инкомпатибилни со живот. Во последните години, преваленцијата на деца со тешки форми на CAKUT се зголемува поради подобрена пери и постнатална заштита.

Инциденцата на CAKUT е повисока кај потомците на фамилии со историја за CAKUT или историја за ренална болест или дијабет кај мајакта [9,10]. Бубрежни малформации се најдени кај околу 10% од блиските роднини на пациентите со CAKUT, иако истите се најчесто асимтоматски [11]. И покрај тоа, се предпоставува дека одреден процент од генетските форми остануваат недијагностицирани и фреквенцијата на фамилијарниот CAKUT веројатно е поголема. Иако CAKUT вообичаено се јавува како изолирана малформација, понекогаш овие малформации се јавуваат асоцирани со други конгенитални малформации надвор од уринарниот тракт. Реналните малформации се асоцирани со екстраренални конгенитални малформации во околу 20-30 % од случаите, објавено во мулти-центричната Европска студија на Wiesel *et al.* [6]. Комбинација на CAKUT со екстраренални аномалии се сретнува кај повеќе од 200 опишани синдроми[12].

Значењето на конгениталните аномалии на бубрезите и уринарниот тракт е ризикот што тие го носат за влошување на бубрежната функција со развој на прогресивна бубрежна болест и бубрежна инсуфициенција. Тие се најчеста причина за бубрежна инсуфициенција и ренална заместителна терапија во детството [13]. Во САД конгениталните аномалии на бубрезите и уринарниот тракт представуваат причина за хронична бубрежна болест кај 34-59% од пациентите и се причина за бубрежна инсуфициенција кај 31% [14,15,16].

Структурните малформации на бубрезите може да се должат на пореметена нефрогенеза. Се предпоставува дека бројни генетски фактори и фактори од околината делуваат во тек на бременоста. Анимални студии докажуваат мултипли молекули есенцијални во морфогенезата на бубрезите и уринарниот тракт кај малформациите на уринарниот тракт [17]. Овие генетски малформации може да се дефинирани во групата на изолирани и синдромски CAKUT.Можноста за генетска основа на несиндромски CAKUT е основана на фамилијарната појава на несиндромска ренална агенезија, хиподисплазија, ренална тубуларна дисгенезија, мултицистични диспластични бубрези или ВУР [18, 19, 20, 21, 22].

Опсервацијата дека различни форми на CAKUT се јавуваат во една фамилија сугерира дека одредени генски мутации може да водат до CAKUT, но финалниот ренален фенотип зависи или од генетски фактори или од фактори на средината. Иако веќе се изолирани бројни гени кај пациентите со несиндромски CAKUT, сеуште недостасува доказ дека несиндромскиот CAKUT се должи на мутација на еден ген [23]. Фенотипската хетерогеност на CAKUT веројатно е резултат на некој од следниве фактори: мутација на еден ген или повеќе гени поврзани со хуманиот CAKUT (24), генетски[25, 26, 27, 28, 29]или епигенетски модификатори [30], сетотоа моделирано од модусот на наследување и околината.Асоцирани аномалии со ренална агенезија се срцеви, коскено/скелетни, гастроинтестинални малформации, малформации на респираторен тракт и жлездени малформации. Тие може да бидат во склоп на синдромсцка појава на CAKUT. Комбинација на CAKUT со екстраренални аномалии се сретнува кај повеќе од 200 опишани синдроми[12].

ЦЕЛИ

Епидемиолошките податоци за преваленција на CAKUT во земјите во развој не се потполни. Не постојат доволно студии за клиничкиот тек, спектарот на малформации, генетските и прогностичките фактори на рано дијагностицираните конгенитални малформации на бубрезите и уринарните патишта.

Целта на оваа студија е да се анализираат демографските карактеристики (пол, возраст, етницитет, фамилијарна пердиспозиција) на новородените со рано дијагностициран CAKUT, типот и тежинатана конгениталните малформации на бубрезите и уринарниот тракт и присуството на екстраренални манифестации.

МАТЕРИЈАЛ И МЕТОДИ

Студијата беше дизајнирана како ретроспективна обсревациона студија. Студијта отфати 100 испитаници со пренатално поставено сомнение за конгенитална малформација на бубрезите и уринарнот тракт. Дијагнозата беше поставена во неонаталниот и раниот доенечки период врз база на податок од родилниот картон за пренатално поставено сомнение со фетална ултрасонографија. Ова пренатално поставено сомнение беше евалуирано само како податок за присуство или отсуство на сомнение за малформација без навлегување во поединости поради нестандардизираност на пренаталната фетална проценка од страна на гинеколозите на примарно, секундарно и терциерно ниво. Прв постнатален ултрасонографски преглед кај новородените со пренатално поставено сомнение за ЦАКУТ беше реализиран 3-7 миот ден после раѓањето, со цел да се избегне погрешна интерпретација на степенот на пелвична дилатација, поради физиолошката дехидратација и малиот уринарен output во првите денови по раѓањето [31]. Испитаниците беа прегледани на Клиниката за детски болести, Скопје.

Обработката на испитаниците со рано дијагностицирани конгенитални малформации на бубрезите и уринарниот тракт опфати ултрасонографија на уринарниот тракт, како прв скрининг, потоа во склоп на додијагностика и микциона уретроцистографија, и диуретска сцинтиграфија (Tc99-DTPA скен), кортикална сцинтиграфија (Tc99-DMSA), поретко компјутеризирана томографија и нуклеарна магнетна резонанца.

Фамилијарен ултрасонографски скрининг беше реализиран од страна на нефорлогкај сродници од прв степен (браќа, сестри и родители). Онаму каде сонографска нефролошка абнормалност беше детектирана кај адултните сродници, истите се упатени на адултен нефролог/уролог за понатамошна обработка и третман, а педијатриските испитаници беа додијагностицирани и третирани на Клиниката за детски болести.

Асоцирани екстраренални абнормалности беа детектирани со детален физикален преглед по дизморфолошки критериуми.

За потребите на оваа студија беше направена база на податоци во која за секој од испитаниците внесени се демографски податоци- име и презиме на испитаникот, пол, возраст на иницијална дијазгностика, фамилна оптеретеност, иницијална дијагноза и екстраренални манифестации.

Податоците се сумирани со употреба на дескриптивна статистика беа анализирани. Фреквенции и пропорции беа какулирани и табеларно прикажанисо Microsoft Excel.

РЕЗУЛТАТИ

Во оваа студија беа вклучени 100 испитаници селектирани со. Табела 1 ги прикажува демографските и клиничките карактеристики. Сите испитаници вклучени во оваа студија имаат пренатално поставено сомнение за CAKUT. Постои предоминација на машки испитаници (78%), во однос на испитаниците од женски пол (22%). Средна возраст на инцијална дијагностика, дефинирана како постнатална проценка со која се потврдува пренатално поставеното сонмение за CAKUT е 43 дена, во првиот месец дијагнозата на CAKUT е поставена кај 58%, а во првите 3 месеци тој процент изнесува 90% од испитаниците. Фамилијарна предисипозија најдена е кај 21% од испитаниците. Во однос на етницитетот, 48%од испитаниците се од македонска, 27% од албанска, 12% се од ромска и 3% се припадници на останатите етнички заедници.

Табела 1. Клинички и демографски карактеристики на пациентите со CAKUT

КАРАКТЕРИСТИКИ	%
Етницитет	
Македонски	55
Албански	30
Ромски	12
Останати	3
Пол	
Женски	22
Машки	78
фамилијарнаанамнеза	
Не	79
Да	21
екстрареналнималформации	
Да	23
Не	77
возрастприиницијалнадијагностика (денови)	
0-7	38
0-30	58
0-90	90

Спектарот на малформации кај испитаниците со рано дијагностициран CAKUT е прикажан во Табела 2. Најчести малформации на бубрезите и уринарниот тракт кај испитаниците вклучени во оваа студија сехидронефроза 24% од испитаниците, VUR кај 23%, обструкција на пиелоуретеричниот спој и везикоуретрална стеноза имаше кај 30%, ектопичен бубрег имаше кај 2% од испитаниците. Паренхимни бубрежни болести (диспластични или хипопластични бубрези, мултицистични диспластични бубрези и ренална агенезија) најдени се кај 32% од испитаниците.

Табела 2. Спектар на малформации нај пациенти со рано дијагностициран CAKUT

МАЛФОРМАЦИИ НА УРИНАРНИОТ ТРАКТ	%
паренхиматозни	
мултицистични/диспластичнибубрези	25
хипоплазија	2
Агенезија	5
аномалијанамиграција и фузија	
ектопиченбубрег	2
потковичестбубрег	1
аномалиинауретра	
валвуланазаднауретра	3
уретроцела	2
дупликаналенсистем	4
уретропелвичнаобструкција	30
везикоуретраленрефлукс	23
хидронефроза	24

Екстраренални манифестации се најдени кај 23% од испитаниците во оваа студија, вклучувајќи кардиоваскуларни малформации, малформации на централен нервен систем, гастроинтестинални малформации и лицев дизморфизам се спектарот на малформации детектирани во оваа група испитаници. 77% имаа изолирана малформација на уринарен тракт.

ДИСКУСИЈА

Раната дијагноза на конгениталните малформаии на бубрезите и уринарниот тракт овозможуваат ран третман и хируршка интервенција и ја одложуваат појавата на бубрежна инсуфициенција. CAKUT опфаќа широк спектар на аномалии како ренална хипо или дисплазија, потковичест бубрег, ектопичен бубрег, пиелоуретерична обструкција, везикоуретрален рефлукс, мегауретер, обструктивна уропатија и неурогена бешика [32]. Голема мултицентрична студија за ренални малформации која опфатила 20 регистри и 12 Европски држави, со вкупно 709,030 живородени и мртвородени испитаници објавува преваленција од 1,6 на 1000 новородени, но е различна во различни европски држави, како резултат на разликите во поставеноста на пренаталниот скрининг, разликите во етничката припадност и религијата. Државите во кои нема етаблиран редовен рутински ултрасонографски скрининг имаат најниска стапка на детекција. Најчеста дијагноза кај опишана испитаниците од оваа студија е дилатација на горните уринарни патишта опишана кај 27% од вкупниот број на испитаници.

Хидронефрозата е најчеста малформација на бубрезите и уринарниот тракт која се детектира антенатално. Од сите испитаници во нашата студија, хидронефроза е нотирана кај вкупно 24 од испитаниците во оваа студија, од нив билатерална кај (5%) и унилатерална кај (95%). Застапенсота на конгенитална хидронефрза во оваа студија корелира со вкупните податоци за преваленција на хидронефроза, која по литературните податоци изнесува 1/500 и представува 2/3 од сите интраутерини уринарни аномалии [33]. Од студијата се искулучени испитаниците кај кои на иницијалниот ултрасонографски постнатален скрининг и на последователните контролни прегледи имало лесен степен на хидронефроза, најчесто во склоп на транзиторна или физиолошка хидронефроза. Машките испитаници почесто имаа хидронефроза и таа почесто е лоцирана на левиот бубрег.

Податоците од оваа студија покажаа ренални

паренхиматозни малформации кај 27% од испитаниците. Во оваа група малформации, доминираа испитаниците со наод на мултицистични диспластични бубрези, најмала беше групата на испитаници со ренална агенезија. Полицистично променетите бубрези се јавуваат со преваленца од 0,57 на 1000 раѓања и представуваат значителен ризик за развој на терминална бубрежна болест кај децата. Пациентите со полицистични бубрези треба веднаш нефролошки да се обработат. Ова се однесува и на членовите на нивните семејства. Преваленцијата на мултицистични диспластични бубрези е 0,4 на 1000 новородени и најчесто е унилатерална. Во испитаниците од оваа студија само во еден случај најдена е билатерална цистична дисплазија. Ренална агенезија, според литературните податоци се јавува кај 0,27 од 1000 раѓања [34].

Аномалии на миграција и фузија на уринарните патишта и аномалиите на бешиката и уретрата се поретки од паренхимските ренални малформации. Во оваа студија аномалиите на миграција и фузија, т.е. ектопични и подковичести бубрези застапени се кај 3 тројца од испитаниците. Аномалиите на бешиката и уретрата-уредероцела и валвула на задна уретра, најдени се кај вкупно 5 од испитаните случаи. Валвула на задна уретра е најчеста причина за обструкција на долните уринарни патишта кај машките бебиња. Се јавува со инциденца 1 на 8 до 25.000 раѓања. Една третина од момчињата родени со постериорна уретрална валвула развиваат терминална бубрежна инсуфициенција. Во нашата студија имаше два пациенти со постериорна уретрална валвула, без екстраренални абнормалности. Комплетни и парцијални двојни канални системи во оваа студија се реферирани во мал процент- 4% од сите испитаници, што веројатно се должи на пропуст во пренаталната дијагностика.

Везикоуретралниот рефлукс кај испитаниците од оваа студија беше застапен кај 23% од испитаниците и најчесто беше унилатерален. Пиелоуретеричните обструкции се среќаваат кај 30 од испитаните новороденчиња и доенчиња. Во оваа студија тие се најчесто унилатерални. Раната дијагноза кај овие пациенти водеше до адекватно планирање на ран оперативен третман и адекватна протективна медикаментозна терапија со цел за очувување на бубрежната функција.

Голема мултицентрична Европска студија [32]објави податоци за асоцијација на бубрежни малформации со екстраренални малформации во 30% од случаите. Нашата студија покажа асоцијација кај 23% од испитаниците. Опишани се повеќе синдроми кои освен малформација на бубрезите и уринарниот тракт имаат есктаренални аномалии со специфично наследување. Важноста на рана дијагноза на бубрежните аномалии е потенцирана со значењето на истовремената детална дијагностика по дизморфолошки критериуми, која овозможува рана детекција на придружни малформации на кардиоваслукарниот, дигестивниот, коскено-скелетниот систем и останатите органи и системи и нуди можност за дополнителна генетска додијагностика.

Оваа студија опишува позитивна фамилијарна анамнеза за конгенитални малформации на бубрезите и уринарниот тракт кај 21% од испитаниците. Фамилијарен скрининг и рано генетско советување е потребно во семејствата со фамилијарен CAKUT, или новодијагностицирани форми на CAKUT кои сугерираат присуство на генетски аномалии.

Преваленцијата на малформации на бубрезите и уринарниот тракт е релативно голема во земјите во развој. Антенатална ултразвучна проценка на бубрезите и уринарниот тракт се прави рутински кај сите бремени жени со цел рана детекција на конгенитални малформации и поставување на стратегија за рана постнатална потврда на пренатално поставеното сомнение за малформација и ран, оптимизиран третман, со цел редукција или одложување на прогресија на детериорација на бубрежната функција и терминална бубрежна болест.

ЛИТЕРАТУРА

1. Queisser-Luft A, Stolz G, Wiesel A, Schlaefer K, SprangerJ."Malformations in newborn: results based on 30,940 infants and fetuses from the Mainz congenital birth defect monitoring system (1990-1998)". *Arch Gynecol Obstet*. 2002;266(3):163
2. Song R, Yosypiv I. V. Genetics of congenital anomalies of the kidney and urinary tract". *Pediatric Nephrology*. 2011;26(3)353–364
3. Gunn TR, Mora JD, Pease P."Antenatal diagnosis of urinary tract abnormalities by ultrasonography after 28 weeks' gestation: incidence and outcome". *Am J Obstet-Gynecol* 1995;172:479-86
4. Livera LN, Brookfield DS, Egginton JA, et al."Antenatal ultrasonography to detect fetal renal abnormalities: a prospective screening programme". *BMJ* 1989; 298:1421-3

5. Sairam S, Al-Habib A, Sasson S, et al." Natural history of fetal hydronephrosis diagnosed on mid-trimester ultrasound". *Ultrasound ObstetGynecol* 2001; 17:191-6
6. Wiesel A, Queisser-Luft A, Clementi M, Bianca S, Stoll C, EUROSCAN Study Group."Prenatal detection of congenital renal malformations by fetal ultrasonographic examination: an analysis of 709,030 births in 12 European countries".*Eur J Med Genet*. 2005;48(2):131
7. Livera LN, Brookfield DS, Egginton JA, HawnaurJM."Antenatal ultrasonography to detect fetal renal abnormalities: a prospective screening programme". *BMJ*. 1989;298(6685):1421
8. Reuss A, Wladimiroff JW, Niermeijer MF."Antenatal diagnosis of renal tract anomalies by ultrasound". *PediatrNephrol*. 1987;1(3):546
9. Shnorhavorian M, Bittner R, Wright JL, Schwartz SM."Maternal risk factors for congenital urinary anomalies: results of a population-based case-control study". *Urology*. 2011 Nov;78(5):1156-61
10. Yang J, Cummings EA, O'Connell C, JangaardK."Fetal and neonatal outcomes of diabetic pregnancies". *ObstetGynecol* 2006; 108:644e50
11. Winyard P, Chitty LS. " Dysplastic kidneys". *SeminFetalNeonatalMed* 2008; 13: 142–151
12. Limwongse C, Cassidy SB."Syndromes and malformations of the urinary tract". *In: Pediatric Nephrology, 5th ed, Avner ED, Harmon WE, Niaudet P (Eds), Williams & Wilkins, Philadelphia* 2004. p.93
13. SchedlA."Renal abnormalities and their developmental origin". *NatRevGenet* 2007; 8: 791–802
14. Rosborough AD, Luger AM, Nolph KD. " Familial unilateral renal agenesis and focal and segmental glomerulosclerosis". *American Journal of Kidney Diseases*. 1993;21(6): 663–668
15. Murugasu B, Cole RB, Hawkins EP, Blanton SH, Conley SB, Portman RJ. " Familial renal adysplasia". *American Journal of Kidney Diseases*, 1991;18(4): 490– 494
16 Eccles MR, Bailey RR, Abbott GD, Sullivan MJ. "Unravelling the genetics of vesicoureteric reflux: a common familial disorder". *Human Molecular Genetics.* 1996; 5:1425–1429
17. GribouvalO, Gonzales M, Neuhaus T et al."Mutations in genes in the renin-angiotensin system are associated with autosomal recessive renal tubular dysgenesis". *Nature Genetics* 2005;37(9):964–968
18. McPherson E."Renal anomalies in families of individuals with congenital solitary kidney". *Genetics in Medicine*, 2007;9(5):298–302
19. Kobayashi M, Kaplan BS, Bellah RD et al."Infundibulopelvic stenosis, multicystic kidney, and calyectasis in a kindred: clinical observations and genetic analysis". *American Journal of Medical Genetics*, 1995;59(2):218–224
20. Song R, Yosypiv IV. "Genetics of congenital anomalies of the kidney and urinary tract". *Pediatric Nephrology*. 2011;26(3) 353–364
21. Nie X, Sun J, Gordon RE, Cai CL, Xu PX. "SIX1 acts synergistically with TBX18 in mediating ureteral smooth muscle formation". *Development*. 2010;137(5) 755– 765
22. Marini M, Giacopelli F, Seri M, RavazzoloR."Interaction of the LMX1B and PAX2 gene products suggests possible molecular basis of differential phenotypes in Nail-Patella syndrome". *European Journal of Human Genetics*. 2005;13(6):789–792
23. Fain PR, McFann KK, Taylor MRG et al."Modifier genes play a significant role in the phenotypic expression of PKD1". *Kidney International*, 2005;67(4):1256–1267
24. Hiesberger T, Shao X, Gourley E, Reimann A, Pontoglio M, Igarashi P, "Role of the hepatocyte nuclear factor-1β (HNF-1β) C-terminal domain in Pkhd1 (ARPKD) gene transcription and renal cystogenesis". *The Journal of Biological Chemistry*. 2005;280(11):10578–10586
25. Kim I, Fu Y, Hui K. et al."Fibrocystin/polyductin modulates renal tubular formation by regulating polycystin-2 expression and function". *Journal of the American Society of Nephrology*. 2008;19(3):455–468
26. Welham SJM, Riley PR, Wade A, Hubank M, Woolf AS."Maternal diet programs embryonic kidney gene expression". *Physiological Genomics*. 2005; 22(1):48–56
27. Sanna-Cherchi S, Caridi G, Weng PL et al."Genetic approaches tohuman renal agenesis/hypoplasia and dysplasia". *PediatrNephrol*2007; 22: 1675–1684
28. Daneman A, Alton DJ. "Radiographic manifestations of renal anomalies". *Radiologic Clinics of North America* 1991;29(2):51–363
29. Lewis MA, Shaw J, Sinha M, Adalat S, Hussain F, and Inward C."UK renal registry 11th annual report (December 2008): chapter 13 demography of the UK pediatric renal replacement therapy population". *Nephron Clinical Practice*, 2009; 111(1):257–267

30. Hattori S, Yosioka K, Honda M, and Ito H."The 1998 report of Japanese National Registry data on pediatric end stage renal disease patients". *Pediatric Nephrology*. 2002;17(6): 456–461
31. Arvind Bagga. "Consensus Statement on management of antenatally detected hydronephrosis". *Indian Pediatrics* 2001; 38:1244-1251
32. Wiesel A, Queisser-Luft A, Clementi M, Bianca S, Stoll C. EUROSCAN Study Group. "Prenatal detection of congenital renal malformations by fetal ultrasonographic examination: An analysis of 709,030 births in 12 European Countries". *Eur J Med Genet*. 2005; 48:131–44.
33. González R, SchimkeCM."Ureteropelvic junction obstruction in infants and children". *PediatrClin North Am*. 2001; 48:1505–18.
34. Parikh CR, McCall D, Engelman C, Schrier RW. "Congenital renal agenesis: Case-control analysis of birth characteristics". *Am J Kidney Dis*. 2002; 39:689–94.

MALFORMATION SPECTRUM IN EARLY DIAGNOSED CONGENITAL ANOMALIES OF THE KIDNEYS AND URINARY TRACT

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ABSTRACT

Congenital anomalies of the kidney and urinary tract- CAKUT are common childhood pathology accounting for 20-30% of perinataly detected congenital anomalies. CAKUT significance implies to the risk they represent to kidney function deterioration and end stage renal disease development. Studies reporting of the clinical spectrum, genetic and prognostic factors of early diagnosed CAKUT are lacking.

The aim of this study is to analyze the demographic characteristics (gender, ethnicity, familial occurrence) of early diagnosed CAKUT, the type of malformations detected and the presence of extra renal malformations.

The study design is retrospective observational study. 100 patients with early diagnosed CAKUT at University children hospital, Skopje, were enrolled in the study. The results from this study represent the clinical and demographic characteristics as well as the spectrum of malformations in the study group.

This study strikes to make a contribution to early diagnosed CAKUT understanding as well as establishing a protocol for early detection and adequate treatment initiation in order to prevent renal function deterioration.

Key wards: malformations, CAKUT, urinary tract, early diagnosis

Original scientific paper

LABIAPLASTY-SURGICAL CORRECTION OF LABIA MINORA

ЛАБИОПЛАСТИКА-ХИРУРШКА КОРЕКЦИЈА НА МАЛИ УСНИ

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ABSTRACT

The labia minora(inner labia) or nymphae of the vulva are two cutaneous-mucosal refolds located between the labia majora, the internal aspect of which is separated by the interlabial cleft. Labia minora needs to be covered by labia majora. It has been regarded that that labia minora should not be larger than 2.4cm in width. The enlargement of the labia minora can occur due to many factors, and most often is constitutively. Surgical techniques for labia minora reduction are various. Some patients are so concerned with the size of herlabia minora that they usually speak about the curtains in pubic part. Process of urination is never aproblem after labiaplasty. Today labiaplasty is really huge mites but on the other hand it's a very simplesurgical procedure.Despiteall the stigma regarding this procedure, it appears that the procedure is in a rising trend, and labial reductionhas been present for centuries. In some society protruding the labia minora represents lower level of attractiveness, and are often compared to the form of Phalaenopsis Orchids.In some cultures in Africa the labia minora are regularly performed at a young age and this is the Kudenga ritual.

Labiaplasty as a procedureintends to improve the appearance of the labia minora subjectively, and provide psychological and functional improvement in theeverydaylife of women.As for every aesthetic procedure, guidelines and recommendations need to be set up and long-term studies are more than necessary.

Keywords: Genital surgery, labioplasty, labia minora reduction.

INTRODUCTION

In 1899 Waldeyerfirst describedthe dimension for labia minora to range from 2.5 to 3.5 cm in width.Today's we findthat labia minora varies between 10 mm and 7 cm. One must not forget that as the woman ages there are physiologic changes in the genital area and the normal fat deposit in mons pubis progressively enlarges through ages asvaginal muscle loses tightness. There areseveral causes for labia minora hypertrophy such aschronic irritation, urinary incontinence, endocrine diseases, dysplastic diseases and hereditary factors. Partial hypertrophy of labia minora is regarded as a variant of normal anatomy. The enlargement can be unilateral or bilateral and is sometimes asymmetric. Hypertrophy of the labia minora can cause dyspareunia, chronic urinary tract infections, irritation, hygienic difficulties, and interference with sports and interferes with the ability to maintain local hygiene and perform intermittent self-catheterization in certain patients. Labia minora longer than 5 cm is a functional and aesthetic problem for many women.

Reduction of the labia minora as an aesthetic procedurehas recently increased in popularity, and many different techniques have been described but no method is superior to the others. There are several technical options and they include direct excision, wedge resection with more variants and de epithelialization, composite reduction and additional procedures like W-shaped resection, Z-plasty, and laser labiaplasty, which have been described in a small number of patients. Studies report that woman go for a prepubescent aesthetic with the labia minora covered in the depths of the labia

majora.For every plastic surgeon surgical procedure like labiaplasty is challenge:

Patient psychology condition is also one of measure element for the acceptance the end of surgery results. Patients need to be over 18 years old, and to signan informed consent form for procedure. Genital surgery is specific but always the first step is perform sexual function.

Labioplasty is not recommended for woman who have concurrent genital illness, infection or a malignancy; smoker can delay quick healing of the wound; and the woman who is unrealistic in her aesthetic goals. Studies suggests labial reduction should not be performed when the patient is under 16 years.

OBJECTIVE

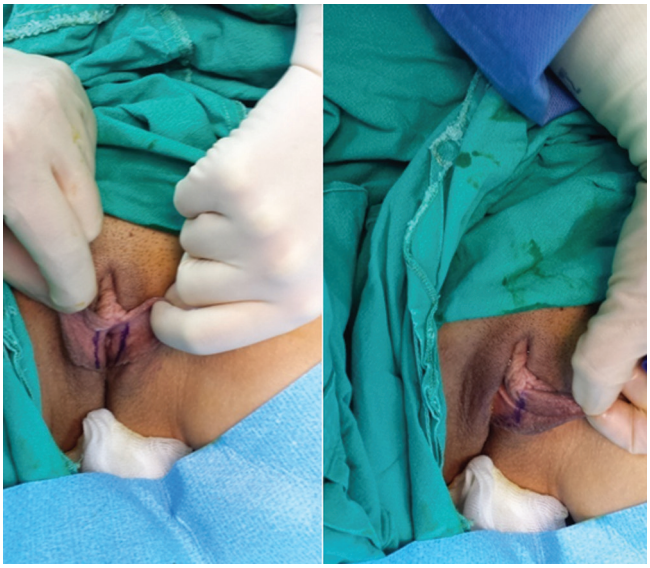
The purpose of this paper is to describe the surgical procedure, evaluate results and outcomes, and its complications and to determine the satisfaction after with surgical reduction of labia minora(patient 1, patient 2, patient 3) in cases of hypertrophy among the patients who had undergone the intervention at the University Clinic for Plastic and Reconstructive Surgery in Skopje, Macedonia. The secondary goal of this article is to present our own experiences in labia minora reduction.

METHODS

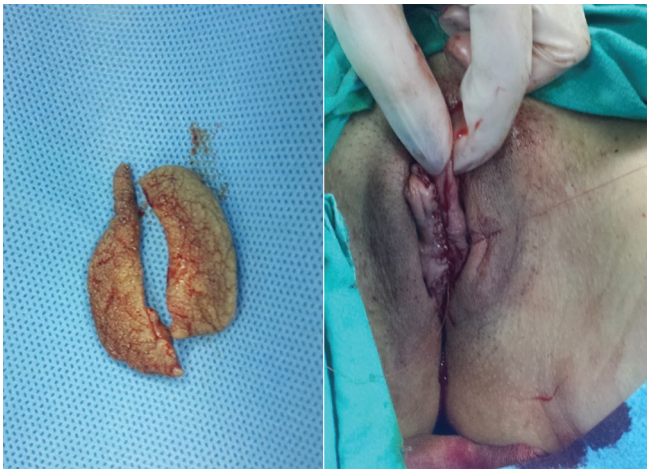
This is a retrospective descriptive review study of the medical records of the patients that have had a surgical approach of hypertrophic labia minora, at the University Clinic for Plastic and Reconstructive Surgery in Skopje, Macedonia over a three years period. Medical records were reviewed of 19 patients who underwent reduction of the labia minora from October 2013 to October 2016. The ages of the patients ranged from 19 to 48 years (mean age of 38 years). The motivations for requesting surgery were aesthetic concernsor functional, with entry dyspareunia, discomfort with exercise, and discomfort in clothing (in swimming suit).The anatomical result was evaluatedat the postoperative consultation, one month later. We performed: elliptical excision-complete amputation 3 (15.8%), partial amputation 6 (31.6%), and modification of V-wedge labioplasty of the protuberant segment of the hypertrophic labium 10 (52.6%). First follow-up was scheduled three days postoperatively, and thenext follow-up after three weeks. The techniquemost oftenemployed was elliptical excision-complete amputation (patient 1, patient 2, patient 3), and in this author's opinion is the simplest one. It is very important preoperative to delineate the borders of the vulvar mucosa and labial redundancy with the patient's needs and expectations. We also need to be careful with clitoral hood. Complete excision of the excess labial tissue (patient 1, patient 2, patient 3) was carried out over its entire length and then the edges were sutured together with absorbable suture in two layers. In majority of cases, the labial reduction was carried out in local anesthesia, although it can be done with conscious sedation, general anesthesia, either as a discrete single surgery, or in conjunction with another gynecologic or cosmetic surgery procedure. The resectionwas facilitated with the administration of an anesthetic solution (lidocaine and epinephrine), that was infiltrated in the labia minora to achieve the local tumescence of the tissues and constriction of the pertinent labial circulatory system, which allowed for partial hemostasis and limited bleeding.Post-operative pain was minimal, and the women were able to leave hospital the same day. We suggested wearing a sanitary pad for comfort. Patients were informed that the reduced labia are often very swollen during the early post-operative period, and were instructed on the proper cleansing of the surgical wound site, two to three times daily for several days after surgery.Post-labiaplasty follow up appointment with the surgeon was recommended within three days after surgery and the patient were advised to return to the surgeon if hematoma started todevelop. Medical complications to a labial reduction procedure are uncommon, but rarely complications like bleeding, infection, labial asymmetry, poor wound-healing, under correction, overcorrection do occur, and might require a revision surgery.

RESULTS

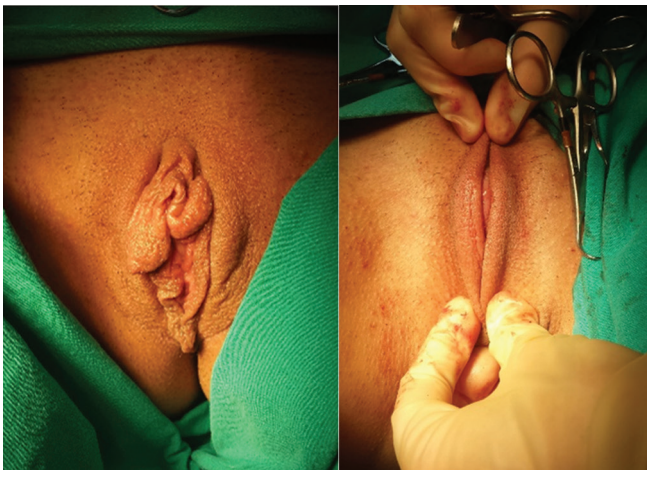
This retrospective studyreviewed19patients that underwent a labia minora reduction surgery. Anatomic and esthetic results were reported satisfactory in all patients and they reported relief from emotional stress. There were no significant surgery-related complications, such as hematoma or wound dehiscence, and allpatients experienced an uneventful postoperative period.No data is available regardingon subsequent vaginal childbirth, and the literature contains no case reports of labiaplasty disruption during parturition.



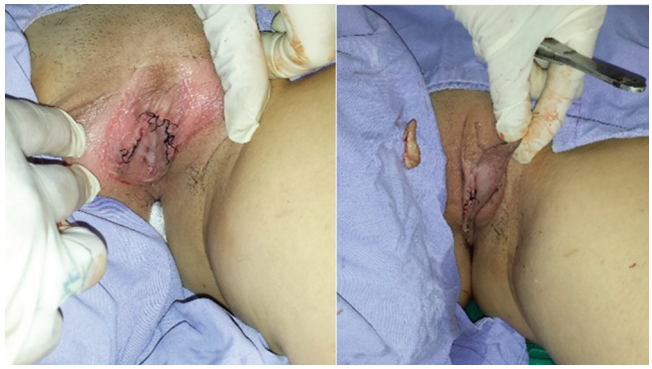
Patient 1



Patient 2



Patient 3



CONCLUSIONS

Majority of our patients underwent reduction of the labia minora for functional reasons and smaller group for aesthetic reasons for subjective enhancement of sexual function and body image, with minimal outside influences affecting their decision for treatment. However, the size of the study patients is low and further studies are warranted. As previously discussed hypertrophy of labia minora is not a pathologic condition but rather a variant of normal anatomy. Indication of the operation is psychical and functional discomfort. The success of the procedure lies in patient selection, careful preoperative planning, adequate intraoperative management and postoperative care, with key areas for intraoperative patient management that include patient anesthesia, resection technique used, wound closure. The direct excision of the protuberant tissue and the excess labia minora (patient1, patient2, patient3) is a good technique and does not produce scar-associated problem. Labia minora reduction is a simple and safe surgical aesthetic intervention associated with a high degree of patient satisfaction.

REFERENCES

1. Julie M.L.C.L. Dobbeleir, M.D., Koenraad Van Landuyt, M.D., Ph.D., and Stan J. Monstrey, M.D., Ph.D., Aesthetic Surgery of the Female Genitalia, Semin Plast Surg 2011;25:130–141. Copyright
2. Sakamoto H, Ichikawa G, Shimizu Y, Kikuchi A, Yamamoto T. Extreme hypertrophy of the labia minora. Acta Obstet Gynecol Scand 2004;83:1225–6.
3. Hodgkinson DJ, Hait G. Aesthetic vaginal labioplasty. Plast Reconstr Surg 1984;74:414–6.

4. Giraldo F, Gonzalez C, de Haro F. Central wedge nymphectomy with a 90-degree Z-plasty for aesthetic reduction of the labia minora. Plast Reconstr Surg 2004;113:1820–5.
5. Laufer MR, Galvin WJ. Labial hypertrophy – a new surgical approach. Adolesc Pediatr Gynecol 1995;8:39–41.
6. Maas SM, Hage JJ. Functional and aesthetic labia minora reduction. Plast Reconstr Surg 2000;105:1453–6.
7. Rouzier R, Louis-Sylvestre C, Paniel BJ, Haddad B. Hypertrophy of labia minora: experience with 163 reductions. Am J Obstet Gynecol 2000;182:35–40.
8. Choi HY, Kim KT. A new method for aesthetic reduction of labia minora (the deepithelialized reduction labioplasty). Plast Reconstr Surg 2000;105:419–22.
9. Radman HM. Hypertrophy of labia minora. Obstet Gynecol 1976;48:S78–80.
10. Chavis WM, Laferla JJ, Niccolini R. Plastic repair of elongated, hypertrophic labia minora – a case-report. J Reprod Med 1989;34:373–5.
11. Munhoz AM, Filassi JR, Ricci MD, Aldrighi C. Aesthetic labia minora reduction with inferior wedge resection and superior pedicle flap reconstruction. Plast Reconstr Surg 2006;118:1237–47.
12. Pardo J, Sola V, Ricci P, Guilloff E. Laser labioplasty of labia minora. Int J Gynecol Obstet 2006;93:38–43.
13. Felicio Y. Labial surgery. Aesthet Surg J 2007;27:322–8.
14. Alter GJ. A new technique for aesthetic labia minora reduction. Ann Plast Surg 1998;40:287–90.
15. Pappis CH, Hadzihamberis PS. Hypertrophy of the labia minora. Pediatr Surg Int 1987;2:50–1.
16, Alter GJ. Aesthetic labia minora and clitoral hood reduction using extended central wedge resection. Plast Reconstr Surg 2008;122:1780–9.
17. Lynch A, Marulaiah M, Samarakkody U. Reduction labioplasty in adolescents. J Pediatr Adolesc Gynecol 2008;21:147–9.
18. Jothilakshmi PK, Salvi NR, Hayden BE, Bose-Haider B. Labial reduction in adolescent population – a case series study. J Pediatr Adolesc Gynecol 2009;22:53–5.
19. Bramwell R, Morland C, Garden AS. Expectations and experience of labial reduction: a qualitative study. BJOG 2007;114:1493–9.
20. Miklos JR, Moore RD. Labiaplasty of the labia minora: patients' indications for pursuing surgery. J Sex Med 2008;5:1492–5.
21. Koning M, Zeijlmans IA, Bouman TK, van der Lei B. Female attitudes regarding labia minora appearance and reduction with consideration of media influence. Aesthet Surg J 2009;29:65–71.
22. Goldstein AT, Roman LJ. Z-plasty reduction labiaplasty. J Sex Med 2007;4:550–3.
23. Maas SM, Hage JJ. Aesthetic labia minora reduction. Ann Plast Surg 1998;412:685–6.
24. Alter GJ. Central wedge nymphectomy with a 90-degree Z-plasty for aesthetic reduction of the labia minora. Plast Reconstr Surg 2005;115:2144–5.
25. Giraldo F, Cagigal L, De Horo F, Gonzalaz C. Central wedge nymphectomy. Plast Reconstr Surg 2005;115:1792.
26. Rubiya S. Aesthetic vaginal labioplasty. Plast Reconstr Surg 1985;75:608.
27. Girling R, Salisbury M, Ersek RA. Vaginal labioplasty. Plast Reconstr Surg 2005;115:1792–3.
28. Selvaggi G. Aesthetic labia minora reduction with inferior wedge resection and superior pedicle flap reconstruction. Plast Reconstr Surg 2006;118:1248–50.
29. Hanna K, Nahai F. Central wedge nymphectomy with a 90-degree Z-plasty for aesthetic reduction of the labia minora. Plast Reconstr Surg 2003;113:1826–7.
30. Laub DR. A new method for aesthetic reduction of labia minora (the deepithelialized reduction labioplasty). Plast Reconstr Surg 2000;105:423.
31. Cartwright R, Cardozo L. Cosmetic vulvovaginal surgery. Obstet Gynaecol Reprod Med 2008;18:265–286.
32. Likes W, Sideri M, Haefner H, Cunningham P, Albani F. Aesthetic practice of labial reduction. J Low Genit Tract Dis 2008;12:210–6.
33. Paarlberg KM, Weijenborg PTM. Request for operative reduction of the labia minora; a proposal for practical guidelines for gynaecologists. J Psychosom Obstet Gynecol 2008;29:230–4.
34. Pauls RN. Nip, tuck and rejuvenate; the latest frontier for the gynecologic surgeon. Int Urogynecol J Pelvic Floor Dysfunct 2007;18:841–2.
35. McGregor JC. Labial surgery – a new phenomenon? J Plast Reconstr Aesthet Surg 2009;62:290.
36. Scholten E. Female genital cosmetic surgery – the future. J Plast Reconstr Aesthet Surg 2009;62:292.
37. Lloyd J, Crouch NS, Minto CL, Liao LM, Creighton SM. Female genital appearance: 'normality' unfolds. BJOG 2005;112:643–6.

ЛАБИОПЛАСТИКА-ХИРУРШКА КОРЕКЦИЈА НА МАЛИ УСНИ

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АПСТРАКТ

Малите (внатрешни усни) во гениталната регија или nymphae на вулвата се два кожно-мукозни набора, кои се сместени помеѓу големите усни, и одвоени со интерлабиално вдлабнување. Малите усни треба да бидат покриени од страна на големите усни. Димензиите на малите усни не треба да бидат поголеми од 2,4 см во ширина. Растењето-хипертрофијата на малите усни може да се случи како резултат на многу фактори, а најчесто е конституција. Хируршки техники за намалување на малите усни има повеќе. Пациентките вообичаено се многу преокупирани со големината на малите усни и ги споредуваат со “пердиња “. Процесот на мокрење никогаш не е афектиран. Денес хипертрофираните усни претставуваат естетскипроблем и прават хигиенски дискомфорт, но од друга страна лабиопластиката е многу едноставна хируршка процедура. Покрај сите дилеми во врска со оваа хируршка процедура, се чини дека лабиопластиката станува неопходна интервенција. Во некои општества испакнати и висечки мали усни во гениталната регија, се поистоветуваат со помала атрактивност на жената,во историјата позанти како Phalaenopsis орхидеи. Во некои култури во Африка малите усни редовно ги намалуваат уште во детска возраст и тоа е познат ритуал како- Kudenga.

Хируршката процедура лабиопластика има за цел објективно, субјективно, психолошко и функционално подобрување на изгледот на гениталиите во секојдневниот живот на жените. Како и за секоја естетска процедура, насоки и препораки се неопходни и за оваа хируршка процедура.

Клучни зборови: генитална хирургија, лабиопластика, намалување на малите усни.

Original scientific paper

HUMAN PAPILLOMA VIRUS INFECTION AND ASSOCIATED CYTOMORPHOLOGIC ALTERATIONS IN ORAL PREMALIGNANT LESIONS

INFEKSIONET ME HUMAN PAPILLOMA VIRUSIN DHE NDRYSHIMET CITOMORFOLOGJIKE TË LEZIONEVE PREKANCEROZE ORALE

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ABSTRACT

Background: Malignant transformation of oral lesions has been directly associated with oncogenic human papillomaviruses (HPVs) which are capable to induce alterations of affected epithelial cells and their early detection is critical.

Thus the aim of this study is to identify the most frequent cytomorphologic alterations common for human papillomavirus infection in oral premalignant lesions as well as determination of the HPV positivity of these lesions with PCR (polymerase chain-reaction).

Subjects and methods: In total 40 patients of both genders diagnosed with oral premalignant lesions were included. Sampling was performed with the method of "cyto-brush" technique, by taking two smears, one from the lesion and another one from healthy mucosa of the same patient, as a control. Samples were stained by modified Papanicolau technique.

Screening, detection and genotypisation of HPV-DNA from the oral smears were done with real- time PCR test.

Results: Koilocytosis was detected in 12.5% of samples (5/40), and dyskeratosis in 15% (6/40). PCR test revealed 30% (12/40) HPV positive cases and the typisation verified the presence of HPV16 in 15% of cases(6/40), HPV56 in 10% (4/40) and HPV18 in 5%(2/40).

Conclusion: Clinical approach and diagnosing procedures testing for HPV in the oral premalignant lesions ought to be comprehensive, by using the superiority of the molecular diagnostic procedures.

Key words: oral premalignant lesions, human papillomavirus, cytomorphology, polymerase chain- reaction

INTRODUCTION

Oral premalignant lesions are considered precursor lesions with high possibility of malignant transformation, moreover a part of these lesions are supposed to be associated with the HPV infection.(1) Oncogenic HPV types stimulate transformation of the epithelial cells in affected genital and respiratory mucosa, resulting in malignant transformation of those lesions, including oral malignancy as well, with high rates of morbidity and mortality, which stands for a significant worldwide health problem. (2,3,4,5) Early detection of such cell alterations is essential in identifying an early stage of cancer. As one of the most widely used diagnostic method, histopathology allows detection of cytopathic alterations common for HPV infection like koylocytosis, dyskeratosis and dyskaryosis.(6) Due to routine screening programs

for cytomorphologic alterations and early detection of HR- HPV the incidence of cervical cancer is declining (7) and yet it is the most common cause of cancer related death among women in the developing nations where such screening is not a practice.(8)

Analogous to cervical screening, researchers confirmed that cytopathic HPV alterations detected in oral squamous cell carcinomas were similar to those of the cervical lesions.(9)

Furthermore studies are focused on the possible appliance of the same screening strategy for secondary prevention and early detection of abnormal cytology in oral lesions and oropharyngeal squamous cell carcinoma (OSCC) with a "Pap- test equivalent" and HPV detection.(10)

The aim of this study was to identify the most frequent cytomorphologic alterations common for human papillomavirus infection in oral premalignant lesions as well as determination of the HPV positivity of the lesions with PCR (polymerase chain reaction) in order to compare the findings and the reliability of brush- biopsy.

SUBJECTS AND METHODS

The investigation was conducted at the Department of oral pathology and periodontology in the Universitiy Dental Clinical Centre "St. Panteleimon"- Skopje, R of Macedonia. Considering the alterations of the oral mucosa, 40 patients of both genders, referred to our department for diagnostic procedures, which were pathohistologically diagnosed with oral premalignant lesions (by two experienced oral pathologists), were included in the investigation. Cytological analyses were performed by a single cytopathologist in the cytological laboratory PZU "St. Mina"- Skopje.

CYTOMORPHOLOGIC ANALYSIS

For the detection of HPV associated cytomorphological alterations, cytomorphologic analysis was performed by obtaining two smears from each patient with oral lesion. One smear was taken from the lesion, and the second one from the nearest site of the unchanged mucosa serving as a control (11), if the lesion was bilateral, and if the lesion was unilateral the control sample was taken from the same opposite site of the patient.

Sampling was performed with the method of exfoliative cytology, "cyto-brush" technique (12), using a sterile brush (Kito Brush, Italy), by brushing the mucosa till point bleeding, and the smear was spread on glass surface of the slide (ISOLAB- Laborgeräte GmbH, Germany). The sample was immediately fixed with Merckofix® spray fixative (Merck KGaA, Germany) till further processing in the cytological laboratory. The samples were stained by modified Papanicolaou stain.(13) Slides were observed and analyzed with light microscope (Leica DM2000), and planachromat objectives x4, x10, x20, x100 were used. Images were done with a camera (Nikon, Coolpix 950), and the pictures were analyzed and processed with a software (Image Analysis Software).

Bethesda Analogous Grade System was used for classification of the lesions as follows: normal, reactive, LGSIL (low- grade squamous intraepithelial lesion), HGSIL (high- grade squamous intraepithelial lesion), Invasive Squamous Cell Carcinoma, other neoplasma.(14)

MOLECULAR ANALYSIS

The determination of the HPV positivity and typisation of the detected types was realized with the method of exfoliative brush cytology.(15) Smears were taken from the oral lesions. Screening, detection and genotypisation of HPV-DNA from the oral smears were done following the working protocol of PureLinc™ Genomic DNA Mini Kit (Invitrogen, USA). Typisation of the detected types was performed by qualitative real- time HPV typing PCR -test: „HPV high risk genotyping multiplex real- time PCR test"(Saccace, Biotechnology, Italy).

All features of the oral lesions were recorded, including the clinical diagnosis, topography and description. Each lesion was photographed as well.

Descriptive statistics, with mean values and percentages, as well as Fisher·s Exact Test, were used to present the results (Microsoft Excel Data Base and Statistica 7 software).

RESULTS

In total 40 patients (n=40) with diagnosed oral premalignant lesions comprised the study group (mean age 51.87, SD+/-6.08). According to the performed clinical examination and the established clinical diagnose, detected oral premalignant lesions and conditions were classified as follows: lichen planus (reticular and erosive form) 77.5% (31/40), leukoplakia 10% (4/40), actinic keratosis (cheilosis)10% (4/40) and erythroplakia 2.5% (1/40). (16)

Table. 1 Distribution of HPV types in oral lesions determined with PCR

Oral HPV	Lichen planus (n/%)	Actinic keratosis (n/%)	Leukoplakia (n/%)	Erythroplakia (n/%)	Total (n/%)
HPVneg	24/60,00	4/10,00	0/0,00	0/0,00	28/70,00
HPV56	4/10,00	0/0,00	0/0,00	0/0,00	4/10,00
HPV16	3/7,50	0/0,00	2/5,00	1/ 2,50	6/15,00
HPV18	0/0,00	0/0,00	2/5,00	0/0,00	2/5,00
Total	31/77,50	4/10,00	4/10,00	1/ 2,50	40/100,00

Our results disclosed 30% (12/40) HPV positive cases and 70% (28/40) of HPV negative (HPVneg) cases, and the typisation verified the presence of HPV16 in 15% of cases (6/40), HPV56 in 10% (4/40) and HPV18 in 5% of the cases (2/40). Association of the HPV detected types with the clinical diagnose is presented in Table1.

According to the cythopathic signs typical for HPV morphology, detected alterations were classified as: positive (evident koilocytosis, dyskaryosis and dyskeratosis), partial (partial signs partial signs of koilocytosis, dyskariosis and dyskeratosis typical for HPV morphology, presence of anysocytosis, parakeratosis, binucleationand inflammatory infective or non-infective alterations) and negative (without signs for HPV infection) (Tab.2).

Table 2. Cytological results according to the clinical diagnosis

Clinical diagnosis	Cytology			Total (n/%)
	Positive (n/%)	Negative (n/%)	Partial (n/%)	
Lichen planus	4/10,00	23/57,50	4/10,00	31/77,50
Actinic keratosis	0/0,00	3/7,50	1/ 2,50	4/10,00
Leukoplakia	2/5,00	1/ 2,50	1/ 2,50	4/10,00
Erythroplakia	0/0,00	0/0,00	1/ 2,50	1/ 2,50
Total	6/15,00	27/67,50	7/17,50	40/100,00

From 31(77.5%) patients with lichen planus, 4(10%) revealed positive cytological results, 23(57.5%) had negative cytology and in 4(10%) smears the results were partial.

From 4(10%) patients with hyperkeratosis, 3(7.5%) had negative cytology, and 1(2.5%) had partial signs.

From 4(10%) patients with leukoplakia, 2(5%) had positive cytology, and in 1(2.5%) smear cytology was negative, and another one patient revealed partial signs 1(2.5%).

The only case diagnosed as erythroplakia (2.5%), revealed partial HPV cytomorphology.

Cytological results associated with certain HPV types are presented in Tab.3.

Table 3. Cytological results according to HPV types

HPV-oral	Cytology			Total (n/%)
	Positive (n/%)	Negative (n/%)	Partial (n/%)	
HPVneg	1/ 2,50	23/57,50	4/10,00	28/70,00
HPV56	2/5, 00	1/2,50	1/ 2,50	4/10,00
HPV16	2/5,00	3/7,50	1/ 2,50	6/15,00
HPV18	1/ 2,50	0/0,00	1/ 2,50	2/5,00
Total	6/15,00	27/67,50	7/17,50	40/100,00

From 4(10%) patients with oral HPV56, 2 cases (5%) had positive cytology, in 1(2.5%) cytology was negative and in another one (2.5%) cytology was partial.

From 6(15%) patients with oral HPV16, 2 of them (5%) had positive cytology, and 3cases (7.5%) had negative cytology, and in one case (2.5%) cytology was partial.

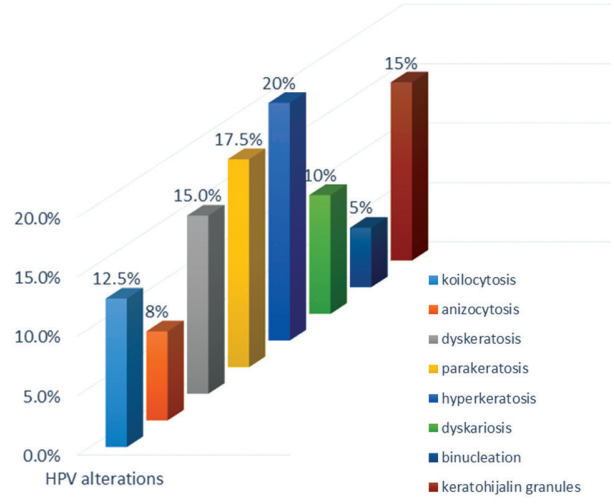
From 2(5%) patients with oral HPV18, 1(2.5%) had positive cytology and 1(2.5%) had partial cytology.

The difference between positive (including partial samples as well) and negative cytological results according to the HPV positivity and estimated with Fisher·s Exact Test was statistically significant (p=0,008).

Estimated sensitivity of the cytological results is 66.7% (95%CI 34.89-90.8) and specificity was 82.14% (95%CI 63.11-93.94).

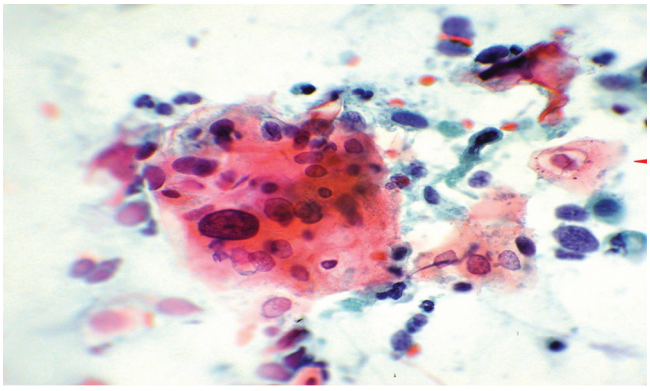
Figure 1 presents the most common cytomorphologic changes associated with HPV presence in the cells from the smears of the study group. It is evident that the major alteration koilocytosis is present with only 12.5%, and dyskeratosis which is considered to be the second most important “indicator” for HPV infection with 15%.

Figure 1. Distribution of the cell alterations common for HPV infection



Altered morphology of HPV positive samples with oral koylocytosis was typical (Fig. 2), and all of the smears from visually healthy mucosa were regular without signs for HPV morphology.

Figure 2. Cytologically identified alterations common for HPV infection in oral leukoplakia, with evident koilocytosis, moderate dysplasia and increased mitotic activity (magnification 10x40)



According to Bethesda Analog Grade System 7.5% (3/40) were recorded as LGSIL (low-grade squamous intraepithelial lesion), 2.5% (1/40) was identified as HGSIL (Fig.2) and the rest of the samples, 90% (36/40), were classified as "reactive". Control samples were all classified as "normal" (100%, 40/40).

DISCUSSION

Cytomorphologic diagnose is based on HPV associated cytopathic features like koilocytosis, as an important and the most frequent morphological marker, as well as dyskeratosis, hyperkeratosis, parakeratosis, binucleation, that typify not only the presence but an active infection with high- risk HPV types.(17,18,19) HPV positivity in the oropharyngeal cytobrushing has been associated with a nearly 5-fold risk of having abnormal cytology.(20) Nevertheless other reports disclose that HPV infection is not necessarily associated with cytologic abnormalities. (21)

In our study cytologic smears were taken from each case with OPL, from the lesion and from the nearest healthy mucosa of the same patient from the study group, as a control. In view of the diagnosis, evident positive HPV cytomorphology was associated with 10% (4/40) of lichen planus, or in total 20% (8/40) considering the partial signs as well, and the leukoplakia lesions disclosed 7.5% (3/40) of cytomorphologic alterations in total. HPV16 and HPV56 were associated with cytopathic features in 7.5% (3/40) of cases and HPV18 with 5% (2/40) of cases. From the smears of the lesion's samples it is evident that koilocytosis, as the major alteration common for HPV infection, is present with 12.5% and dyscaryosis, which is being considered the second most important cytopathic effect of HPV infection, was present with 10%, thus dyskeratosis with 15%. Our results are consistent with literature data identifying koilocytosis in 13% of the cases.(22) A variety presence of koilocytosis is evidenced in analyzed oral cavity samples(2), thus a study has verified koilocytosis in 3 of four leukoplakias.(24) Another investigation reveals koylocytosis in 37.3% (31/83) of analyzed OSCC biopsies thus additionally the same study showed no statistically significant correlation between the presence of histopathological aspects suggestive of HPV infection and the presence of HPV DNA confirmed by PCR.(25) However some reports don't support the diagnostic importance of koylocytosis as an accurate indicator of HPV infection due to 30% of false positive results.(26,27)

Literature data reveal an increased accuracy of the brush-biopsy technique, and array of sensitivity and specificity between 79%- 97% and 95.1%- 99.5%.(28) Herewith we report for sensitivity of 66.7% (95%CI 34.89-90.8) and specificity of 82.14% (95%CI 63.11-93.94). Although the oral cytology technique is considered as simple, non-aggressive, relatively painless and well tolerated by patients(29), the inconsistency of the results considering this methodology are generally attributed to subjectivity of the cytological evaluation.(30)

Considering cytopathic alterations as indirect markers of the viral presence we are in agreement that they should be considered only as indicators of possible HPV

infection (20) with high indication and recommendations for further performing of more sensitive procedures (31) in order to verify the presence of the virus.

The use of cytolomorphological tests in parallel with detection and typing of HPV, as co- testing in first-line screening for improving of sensitivity in cervical lesions is considered much efficient diagnostic approach.(32) Similar diagnosing combined modalities have been suggested in oral lesions as well thus combined brush biopsy with cytological/ DNA- cytometric examination for microscopic evaluation of white or red patches of the oral cavity has been proposed, as the nuclear DNA- content in cells of oral leukoplakia may be used to predict the risk of oral epithelial dysplasia up to 5 years before histological diagnosis.(33)

Our results demonstrated that positive HPV status doesn't associate with abnormal cytomorphology typical for the HPV infection, therefore the clinical approach and diagnosing procedures testing for HPV in the oral premalignant lesions ought to be comprehensive, by using the superiority of the molecular diagnostic procedures.

REFERENCES

1. Herrero R: Human papillomavirus and cancer of the upper aerodigestive tract. J Natl Cancer Inst Monogr.2003, 31: 47-51.
2. Flores Y, Shah K, Lazcano E, Hernández M, Bishai D, Ferris DG, Lorincz A, Hernández P, Salmerón J, Morelos Study Collaborators: Design and methods of the evaluation of an HPV- based cervical cancer screening strategy in Mexico: The Morelos HPV Study. Salud Publica Mex 2002,44:335-344.
3. Villa LL. Overview of the clinical development and results of a quadrivalent HPV (types 6, 11, 16,18) vaccine. Int J Infect Dis 2007.11(Suppl.2):S17-S25.
4. Kademani D. Oral cancer. Mayo Clin Proc. Jul2007;82(7):878-87.
5. Silverman S, Jr. Demographics and occurrence of oral and pharyngeal cancers. The outcomes, the trends, the challenge. J Am Dent Assoc. 2001; 132 Suppl:7S-11S.
6. Singh M, Chaudhary AK, Pandya S, et al. Morphometric analysis in potentially malignant head and neck lesions: oral submucous fibrosis. Asian Pac J Cancer Pev. 2010;11(1):257-60.
7. Saslow D, Runowicz CD, Solomon D, Moscicki AB, Smith RA, Eyre HJ, Cohen C. American Cancer Society Guideline for the Early Detection of Cervical Neoplasia and Cancer. J Low Genit Tract Dis.2003;7:67-86.
8. NIH Fact Sheets- Cervical Cancer. http://report.nih.gov/nihfactsheets/viewfactsheet.asp.
9. Syrjänen KJ, Pyrhonen S, Syrjänen SM, Lamberg MA. Immunohistochemical demonstration of human papilloma virus antigens in oral squamous cell lesions. Br J Oral Surg 1983;21:147–53.
10. Fakhry C, Rosenthal TB, Clark PD, Gillison LM. Associations between oral HPV 16 infection and cytopathology: evaluation of an oropharyngeal "Pap-test equivalent" in high-risk populations. Cancer Prev Rev (Phila).2011; 4(9):1378-1384.
11. Cowpe JG, Longomare RB, Green MW. Quantitative exfoliative cytology of abnormal oral mucosal smears. J R Soc Med 1988;81:509-13.
12. Boon ME, Alons-van Kordelaar JJM, Rietveld-Scheffers PEM. Consequences of the introduction of combined spatula and cytobrush sampling for cervical cytology improvements in smear quality and detection rates. Acta Cytol.1986;30:264-70.
13. Gupta S, Chachra KL, Bhadola P, Sodhani P. Modified Papanicolaou staining protocol with minimum alcohol use: a cost- cutting measure for recource- limited settings. Cytopathology.2010;21(4):229-33.
14. Afrogheh A, Wright CA, Sellars SL, Pelsar A, Wetter J, Schubert PT, Hille J. An evaluation of the Shandon PapSpin liquid based oral test utilizing a novel cytologic scoring system. Oral Surg Oral Med Oral Pathol.2012;113:799:807.
15. Koch FP, Kenkel M, Biesterfeld S, Wagner W. Diagnostic efficiency of differentiating small cancerous and precancerous lesions using mucosal brush smears of the oral cavity- a prospective and blinded study. Clin Oral Invest.2011;15(5):763-9.
16. WHO Report of a meeting of investigators on the histological definition of precancerous lesions. Geneva: World Health Organization; 1973.
17. Fornatora M, Jones AC, Kerpel S, Freedman P. Human papillomavirus- associated oral epithelial dysplasia (Koilocytic dysplasia): an entity of unknown biologic potential. Oral Surg Oral Med Oral Pathol Oral RadiolEndod 1996;82:47-56.
18. Krawczyk E, Suprynowicz FA, Liu X, Dai Y, Hartmann DP, Hanover J, Schlegel R. Koilocytosis: a cooperative interaction between the human papillomavirus E_5 and E_6 oncoproteins. Am J Pathol 2008; 173: 682-688.
19. Aggarwal S, Arora VK, Gupta S, Singh N, Bhatia A. Koilocytosis: correlations with high- risk HPV and its comparison on tissue sections and cytology, urothelial carcinoma. DiagnCytopathol 2009;37:174-177.

20. Dona MG, Giuliani M, Vocaturo A, Spriano G, Pichi B, Rollo F, Ronchetti L, Covello R, Pescarmona E, Benevolo M. Cytology and human papillomavirus testing on cytobrushing samples from patients with head and neck squamous cell carcinoma. Cancer. 2014: 120(22): 3477-84.

21. Juckett G, Hartman- Adams H. Human Papillomavirus: Clinical Manifestations and Prevention. Am Fam Physician.2010.15;82(10): 1209- 1214.

22. Sarruf MBJM, Dias EP. Avaliaçãocitopatológica da cavidadebucalem pacientesportadores de infecção genital pelopapilomavírushumano (HPV). J Bras Doenças Sex Trans 1997, 9(2):4-18.

23 Giraldo PC, Simões JA, Ribeiro Filho DA, Tambascia JK, Dias ALV, Pacello PCC. Avaliaçãocitológica da orofaringe de mulheresportadoras do HPV genital. Rev Bras GinecObstet 1996, 18(3):737-42.

24. Löning T, Meichsner M, Milde- Langosch K, Hinze H, Orlt I, Hormann K, Sesterhenn K, Becker J, Reichart P. HPV DNA detection in tumors of the head and neck: a comparative light microscopy and DNA hybridization study. ORLJ OtorhinolaryngolRelat Spec 1987;49:259- 269.

25. Miyahara GI, Simonato LE, Nattar NJ, CAmilo DJ, Biasoli ER. Correlation between koillocytes and human papillomavirus detection by PCR in oral and oropharynx squamous cell carcinoma biopsies. Mem Inst Oswaldo Cruz 2011;106; 2.

26. Salvia PN, Bergo SM, Bonesso- Saabadini PI, Tagliarini EB, Hackel C, De Angelo Anrdrade LA. Correlation between histological criteria and human papillomavirus presence based on PCR assay in cervical biopsies. Int J Gynecol Cancer 2004. 14;126-132.

27. Rick GM, Slater L. Oral brush biopsy: the problem of false positives. Oral Surg Oral Med Oral Pathol Oral RadiolEndod 2003, 96:252.

28. Merhotra, R. Oral Cytology/ A Concise Guide; Springer, New York, NY,USA.2013;p27.

29. Driemel O, Kunkel M, Hullmann M, et al. Diagnosis of oral squamous cell carcinoma and its precursor lesions. J German Soc Derm.2007,5:1095-100.

30. Nichols ML, Quin FB Jr, Schnadig VJ, Zaharopoulos P, Hokanson JA, Des Jardins L, et al. Interobserver variability in the interpretation of brush cytologiczstudies from head and neck lesions. Arch Otolaryngol Head Neck Surg 1991, 117:1350-5.

31. Zuna RE, Wang SS, Schiffman M, Solomon D.Comparison of human papillomavirus distribution in cytologic subgroups of low-grade squamous intraepithelial lesion. Cancer 2006;108:288-297.

32. Chan KSP, Picconi AM, Cheung HT, Giovannelli L, Park SJ. Laboratory and clinical aspects of human papillomavirus testing. Crit Rev Clin Lab Sci.2012;49(4):117-136.

33. Sudbø J, Kildal W, Risberg B, Koppang HS, Danielsen HE, Reith A: DNA content as a prognostic marker in patients with oral leukoplakia. N Engl J Med 2001, 344(17):1270-8.

INFEKSIONET ME HUMAN PAPILLOMA VIRUSIN DHE NDRYSHIMET CITOMORFOLOGJIKE TË LEZIONEVE PREKANCEROZE ORALE

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ABSTRAKT

Hyrje: Transformimi malinj i lezioneve orale ndërlidhet direkt me llojet onkogjene të Human papilloma viruseve (HPVs), dhe duke marrë në konsideratë aftësinë për nxitjen e ndryshimeve në qelizat e infektuara epiteliale, zbulimi i tyre i hershëm është kritik.

Nga kjo pikëpamje, qëllimi i këtij studimi është të identifikojë ndryshimet citomorfologjike, karakteristike për infeksionin me HPV, në lezionet prekanceroze orale, si dhe përcaktimin e HPV pozitivitetit të këtyre lezioneve me reaksionin zinxhiror të polimerazës PCR (real- time PCR).

Subjektet dhe metodat: Në këtë studim janë përfshirë gjithsej 40 pacientë të të dy gjinive të diagnostikuar me lezione prekanceroze orale. Marrja e mostrave është bërë me metodën eksfolijative dhe teknikën "cyto-brush", duke marrë dy prova, një nga lezioni dhe një tjetër nga mukoza e shëndoshë të të njëjtit pacient, si një kontroll. Mostrat janë ngjyrosur me teknikën e modifikuar Papanicolau.

Skriningu dhe genotipizimi i HPV-DNA janë bërë me metodën molekulare PCR (real- time PCR).

Rezultatet: Koilocitoza u evidentua në 12.5% të mostrave (5/40), dhe diskeratoza në 15% (6/40). Me testin PCR u konstatua HPV pozitivitet në 30%(12/40) të rasteve dhe me genotipizim u verifikua prezenca e HPV16 në 15% të rasteve (6/40), HPV56 në 10% (4/40) dhe HPV18 në 5% (2/40) të rasteve.

Përfundimi: Qasja klinike dhe procedurat e diagnostikimit për praninë e HPV në lezionet prekanceroze orale duhet të jenë gjithëpërfshirëse, me përparësi të superioritetit të procedurave diagnostike molekulare.

Fjalët kyçe: lezione prekanceroze orale, Human papilloma virus, citomorfologjia, PCR

Original scientific paper

TYPE 2 DIABETIC PATIENTS WITHOUT EDUCATION FOR DIABETIC FOOT HAVE A HIGHER RISK FOR FOOT ULCERATION AND HIGHER GRADE OF NEPHROPATHY

PACIENTËT ME DIABET TË TIPIT 2 QË NUK KANË EDUKIM PËR KËMBËN DIABTIKE KANË REZIK MË TË LARTË PËR ULCERACION DHE SHKALLË MË TË LARTË TË NEFROPATISË

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ABSTRACT

Aim: To assess the impact of education of individuals with Type 2 Diabetes Mellitus (T2DM) in general, education for foot care and impact of diabetic retinopathy on progression of diabetic foot and diabetic nephropathy.

Patients and methods. Observational study, 107 T2DM patients of age 35–65 years, both sex, duration of DM >1 year. The patients were examined and tested for diabetic foot and classified according to the International Working Group for diabetic foot - IWGDF into 2 groups: high risk and very high risk foot. They were also examined for chronic kidney disease according KDOQI (Clinical Practice Guideline for Diabetes and CKD) and classified in degrees (2-4) according to eGFR MDRD formula. Diabetic retinopathy was classified in non prolipherative (NPDR) and prolipherative diabetic retinopathy (PDR).They were interviewed with a questionnaire of 'yes' or 'no' questions on foot care knowledge in practice. Score of 1 was given for each 'yes' answer.

Results. From 107 T2DM patients 54 (50,5%) were male and 52 (49.5%) female. Mean age was 59.45±6y, duration of T2DM 12.45y±9 y. Average HbA1c 9.5%±1.9, BMI 28%±3.3 kg/m^2, systolic BP 136±6 mmHg, TG 2.4±1.7mmol/L, LDL 2.9±1.3 mmol/L. Education for diabetic foot in risk score groups was as follows: Non appropriately educated 71 (66.1%) with score 1 – 38 (35.6%) not educated, score 2-22 (16.8%) , and score 3–16 (14%) score. Education for T2DM appropriate Foot care was in 36 (33.6%) patients. Non educated patients associated with the grade of nephropathy as follows, grade 2 in 35.6%, grade 3 in 17.7% and grade 4 in 8.4% of patients. Retinopathy was present in 69.2% (NPDR 47.7% and PDR 21.5%).

Conclusion: Metabolic risk factors, lack of education and presence of diabetic retinopathy have significant impact on the progression of the risk score for foot ulceration and chronic kidney disease.

Key notes: diabetes, complications, Education, foot care, nephropathy.

INTRODUCTION

Diabetes is a systemic chronic disease, characterized by chronic micro and macrovascular complications. Type 2 diabetes mellitus (T2DM), also called as "silent killer" disease is very often not detected on time. As it has been shown previously that almost 46% of people with diabetes are not aware that they have it and the reason for this is very frequently masked symptomatology in the early phase of the disease (1). This is the reason why in some people

with T2DM, have chronic complications (Macro and micro vascular) detected only from diagnosis. In previous studies it has been shown that basic pathophysiologic mechanism of macro vascular complication (coronary artery disease - CAD, insult -CVI, and peripheral artery disease PAD) and micro vascular level (retinopathy, neuropathy and nephropathy) is atherosclerosis. Furthermore, diabetic foot is a complex, heterogenous complication which is consisted of microvascular manifestations like distal symmetric sensory polyneuropathy and macrovascular manifestations like PAD, and deformities. Most of the clinical experience showed that these changes frequently led to ulceration and/or infection and amputation of the foot (2). Diabetes, especially T2DM frequently is associated with others metabolic risk factors such are hypertension, dyslipidemia and obesity (as they been called the "deadly quartet") (3). Thesefactors rapidly lead to progression and worsening of complications, and the final consequences are invalidity and mortality. It has been shown for example, that risk for mortality from CAD and CVI is 2-4 times higher in type 2 diabetes as compared with non diabetic patient (3). As recommended by American diabetes association (ADA) the main goal for good metabolic control of diabetes is HbA1c<7% and control of others parameters like BP<140/90 mmHg, LDL<2, 5 mmol/L, TG<1, 7%, and smoking cessation which are of great importance in management of diabetes (4). Moreover, the treatment of patients with type 2 diabetes should be focused on non pharmacologic treatment (life style intervention, appropriate diet and physical activity) and pharmacologic treatments (oral antidiabetics, insulins, and the new drug generation such GLP 1 agonists.

Education of diabetes in general is the basis for prevention of complications. Each person with diabetes should take basic knowledge for symptoms, complications and treatment modes (5). Special education such is education for foot care should undergo every patient with the risk for foot ulceration. Diabetic retinopathy, the leading cause of visual impairment and blindness, frequently is associated with the worsening of diabetic foot and diabetic nephropathy (reno-retinal syndrome).

MATERIAL AND METHODS

The type of study is Cross sectional, performed at the university Clinic of endocrinology, Skopje. 107 hospitalized type 2 diabetic patients were investigated for metabolic control(glucose, HbA1c, urea, creatinine,lipids, blood pressure), smoking habits. Measurements for diabetic foot and stratification of the risk score for ulceration according the IWGDF were performed at diabetic foot unit and patients classified in two risk score groups risk (4): 1 – medium risk 2 – high risk and risk 3 – very high risk. Measurements for diabetic foot included: presence of sensory neuropathy, ankle brachial index (ABI), presence of deformities, inapropriate shoes, intact skin.People with risk score 0 and 1 were excluded. Calculation of eGFR according MDRD were used for stratification for grading nephropathy according KDOQI (Clinical Practice Guideline for Diabetes and CKD) (6) and classified in 3 grades: grade 2≥60, 3≥30 <60 and4≥15 и<30 ml/min/1.73 m^2). Grade 1 and 5 were excluded from this study for analizys. Diabetic retinopathy was estimated by ophtalmologist and patients were classified into the groups according changes in the fundus (non prolipherative retinopathy, prolipherative retinopathy). The level of education was performed with questinnairebased on the International Consensus on the Diabetic Foot guidelines Patient were classified in groups after we made complete calculations. Statistic program SPSS v. 20 was used for descriptive and analitic methods.

RESULTS

From 107 patients with type 2 diabetes, 54 of them were male (50,5%) and 53 female (49,5%). Mean age of patients is 59,12 ±5,88 years, the average duaration of diabetes is 12,93 years. Mean HbA1c shows bad glucose regulation 9,54±1,86%. BMI shows that our patients are overweighted, with the systolic BP that tends to be for hypertensive patients, higher than normal TG, LDL and average normal HDL cholesterole

Table 1. Demographic caracteristics of patients

variable	V1
Age (years)	59,12 ±5,88
Smoking cigarettes	23 (21,5%)
Duration of T2 diabetes(years)	12,93 ±6,15
HbA1c (%)	9,54±1,86
TT (kg)	75,79± 8,59
BMI (kg/m^2)	28,03 ± 3,3
Systolic BP (mmHg)	136,18 ± 17,93
Triglycerides (mmol/L)	2,42± 1,66
LDL (mmol/L)	2,91± 1,29
HDL (mmol/L)	1,11± 0,42

In the table 2 it is analyzed the distribution of the risk score groups and the average HbA1c. High levels of HbA1c are noted in all groups with small dominance in groups with high and very high risk.

Table 2. Mean HbA1c in risk score for foot ulcerations groups

Risk score	N	HbA1c mean.	SD	min	max
medium	65	9,39	1,9	5,1	14
high	22	9,98	1,67	6,7	13,3
very high	16	9,63	2,11	6,3	14
Total	107	9,54	1,86	5,1	14

Table 3. estimation of education for diabetic foot and risk score

Risk score Yes		Education for diabetic foot		Total
		Non		
	0. minimal	3	1	4
	1. Medium	28	37	65
	2. High	4	18	22
	3. Very high	1	15	16
Total		36	71	107

In the table 3 and table 4 it is estimated distribution of the patients with risk scores for the diabetic foot, thestages of nephropathy and education for diabetic foot.Non appropriately educated (66.1%) are with the Risk scores for ulceration as follows: score 1 % 35.6% not educated, score2-16.8% , and score 3- 14%.Non educated patients associated with grade of nephropathy is: grade 2 - 35.6% not educated, grade 3 – 17.7% and grade 4 – 8.4%.

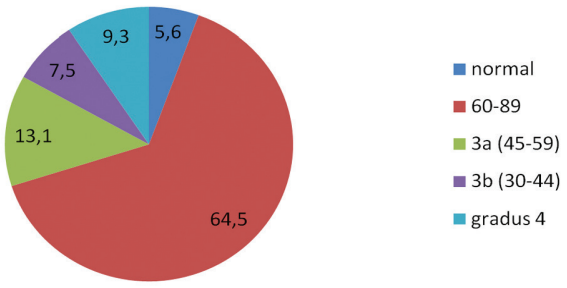

Figure 1. Distribution of grade of nephropathy in T2DM patients

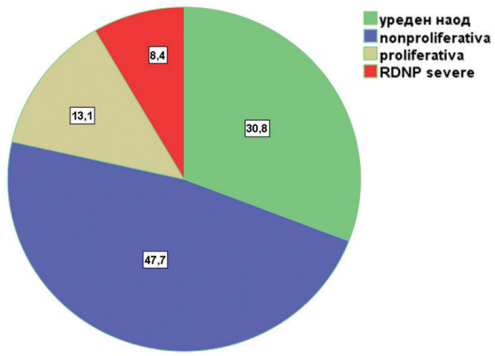

Figure 2. Distribution of diabetic retinopathy

The table 4 evaluates correlations between education and retinopathy. From the results we can conclude that people without education for diabetic foot have more retinopathy compared with educated type 2 diabetic patients (p<0,001) and higher risk for foot ulceration (U=799; p<0,001 (p=0,029).

Table 4. Association between risk score for ulceration, educational state and retinopathy

Risk score (1 -medium, 2 - high, 3–very high)		V1	
Education for diabetic foot	Yes	Avg range 40,69	U=799; p<0,001
	Non	Avg range60,75	
Retinopathy	Normal fundus	Avg range41,50	Kruskal Wallis χ^2=14,78; p=0,001
	non-proliferative	Avg range55,31	
	proliferative	Avg range65,54	
	RNDP severe	Avg range74,44	

Table 5. Association between risk grades of nephropathy, educational state and retinopathy

Grades of nephropathy 2 -60-89, 3 - 3a(45-59), 4 - 3b(30-44), 5 - grade 4 (15-29)		V1	
Education for diabetic foot	Yes	Avg range 46,78	U=1018; p=0,045
	Non	Avg range 46,7857,66	
Retinopathy	Normal fundus	Avg range 46,7843,89	Kruskal Wallis χ^2=7,77; p=0,045
	non-proliferative	Avg range 46,7856,66	
	proliferative	Avg range 46,7861,67	
	RNDP severe	Avg range 46,78 63,21	

The values in the table 5 demonstrate significant association of higher grade of nephropathy in patients without education for diabetic foot (U=1018; p=0,045) и and increased grade of nephropathy (Kruskal Wallisχ2=7, 77; p=0,045).

DISCUSSION

Our study group is of age 59±5,88 years. The age more than 60 years of patients is independent risk factor for chronic complications (7). On the other hand, only duration of diabetes, as independent risk factors is associated with microvascular complications. In our study group, mean duration of diabetes was 12, 93 ± 6, 15 which is optimal duration for micro and macrovascular complications. According HbA1c high values of HbA1c in our study group shows that long time bad glucose regulation, increase the risk of death for 2-4 times. The opposite of this when the HbA1c decrease 1%, reduces microvascular complications for 34%, macrovascular complications for 14% (8). People with high values of HbA1c would have more benefit if they reduces more HbA1c, even every minimal reduction of hbA1c is important for prevention of chronic complications(7). The new recommendations of ADA – American Diabetes Association, for hypertension in a people with diabetes prefer the BP >140/90 mmHg (4). High systolic BP>140 mmHg was registered in 42.7% of our patients). The higher values of triglycerides in our patients (2, 4 mol/L) than in non diabetic population suggests for the risk acceleration of macrovascular and microvascular incidents. Investigations in our study group and determination of risk score for ulceration according the IWGDF (9) criteria and determination of grade of nephropathy accordingKDOQI criteria, prove the positive significance between this two conditions. The higher risk score groups - 2,3 have higher grade of CKD - 3,4, (p<0,001).The average risk score increased with the increased grade of nephropathy (grade 3 – score 1, 77, grade 4 –risk score 2,10). In our study group it is clearly was proved that people without education for diabetic foot and with poor vision as a consequence of diabetic retinopathy have higher risk for nephropathy and foot ulceration. There are conflicting data on the effect of education on the incidence of foot complications. Reductions have been noted in some studies (10) but there is no consensus for ideal concept of structured education for foot care.

REFERENCES

1. IDF Diabetes Atlas Seventh Edition 2015, International Diabetes Federation. Available www.diabetesatlas.org
2. Diabetic foot problems: preDiabetic foot problems: prevention andmanagement NICE guideline. Published: 26 August 2015. nice.org.uk/guidance/ng19
3. Kaplan NM. The deadly quartet. Upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension. Arch Intern Med 1989;149:1514–20
4. AMERICAN DIABETES ASSOCIATION STANDARDS OF MEDICAL CARE IN DIABETES—2017 Cardiovascular Disease and Risk Management. Diabetes Care 2017;40(Suppl. 1):S75–S87
5. Laura M. Raffield, Fang-Chi Hsu, Amanda J. Cox, J. Jeffrey Carr, Barry I. Freedman and, Donald W. Bowden Predictors of all-cause and cardiovascular disease mortality in type 2 diabetes: Diabetes Heart Study *Diabetology & Metabolic Syndrome*2015 7:58
6. National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. Am J Kidney Dis 2012;60:850–886
7. Annette M. Chang, Jeffrey B. Halter. Aging and insulin secretion. American Journal of Physiology - Endocrinology and Metabolism Published 1 January 2003 Vol. 284 no. 1
8. IM Stratton, A. I Adler, H Andrew W Neil, D. R Matthews, S. E Manley, C. A Cull, D.Hadden, R. C Turner, R. R Holman on behalf of the UK Prospective Diabetes Study Group. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study.BMJ VOLUME 321 12 AUGUST 2000.
9. International Working Group on the Diabetic Foot. Practical Guidelines on the Management and Prevention of the Diabetic Foot. Available at http://www.iwgdf.org/index Last accessed 18 November 2009
10. S. Zoungas, M. Woodward, Q. Li & Mark, E. Cooper,P. Hamet,S. Harrap,S. Heller,M. Marre,A. Patel,N. Poulter,B. Williams,J. Chalmers, for the ADVANCE Collaborative group. Impact of age, age at diagnosis and duration of diabetes on the risk of macrovascular and microvascular complicationsand death in type 2 diabetes. Diabetologia (2014) 57:2465–2474)
11. McInnes A. No consensus between HCPs on diabetic foot care education. Diabetic Foot. 2010;13:29–38.

PACIENTËT ME DIABET TË TIPIT 2 QË NUK KANË EDUKIM PËR KËMBËN DIABTIKE KANË REZIK MË TË LARTË PËR ULCERACION DHE SHKALLË MË TË LARTË TË NEFROPATISË

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REZYME

Qëllimi: Të vlerësohet rëndësia e edukimit të personave me diabet të tipit 2 (T2DM) në përgjithësi, rëndësia e edukimt të këmbës diabetike dhe ndikimi i retinopatisë diabetike në në këmbën diabetike dhe nefropatinë diabetike.

Pacientët dhe metodat. Studimi ishte observacional, ishin të kyçur 107 pacientë me T2DM të moshës 35–65 vjeçe, të dz gjinive, me kohëzgjatje të DM>1 vjet. Pacientët u vrojtuan dhe testuan për këmbën diabetike dhe klasifikuan sipas rekomandimeve te Grupit ndërkombëtat për këmbën diabetike, në 2 grupe: rezik të lartë dhe rezik shumë të larte për ulceracion. U ekzaminuan edhe për sëmundje kronike të veshkës sipas KDOQI (Clinical Practice Guideline for Diabetes and CKD) dhe klasifikuan ne grade (2-4) në bazë të vlerave të eGFR me MDRD formulën. Retinopatia diabetike u klasifikua në retinopati jo proliferative (NPDR) dhe proliferative (PDR).Pacientët u intervjuan perms pyetësorit rreth edukimit për këmbën diabetike. Përgjigja ishte me 'po' apo'jo'.

Rezultatet. Nga 107 T2DM pacientë 54 (50,5%) ishin meshkuj dhe 52 (49.5%) femra. Mosha mesatare ka qenë 59.45±6v, kohëzgjatje e T2DM 12.45y±9 v. Mesatarja e HbA1c 9.5%±1.9, BMI 28%±3.3 kg/m^2, TA sistolik 136±6 mmHg, TG 2.4±1.7mmol/L, LDL 2.9±1.3 mmol/L. Edukimi te pacientët e rradhitur sipas skorimit për rezik të ulcerimit të këmbës diabetike ka qenë: Pa edukim kanë qenë 71 (66.1%) are with Risk scores for ulceration as follows: score 1 – 38 (35.6%) not educated, score 2-22 (16.8%) , and score 3–16 (14%) score 1 - Edukim për T2DM dhe kujdes të këmbës diabetike kanë pasur 36 (33.6%) pacientë. Pacientët jot ë edukuar kanë qenë të shoqëruar me grade të nefropatisë sin ë vijim: gradë 2 në 35.6%, gradë 3 në 17.7% dhe gradë 4 në 8.4% të pacientëve. Retinopatia diabetike ishte prezente në 69.2% (NPDR 47.7% dhe PDR 21.5%).

Konkluzioni: Te pacientët me diabet të tipit 2 faktorët metabolik të rrezikut, mungesa e edukimit për këmbën diabetike dhe prezenca e retinopatisë diabetike kanë ndikim significant në progresionin e skorimit për rezik të ulcers diabetike dhe sëmundjes kronike të veshkës te diabeti.

Fjalët kyçe: diabeti, komplikimet, Edukimi, këmba iabetike, nefropatia.

Original scientific paper

ANESTHESIA AND SURGERY AS A RISK FACTOR FOR POSTOPERATIVE DELIRIUM IN NON-CARDIAC SURGERY

АНЕСТЕЗИЈА И ХИРУРГИЈА КАКО РИЗИК ФАКТОР ЗА ПОЈАВА НА ПОСТОПЕРАТИВЕН ДЕЛИРИУМ ВО НЕКАРДИЈАЛНАТА ХИРУРГИЈА

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ABSTRACT

Introduction/Purpose: The risk factors that contribute to postoperative cognitive deficits depend on patient characteristics, type of surgery and type of anesthesia. The cognitive deficit influences postoperative recovery and release patients 's release date.

Methods: This was a prospective study of 60 patients over the age of 60 during a six month period. A preoperative anesthetic assessment was used to evaluate overall health and to determine the degree of risk interventions (ASA status) according to age, type of operation, the choice of anesthesia, and level of education. A questionnaire was devised based on demographics and clinical data. To test mental status we used the Blessed test for orientation, memory and concentration (BOMC). We used the test to evaluate cognitive changes four times: pre-operative, and then on the first, second, and seventh days following the operation. We then performed a statistical analysis of the results.

Results: The results obtained from the post-operative BOMC test suggest cognitive changes in patients with orthopedic, urologic, and digestive surgery. There were significant results in ten patients.

Conclusion: The preoperative assessment of mental and physical health is important to adequately assess the risks and benefits of a planned surgical intervention. Early recognition of POD (postoperative delirium) and POCD (postoperative cognitive deficit) allows for the proper steps towards eventual treatment. POD and POCD are predictors of mortality and morbidity in patients in the first year after surgery.

Keywords: anesthesia, postoperative cognitive dysfunctions, non-cardiac surgery

INTRODUCTION

Anesthesia alters brain function by reducing the level of awareness, attention, memory, and reaction time in a patient. Among elderly patients, those sorts of mental changes are often encountered in the post-operative phase and in the intensive care unit. Patients can have complete amnesia for hours after anesthesia, and in some cases even longer. That is because modern anesthesia is still not clear when and how brain function is completely restored after the surgery and anesthesia [1].

New methods and techniques have improved surgical treatment and reduced mortality, especially in the first year after surgery [2].

There is a long a history of research on mental functions following cardiac surgery, but since the beginning of the 20th century, anesthesiologists have begun focusing on changes in the mental status of patients in non-cardiac surgery. Patients with orthopedic, urologic, and digestive surgery have been of particular interest[3]. Changes in

cognitive status are especially observable in patients with hip fractures and those with urological interventions[4]. Those patients have significantly greater mortality in the first year after operation when compared to general population of the same age [5].

Age is not a contraindication for surgery, but the dosage of anesthetic drugs should be very closely monitored[6] Older patients often take many medications that produce psychological and physiological changes, and eliminating medications can also produce changes in the mental status of patients [7].

Current research shows that the human lifespan is getting longer, indicating a need for standards in anesthesiology for patients over 60 years of age who undergo surgery [8].

According to Silbert et al., the anesthesiologist is ideally situated to follow patients in the pre-, peri-, and post-operatives stages, and can contribute new data and knowledge for the clinical management of patients with MCI (minimal cognitive impairment) [9].

GOAL OF THE STUDY

The goal of this paper is to examine if the general endotracheal anesthesia (GEA) and regional anesthesia (RA), the type of surgery (non-cardiac), and the patient's age (over 60) are risk factors for the cognitive status of patients in the early post-operative period.

METHODS

This prospective clinical study examined sixty (60) patients for a six month period between January and June of 2015. All patients were treated with a pre-operative anesthetic assessment to examine the most common predictors for the occurrence of cognitive disorders, including general health, age, the degree of anesthetic risk according to the ACA (American Association of Anesthesiologists), the type of anesthesia, type of operation, level of education, and cognitive status. We then designed a specific questionnaire based on those demographic and clinical indicators.

To determine the mental status of patients we used the Blessed Test of orientation, memory, and concentration (BOMC). All answers were scored and added together to get the final result. Changes in mental status were observed at four specific times: pre-operative, and then on the first, second, and seventh days following the operation. Based on those results we followed pre- and post-operative mental status of the patients.

We chose this test because it is fast, simple, and suitable for the frenetic work that is surgery.

RESULTS

In the study group, 60% of the patients were male and 40% were female. The average age was 72 ± 5.6 years. With respect to the age structure, 60% were between the ages of 65 and 74, while 41.6% of the respondents had a high school level of education. The analysis of clinical parameters includes the ACA score, according to which 65% are respondents with ACA 2. One third of the operations were digestive, another third were urological, and the final third were orthopedic. Just over 53% of the patients received general anesthesia, while 46% received regional anesthesia (Table 1).

Table 1 shows the distribution of socio-demographic and clinical characteristics of the 60 participants.

Table 1: Socio-demographic and clinical characteristics of the sample

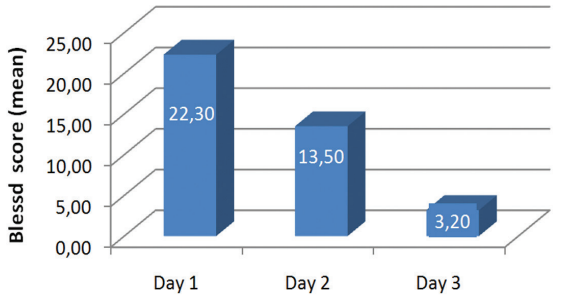
Variable	N (%)	Variable	N (%)	Variable	N (%)
Sex		Age	Min=60, max=88, SD 72±5,6	ASA Score	
Males	36 (60%)	60-64	7 (11.67%)	1	12 (20%)
Females	24 (40%)	65-74	36 (60%)	2	39 (65%)
		75-89	17 (28.33%)	3	9 (15%)
Variable	N (%)	Variable	N (%)	Variable	N (%)
Type of Operation		Type of Operation		Educational Attainment	
Digestive	20 (33,33%)	OEA	32 (53.33%)	4th grade	8 (13.33%)
Orthopedic	20(33,33%)	RA	28 (46.67%)	8th grade	18 (30%)
Urologic	20(33,33%)			High School	25 (41.67%)
				College	9 (15%)

All patients were evaluated pre-operatively upon admission to surgery according to cognitive status, which was then compared with the cognitive results on the first, second, and seventh post-operative days. The cognitive status of respondents were analyzed using the Blessed scale, according to which a score greater than ten indicates dementia.The points for each of the six criteria are added together to yield the total number of points. Every wrong answer to the questionnaire gets one point, and if the total reaches ten, it indicates the presence of dementia. In ten (16.67%) of the patients included in this study, the values of the Blessed test show a deviation or impairment in post-operative cognitive function [10].

The average values of the Blessed scores amounted to 22.3 ± 9.8.5 on the first day after operation, 13.5 ±12.1 on the second day, and 3.2 ± 1.1 one week following the operation (Table 2, Graphic 1).

Table 2: Results of the Blessed scale analysis

Score	mean±SD
Day 1	22.3 ± 9.8
Day 2	13.5 ±12.1
Day 7	3.2 ± 1.1



Graphic 1: Results of the Blessed scale analysis

The distribution in Table 3 shows that symptoms of transient cognitive dysfunction as a result of operative intervention developed in five patients on the first day after surgery and in three on the second day after the operation, with a maximum of 28 points on the first day, and there were two patients 7 and 9 points, respectively (Table3).

Table 3: Distribution of Respondents' Blessed Scores

Result	Day 1	Day 2	Day 7
0			
2		1(1.67%)	3 (5%)
4		2 (3.33%)	3 (5%)
7	1 (1.67%)	2 (3.33%)	
9	1(1.67%)		
12			
28	5 (7.46%)	3 (5%)	
Total	7 (10, 80%)	8 (13, 33%)	6(10%)

A score greater than 10 is significant and related to transient changes in cognitive status(table4).

Table 4: Results from the Blessed Score Analysis

Score	Day 1	Day 2	Day 7
0 - 10	2(3.33%)	5 (7.46%)	6 (10%)
> 10	5 (7.46%)	3 (5%)	

According to the results obtained from the types of anesthesia, 10 patients deviated from the norm. Of those, 4 had general anesthesia and 4 had regional anesthesia, with a maximum of 28 points and two patients from regional anesthesia under ten points (Table 5).

Table 5: Types of Anesthesia Administered

Score	Day 1		Day 2		Day 7	
	General Anesthesia	Spinal Anesthesia	General Anesthesia	Spinal Anesthesia	General Anesthesia	Spinal Anesthesia
0	29 (48.33%)	24 (40%)	29 (48.33%)	23 (38.33%)	30 (50%)	24 (40%)
2				1(1.67%)	1(1.67%)	2 (3.33%)
4			1(1.67%)	1(1.67%)	1(1.67%)	2 (3.33%)
7		1(1.67%)	1(1.67%)	1(1.67%)		
9		1(1.67%)				
12						
28	3 (5%)	2 (3.33%)	1(1.67%)	2 (3.33%)		
Total	32	28	32	28	32	28

With respect to the structure of operational interventions related to cognitive disorders there were two operations for hip fracture, one hip replacement and one knee replacement surgery. Of the urological operations there were two Turpan interventions, 1 adenoidectomy on the prostate BPH, and one TURT operation on the bladder. Of the digestive operations there was one malignancy on the rectosigmoid part of the large intestine and one total gastrectomy(Table6).

Table 6: Types of Operation Administered

Score	Day 1			Day 2			Day 7		
	Digestive	Orthopedic	Urologic	Digestive	Orthopedic	Urologic	Digestive	Orthopedic	Urologic
0	18 (30%)	17 (28.33%)	18 (30%)	19 (31.67%)	16 (26.67%)	17 (28.33%)	19 (31.67%)	18 (30%)	17 (28.33%)
2					1(1.67%)		1(1.67%)	1(1.67%)	1(1.67%)
4					1(1.67%)	1(1.67)		1(1.67%)	2 (3.33%)
7		1(1.67%)		1(1.67%)	1(1.67%)				
9			1(1.67%)						
12									
28	2 (3.33%)	2 (3.33%)	1(1.67%)		1(1.67%)	2 (3.33%)			
Total	20	20	20	20	20	20	20	20	20

The results of our study speak to results from similar studies in other locations. Transient changes in the form of PSC and POKD appeared in ten patients (17%). On the first postoperative day there were 5 patients displaying changes in the clinical picture of delirium, with maximum points from BOMC. Of those, 3 received general anesthesia (2 patients of digestive surgery and one of orthopedics), and two received regional anesthesia (one each from orthopedics and urology). On the second postoperative day, 3 patients recorded maximum points, 1 from general anesthesia (urology) and 2 from regional (urology and orthopedics). Visual hallucinations, agitation, and confusion were the dominant manifestations of delirium in all patients. In both groups there was a reduction in symptoms on the next day. Patients became communicative with others and needed assistance with small lapses in memory and concentration, causing them to get points on the BOMC scale as is shown in the table. Nonetheless, the scores were still below ten.

On the first post-operative day, two patients who received regional anesthesia (orthopedics and urology) showed difficulty with memory, counting backwards and recalling the months in reverse order. One received a score of 7 on the BOMC and the other received 9 points. Concentration and memory improved the next day, but one should keep in mind that patients had lower levels of educational attainment (4^{th} and 8^{th} grade, respectively). One the seventh day the general condition of the patients had improved. Only six patients needed help with answers and with self-correction, and the results were improved a minimum of one or two incorrect points.

DISCUSSION

Current clinical trials are designed to examine the effects of anesthesia as a factor for cognitive changes among elderly people after non-cardiac surgery. Although some draft papers for cognition and anesthesia were published more than a decade ago, only recently has anesthesiology become a specialty focused on the science of consciousness. The medical specialty of anesthesia is a unique way to deepen our knowledge about consciousness and memory by using different doses to cause different levels of changes in awareness from amnesia to unconsciousness [11].

Modern society must now face the new challenge of an aging population. This research is intended to find the cause-and effect relationships between age, sex, educational attainment, type of anesthesia, type of

surgery and the occurrence of postoperative dysfunctions in the form of POD and POKD [12].

It is believed that between five and ten percent of patients admitted to the hospital have a hidden symptom of cognitive impairment functions, while 10 to 50% of disorders occur during hospitalization [13].

Postoperative delirium is the most common form of mental disorder in the elderly and the most common postoperative complication in hospitalized patients. The etiology is multifactorial and understanding of the pathophysiological mechanism is still limited. One of the hypotheses about the emergence of delirium is an imbalance in the synthesis and release of neurotransmitters that control cognitive function, behavior and mood, with the greatest emphasis on dopamine and acetylcholine. Imbalance in the form of excess dopamine or acetylcholine deficiency is associated with delirium [14].

Clinical trials show an overall experience in a large span of confusion, disorganization, and disorientation in space and time. People are often easily distracted, and may feel drowsy during the day and awake and anxious at night in a phenomenon referred to as Sunset. Often, but not always, delusions and hallucinations (visual, auditory, tactile) may appear to be vivid and frightening. Symptoms are seen mostly at night on the first or second postoperative day. In addition to hyperactive (upset) delirium, so-called hypoactive (silent) delirium can also be observed. That is associated with reduced mental and physical performance and is the most common form of delirium, but often goes unnoticed [15].

In a number of studies, POD and POKD are jointly analyzed, although there is a difference in the manifestation of the clinical picture, as well as in the appearance of symptoms after surgery [16].

POKD is subtle impairment to the memory, attention, concentration and speed of processing information. Unlike patients with delirium, typical patients with POKD is orientated, but show a decline in their basic level of performance in more neurological functions [17].

Taking into account the current research, we would expect POD and POKD in older patients and in those with longer interventions and with lower educational attainment. Whether or not general or regional anesthesia is the primary factor behind cognitive deficits is still the subject of research. A number of comparative studies discuss a change in mental status in patients after major non-cardiac surgical interventions in the first 3 months, but the results are not strong enough to assert that most changes occur in following general anesthesia. There are claims that the type of anesthesia influences cognitive dysfunction, but other results show that during the first week following regional anesthesia the occurrence of cognitive disorders is lower compared to general anesthesia, but these results balance out after three months [18].

The survey results of a large, international multi-center prospective study called ISPO-CD showed that the incidence of POKD following non-cardiac surgery is lower than in cardiac surgery. Transient POKD, which dissipates after one week, was observed in 25.8% of patients, of which 9.9% were elderly. The symptoms persisted for 3 months, and 1% they continued for up to 2 years [19].

CONCLUSION

This survey demonstrated that both types of anesthesia in non-cardiac surgery can cause changes in the mental status of patients. It is expected that with the increasing number of elderly patients undergoing surgery there will be an increased occurrence of changes in mental status. The number of occurrences is relatively small and has no statistical significance there were not enough respondents to produce a strong conclusion. Recognizing the existence of cognitive dysfunction after surgery, especially in older patients, highlights the importance of early perioperative care for patients and of the cognitive outcomes following the surgery. When explaining to patients the importance of POD and POKD, anesthesiologists should consider the benefits of the proposed operation. On the other hand, by familiarizing themselves with the patients before and after surgery, anesthesiologists can best observe the differences, notice cognitive dysfunctions, and participate in their mental and social recovery in a timely and active manner. Furthermore, reducing the length of hospital stays also has an economic implication.

REFERENCES

1. Newman SD, Stygall J, Hirani S, Shaefi S, Maze M. Postoperative cognitive dysfunction after noncardiac surgery: a systematic review. Anestesiology2007; 106 (3): 572–90.
2. Ristić B, Ignjatović-Ristić D, Miličić B, Obradović Z. Faktori koji utiču na postoperacioni mortalitet kod bolesnika sa prelomom kuka. Vojnosanit Pregl 2006; 63(1):49-53.

3. European Academy of Anaesthesiology. Editorial Postoperativecognitive deficits: more questions than answers. Eur J Anaesthesiol 2004; 21:85-8.
4. Gustafson Y, Berrgren B. Acute confusional states in elderly patients treated for femoral neck fracture. J Am GeriatrSoc 1988;36:525-5.
5. Kenzora JE, McCarthy RE, Lowell JD, Sedge CB. Hip fracture mortality. Relation to age, treatment, preoperative illness, time of surgery, and complications. ClinOrthopRelat Res 1984; 186: 45-56.
6. Davidovic M, Kosanovic M, Barjaktarovic N, Trailov D. Starost i starenje. In: Davidovic M i urednici. Gerijatrija. Beograd: MedicinskiFakultet, Univerzitet u Beogradu; 1998:3-22.
7. Cohen HJ, Fenssner JR, Weinberger M, Carnes M, Hamdy RC, Hsien F. et al. A controlled trial of inpatient and outpatient geriatric evaluation and management. N Engl J MED 2002; 346(12):905-12.
8. Godfrey A, Conway R, Leonard M, Meagher D, Olaighin GM. Motion analysis in delirium: a discrete approach in determining physical activity for the purpose of delirium motoric subtyping. Med EngPhys 2010; 32(2):101-10.
9. Silbert BS, Scott DA, Evered LA, Lewis MS, Maruff PT. Preexisting cognitive impairment in patients scheduled for elective coronary artery bypass graft surgery. Anesth Analg 2007; 104:1023–8.
10. Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of eldery subjects. Br J Psychiatry 1968; 114(512):797-811.
11. Blagojevic V, Milakovic B. Anstezija u neurohirurgiji. In: Lalevic P. Anesteziologija. Beograd: Zavodzaudzbenike I nastavna sredstva;1999.
12. Wice MG, Hilty DM. Delirium (confusion states). In: Psychiatry in the medically ill. Washington DC: American Psychiatry Publishing, inc; 2002:257-72.
13, Rasmussen LS. Postoperative cognitive dysfunction: incidence and prevention. Best Practice & Research Clinical Anaesthesiology2006; 20(2): 315–30.
14. Lipowski ZJ. Acute Confusional States (Delirium) in the elderly. In: Albert ML, Knoefel JE (eds). Clinical Neurology of aging. 2nd ed, New York: Oxford University Press;1994.
15. Tune LE. Postoperative delirium. IntPsychogeriatr 1991; 2:325-32.
16, Rassmussen LS, Larsen K, Houx P, Skovgaard LT, Hanning CD, Moller JT. The assessment of postoperative cognitive function. ActaAnesthsiolScand 2001;45:275-89.
17. Deiner S, Silverstein JH. Postoperative delirium and cognitive dysfunction. Br J Anaesth 2009; 103 (Suppl 1): 41-6.
18. Nielson WR, Gelb AW, Casey JE et al.Long-tern cognitive and social sequelae ofgeneral versus regional anaesthesia during arthroplasty in the elderly. Anesthesiology 1990; 73: 1103 –9.
19. Moller JT, Cluitmans P, Rasmussen LS, et al. Long-term postoperative cognitive dysfunction in the elderly ISPOCD study. ISPOCD investigators. International study of post-operative cognitive dysfunction. Lancet 1998; 351(9106):857-61.

АНЕСТЕЗИЈА И ХИРУРГИЈА КАКО РИЗИК ФАКТОР ЗА ПОЈАВА НА ПОСТОПЕРАТИВЕН ДЕЛИРИУМ ВО НЕКАРДИЈАЛНАТА ХИРУРГИЈА

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АПСТРАКТ

Вовед /цел: Факторите на ризик кои допринесуваат за постоперативен когнитивен дефицит се класифицираат во зависност од карактеристиките на пациентот, видот на операцијата и видот на анестезија. Когнитивниот дефицит влијае на постоперативното заздравување и на времето на излгување на пациентот од болница.

Методи: Направена е проспективна студија кај 60 пациенти на возраст над шеесет години во временски период од шест месеци.Со предоперативна анестезиолошка проценка се евалуирани општата здравствена состојба,одреден естепенот на ризик од интервенции(АСА статус)возраста,видот на операцијата, изборот на анестезија,степенот на образование.Од демогравските и клинички податоци направивме дизајниран прашалник.

За испитување на менталниот статус го користевме Блеседовиот тест за ориентација, меморија и концентрација (БОМК). Евалуацијата на когнитивните промени ја следевме користејќи го тестот 4 пати (предопративно, првиот, вториот и седмиот постопративен ден).Направена е статистичка анализа на добиените резултати.

Резултати: Добиените рзултати од БОМК при прием и резултатите постоперативно укажуваат на евалуацијата на когнитивните промени кај пациентите од ортопедија ,урологија и дигестивна хирургија.Значајни промени добивме кај 10 пациенти.

Заклучок: Проценката на физичкото и ментално здравје предоперативно е важно за адекватна процена на ризикот и бенефитот од планираната хируршка интрвенција.Навременото препознавање на ПОД(постоперативен делириум) и ПОКД (постоперативен когнитивен дефицит)овозможува правилен пристап и евентуалното лекување.ПОД иПОКД се предиктори за морталитетот и морбидитетот кај болните во првата година по операцијата.

Клучни зборови: анестезија,постоперативни когнитивнидисфункции,некардијална хирургија

Original scientific paper

ПОВРЗАНОСТ НА ЕКСПРЕСИЈАТА НА ГЕНОТ *TOB1* СО СТАДИУМОТ И АНАТОМСКАТА ЛОКАЦИЈА НА КОЛОРЕКТАЛНИОТ КАРЦИНОМ

ASSOCIATION OF *TOB1* GENE EXPRESSION WITH COLORECTAL CANCER STAGE AND ANATOMICAL TUMOR LOCATION

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АБСТРАКТ

Генот *TOB1* претставува тумор супресор кој делува како негативен регулатор на рецепторот на тирозин киназата *ERBB2* со анти-пролиферативен, проапототичен и анти-инвазивен ефект врз малигните клетки. Инактивацијата на *TOB1* или неговата намалена експресија е идентифицирана кај повеќе хумани неоплазми. Целта беше да се истражи асоцијацијата меѓу стадиумот и локација на туморот со нивоата на експресија на генот *TOB1* кај пациенти со колоректален канцер.

Во оваа студија беа анализирани примероци од група на 42 пациенти со колоректален карцином. Примероците од туморското ткиво беа земени по хирушката ресекција и замрзнати до анализата. Како контрола, мукозен примерок на растојание од >10 cm од туморот беше колектиран од секој пациент. Вкупната *RNA* беше изолирана, cDNA беше синтетизирана со реверзна транскрипција и експресијата на *TOB1* беше определена со квантитативна Real-Time PCR.

Средните вредности на експресија на *TOB1* беа 3,2 пати повисоки кај пациенти со стадиумот IIa во споредба со пациенти со IIIb и повисоки стадиуми (p=0,038) и беа 4,9 пати пониски во проксималниот во споредба со дисталниот хемиколон и ректум (p=0,026).

Резултатите сугерираат дека *TOB1* генската експресија е поврзана со пониски стадиуми и локализација во проксималниот дел од дебелото црево. Тоа е во прилог на анти-пролиферативната улога на овој ген во патогенезата на колоректалниот канцер.

Клучни зборови: колоректален карцином, стадиум, *TOB1*, експресиски нивоа, qRT-PCR

ВОВЕД

Колоректалниот карцином (КРК) претставува малиген тумор кој потекнува од епителните клетки на колонот и/или ректумот. КРК е најчесто малигно заболување на гастроинтестиналниот тракт со мултифакторијална етиологија каде што генетската основа, факторите на околината и/или инфлматорните заболувања на цревото доведуваат до малигна трансформација на нормалниот епител на слузницата на колонот и/или ректумот преку неколкугодишен етапен процес на акумулација на генетски и епигенетски алтерации.

Веќе 25 години е познато дека малигната трансформација и постепената прогресија на промените од нормалниот епител на дебелото црево, преку аденомот, карциномот *in situ*, па сè до инвазивниот карцином, е проследена со последователна низа на молекуларно-генетски нарушувања (1). Резултатите од исклучително големиот број на спроведени студии утврдиле голем број на поединечни молекуларни абнормалности какви што се: генските мутации, промените на нивоата на генската

експресија, единечните нуклеотидни полиморфизми (SNP), DNA-метилацијата, геномската нестабилност, хромозомски аберации, како и други промени (2). Сите овие молекуларно-генетски и епигенетски нарушувања имаат клучна улога, не само врз самиот процес на малигна трансформација на епителот на колонот, туку и врз вродената предиспозиција, приемчивоста кон оваа неоплазма, текот на болеста и терапевтскиот одговор. Канонскиот модел на колеректална малигна трансформација се базира на секвенционално, постепено акумулирање на генски мутации како и епигенетски промени кои афектираат неколку клучни други онкогени, тумор-супресорски и други гени, вклучувајќи ги *APC, RAS, BRAF, TP53, TGF*-β, *PI3KCA, SMAD4*, групата гени *MMR, MYH, EPCAM* и други (3).

Досега се направени повеќе обиди за класификација на карциномите на колоректумот, базирана на молекуларните и генетските разлики. Според една од нив, најчестиот тип кој е присутен кај 60-70 % од сите случаи на спорадичен колоректален карцином е карактеристичен по хромозомската нестабилност (CIN) и разни хромозомски нумерички аберации и анеуплоидии, како и со мутации во определени гени, од кои најистражени се: *APC, KRAS, PIK3CA, BRAF, SMAD4, TP53* и други (4). Според истата класификација, вториот тип е застапен кај 10-15 % од сите случаи на спорадичен карцином и е карактеристичен по геномската нестабилност. Овој тип најчесто се детектира по микростаелитната нестабилност (MIN) предизвикана од дисфункција на гените задолжени за репарација на мутациите. Третиот тип се наоѓа кај приближно 5 % од сите спорадични случаи и е карактеристичен по обемната метилација на CpG островчињата лоцирани во генските промотори што ја потиснува експресијата на афектираните гени (5). Останатите случаи имаат определеана комбинација или, пак, немаат ниту една од овие три молекуларни и генетски карактеристики.

Со напредни статистички анализи на податоците од голем број молекуларно-генетски и патолошки студии, неодамна е претпоставено дека постојат четири основни консензусни молекуларни субтипови (CMS) на колоректален карцином: CMS1 (хипермутаторен фенотип со микросателитна нестабилност и силна имунолошка активација); CMS2 (канонски епителен тип, нагласена активација на сигналните патишта *WNT* и *MYC*); CMS3 (метаболички тип со јасна епителна и метаболна дерегулација) и CMS4 (месенхимален тип со проминентна активација на TGF-β, со нагласена стромална инвазија и ангиогенеза (6).

Од хируршки аспект, мошне е интересно што неколку студии спроведени во текот на последниве години индицираат дека колоректалниот карцином е хетероген и по однос на локацијата на туморот. Имено, како што произлегува и од ембриолошките и анатомските истражувања, десниот-проксимален дел од колонот кој се протега сè до спленичната флексура и левиот-дистален дел од флексурата до ректумот се всушност два различни ентитети. Утврдено е дека молекуларно-генетските промени во голема мерка се разликуваат меѓу овие два дела на дебелото црево (7, 8). Микросателитната нестабилност и нарушувањата на функцијата на гените вклучени во репарацијата на мутациите доминираат во проксималниот дел од колонот, додека хромозомските абреации и мутациите во определени гени се почести кај карциномите во дисталниот дел од колонот и ректумот. Овие две големи групи на молекуларни абнормалности содржат голем број на поединечни мутации и нарушувања на нивоата на експресија на определени гени. Понатаму, најдена е и поврзаност на ваквите разлики со клиничкиот исход, односно прогнозата на болеста.

Генот *TOB1* е член на фамилија *Tob/BTG* гени кои кодираат антипролиферативни протеини вклучени во регулацијата на клеточниот циклус. Поновите истражувања индицираат дека *TOB1* е кандидатен тумор-супресорски ген лоциран на хромозомскиот локус 17q21, чиј протеински продукт е сигнален трансдуктор на erbB-2 рецепторната тирозин-протеинска киназа, а влегува и во меѓупротеински интеракции со низа пролиферативни протеински молекули, делувајќи инхибиторно на нив, а со тоа попречувајќи ја прогресијата на клеточниот циклус и запирајќи го во G_0/G_1 точката на транзиција (9). Покрај тоа, експериментите утврдиле и дека лабораториските глувци кои имаат нефункционален ген *TOB* имаат висока инциденција на спонтани тумори.

Мал број истражувања на експресиските нивоа на генот се направени досега кај хепатоцелуларните, тироидните и карциномите на дојка (10). Спротивно на тоа, опишано е дека кај колоректалните карциноми, експресијата на *TOB1* генот е зголемена во однос на немалигните ткива и дека нивоата на генска експресија сигнификантно корелираат со клиничко-патолошкиот

стадиум на болеста, а прекумерната експресија статистички значајно корелира со метастазите во лимфните јазли (11).

ЦЕЛИ

Целта на овој семинарски труд беше да се истражи асоцијацијата меѓу стадиумот и локација на туморот со степенот на експресија на генот *TOB1* кај пациенти со колоректален канцер.

Покрај научната перспектива, посебен предизвик е и хируршката сигнификантност на потенцијалната поврзаност на некои од генските параметри со анатомската локализација на туморот, како и перспективната употребливост на сознанијата за молекуларна субтипизација, клиничко-патолошка проценка, предвидување на текот на болеста и други практични примени.

МАТЕРИЈАЛ И МЕТОДИ

Примероците од пациенти со колоректален карцином беа обезбедени од пациенти лекувани на ЈЗУ Универзитетска клиника за дигестивна хирургија во Скопје, со претходна пишана согласност, како и со одобрение од Етичката комисија при Медицинскиот факулет во Скопје.

Примероците од туморското ткиво од вкупно 42 пациенти со хистопатолошки конфирмиран колоректален аденокарцином, беа колектирани веднаш по хирушката ресекција и беа замрзнати до моментот на молекуларната анализа. Примерок од здраво мукозно ткиво, на растојание од >10 cm од туморот, беше колектиран од секој пациент. Целокупната RNA беше изолирана со помош на TRI© реагенс и од неа се синтетизираше комплементарна DNA (cDNA) преку реверзна транскрипција. Амплификација и релативна квантитативна полимеразно-верижна реакција (qRT-PCR) беше извршена со помош на специфични TaqMan© проби. *TOB1* експресијата беше пресметана релативно кон референтниот ген *GAPDH*, а нормализацијата беше направена во однос на примерокот од здрава мукоза со помош на методот на пресметка: ΔΔCt.

При qRT-PCR анализата на транскриптите од генот *TOB1* се користеа TaqMan флуоресцентни сонди со нуклеотидна секвенца, специфична за соодветниот амплифициран регион од транскриптот, обележани на 5'-крајот со флуоресцентниот обележувач FAM, додека на 3'-крајот со избледувачот NFQ. Во истата реакциска смеса се додаваа и TaqMan сонди за соодветнот референтен ген GAPDH обележани на 5'-крајот со флуоресцентниот обележувач VIC, а со NFQ на 3'-крајот. Нуклеотидните секвенци на прајмерите и на сондите се според студијата на Wu со сор., 2010 (11).

Отчитаните криви и добиените податоци се изработија со софтверот StepOne (Applied Biosistems) кој е интегрален дел од системот.

Вредностите на генската експресија добиени со qRT-PCR беа изразени нормализирани во однос на референтниот ген, односно колку пати е повисоко или пониско нивото на експресија на испитуваниот во однос на референтниот ген, со што се овозможува споредување меѓу различните примероци. Споредбата со контролниот примерок од здраво ткиво се искористи за определување на отстапувањето во однос на туморското ткиво.

Статистичката анализа се правеше со споредување на предвидените клиничко-патолошки параметри, кои произлегуваат од pTNM класификацијата и анатомската локација на неоплазмата: десен, лев хемиколон или ректум, со вредностите на нивоата на експресија на генот *TOB1* добиени со квантитативната RT-PCR анализа.

Поврзаноста на клиничко-патолошките со молекуларните податоци од пациентите беше пресметана со Student-овиот *t*-тест кај параметриските вредности со нормална дистрибуција, односно со Mann-Whitney U-тестот при постоење отстапувања од нормалната дистрибуција на вредностите на соодветниот параметар. За статистички сигнификантни се сметаа вредностите на $p<0,05$.

Статистичките пресметки беа вршени со користење на софтверските додатоци XLSTAT 2015, RealStatistics 2015 и GenAlEx 6.5 инсталирани на Microsoft Excel 2016.

РЕЗУЛТАТИ

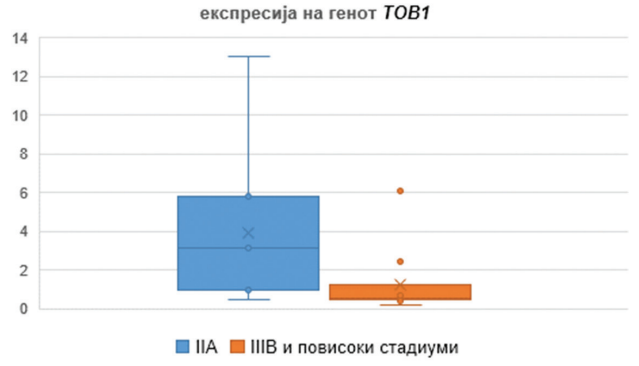
Основните демографски податоци за вкупно 42 анализирани пациенти со колоректален карцином, како и нивните клиничките параметри кои се релевантни за овој семинарски труд, се прикажани во табелата 1.

Табела 1. Податоци за групата пациенти со колоректален карцином

параметар			
возраст	**средна вредност ± SD**	**минумум**	**максимум**
	66,48 ± 7,80	85	52
		n	%
пол	машки	30	71,43
	женски	12	28,57
	вкупно	**42**	**100,00**
стадиум	IIa	14	33,33
	IIIb и повисоки	28	66,67
	вкупно	**42**	**100,00**
локација	лев хемиколон	10	23,81
	десен хемиколон и ректум	32	76,19
	вкупно	**42**	**100,00**

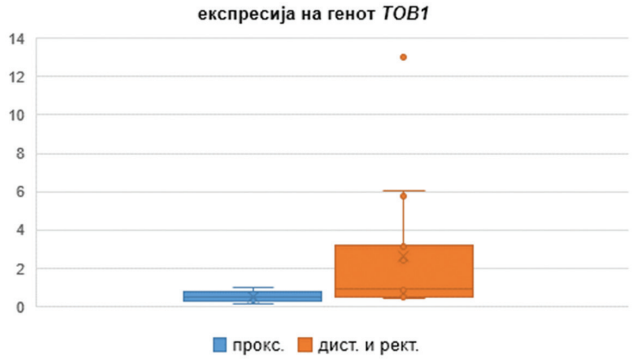
SD = стандардна девијација

Средната вредност на генската експресија на *TOB1* кај подгрупата пациенти со стадиум IIa (n= 14) изнесуваа **3,93 ± 4,41**, додека кај пациентите со стадиум IIIb и повисоки (вклучени се пациенти со стадиумите: IIIb, IIIc и IVb) (n=28) беше **1,20 ± 1,58**. Оттаму произлегува дека средните вредности на експресијата на генот *TOB1* беа 3,2 пати повисоки кај пациенти со стадиум IIa во споредба со пациенти со IIIb и повисоки степени, што претставува статистички сигнификантна разлика (*p*=0,038).



Сл. 1: Разлики во нивоата на експресија на генот TOB1 кај примероци на колоректален карцином со стадиум IIa во споредба со стадиум IIIb и повисок. Вредностите се изразени во арбитрарни единици.

Понатаму, средната вредност на експресија на генот TOB1 кај подгрупата пациенти со карцином анатомски лоциран во левиот хемиколон (n= 10) изнесуваа **0,53 ± 0,30**, додека кај пациентите со карцином лоциран во десниот хемиколон и во ректумот (n=32) изнесуваа **2,60 ± 3,34**. Средните вредности на експресијата на генот ***TOB1*** беа 4,9 пати повисоки кај пациенти со карцином на десниот хемиколон и во ректумот во споредба so тие со карцином на левиот хемиколон, односно е статистички значајно (*p*=0,026).



Сл. 2: Разлики во нивоата на експресија на генот TOB1 кај примероци на колоректален карцином лоцирани во проксималниот колон во споредба со дисталниот колон и ректумот. Вредностите се изразени во арбитрарни единици.

Заради прегледност, статистичките пресметки за нивоата на експресија на генот *TOB1* при наведените клиничко-патолошки параметри се прикажани во во табелата 2.

Табела 2. Разлики во нивоата на експресија на генот TOB1 кај примероци на колоректален карцином со стадиум IIa во споредба со стадиум IIIb и повисок, како и карциноми лоцирани во проксималниот колон во споредба со дисталниот колон и ректумот

параметар		средна вредност ± SD	минумум	максимум	p-вредност
стадиум	IIa	**3,93** ± 4,41	0,45	13,00	*p*=0,038 *
	IIIb, IIIc и IVb	**1,20** ± 1,58	0,16	6,05	
локација	лев хемиколон	**0,53** ± 0,30	0,16	0,97	*p*=0,026 *
	десен хемиколон и ректум	**2,60** ± 3,34	0,45	13,00	

* статистички значајна разлика; SD = стандардна девијација

ДИСКУСИЈА

Во рамките на овој семинарски труд, прикажани се прелиминарните резултати од истражувањето на асоцијацијата на експресијата на генот *TOB1* со стадиумот и локацијата на колоректалниот

карцином. Обработени се податоците за 42 пациенти од предвидените повеќе од 100 во поднесокот за докторската дисертација.

Со обработка на податоците од овие прелиминарни стражувања, регистрирана е статистички сигнификантна, инверзна корелација меѓу нивоата на генска експресија на *TOB1* во примероците од колоректалните карциноми со стадиумите на развој на колоректалниот карцином, како и помеѓу експресијата и локализацијата на туморите.

Нашите резултати сугерираат дека генската експресија на *TOB1* е поврзана со пониските степени на развој на колоректален канцер и локализација на канцерот на проксималниот дел од дебелото црево. Тие резултати се во прилог на анти-пролиферативната улога на овој ген во патогенезата на колоректалниот канцер.

Иако постои косензус за улогата на тумор-супресорните гени и нивните протеински продукти во инхибицијата на неопластичниот раст, сепак кај некои гени кои се несомено класифицирани во оваа категорија, постојат и контрадикторни податоци. Повеќето истражувачи регистрирале намалување на експресијата на генот *TOB1* кај малигните неоплазми и негативна корелација со метастатскиот потенцијал (12, 13, 14), но во ретките студии кај колоректалниот карцином, парадоксално, опишана е и позитивна корелација меѓу експресиските нивоа и малигниот потенцјал на туморот (11).

Таквите контрадикторни наоди можат да се должат на различни фактори кои вклучуваат, но не се ограничени на: разлики во критериумите за вклучување и исклучување на пациентите во студијата, различниот генетски и етнички состав на пациентите, разликите во методологијата на анализа на генската експресија, изборот на алатки за статистичка обработка и други, но и на можните разлики во експресискиот профил кај различни малигни неоплазми.

Практичната клиничка апликативност на ваквите истражувања е особено интересна кај хируршкиот пристап во дијагностиката, терапијата и прогностиката на колоректалниот карцином, каде, поради различната васкуларизација, лимфна и венска дренажа, како и други фактори, постојат разлики меѓу анатомската локација на карциномите кај левиот, проксимален хемиколон, во однос на десниот, дистален хемиколон, вклучувајќи го и ректумот.

Понатамошни истражувања се потребни за да се расветлат молекуларните механизми кои се активираат при абнормалната промена на експресијата на генот *TOB1*, како и да се утврди можната употреба на овој молекуларен маркер во дијагностички и/или во прогностички цели (13).

Со оглед на тоа дека се предвидени поголем број на пациенти за анализа, истражувањата ќе опфатат и други клинико-патолошки параметри, покрај стадиумот и анатомската локација на колоректалниот карцином: хистопатолошкиот градус на диференцијација, други стадиуми кои не се опфатени кај прелиминарната група од 42 пациенти прикажани во овој семинарски труд, постоењето на докажани метастази, бројот на метастатски лимфни јазли и други.

ЛИТЕРАТУРА

1. Fearon ER, Vogelstein B: A genetic model for colorectal tumorigenesis. *Cell*. 1990; 61:759-67.
2. De Rosa M, Pace U, Rega D, Costabile V, Duraturo F, Izzo P et al. Genetics, diagnosis and management of colorectal cancer (Review). *Oncology Reports*. 2015; 34: 1087-96. doi: 10.3892/or.2015.4108.
3, Markowitz SD, Bertagnolli MM. Molecular origins of cancer: Molecular basis of colorectal cancer. *N Engl J Med*. 2009; 361(25): 2449-60. doi: 10.1056/NEJMra0804588.
4. Bogaert J, Prenen H. Molecular genetics of colorectal cancer. Ann Gastroenterol. 2014; 27(1): 9–14.
5. Simons CC, Hughes LA, Smits KM, Khalid-de Bakker CA, de Bruïne AP, Carvalho B et al. A novel classification of colorectal tumors based on microsatellite instability, the CpG island methylator phenotype and chromosomal instability: implications for prognosis. *Ann Oncol*. 2013; 24(8):2048-56. doi: 10.1093/annonc/mdt076.
6. Guinney J, Dienstmann R, Wang X, de Reyniès A, Schlicker A, Soneson C et al. The consensus molecular subtypes of colorectal cancer. *Nat Med*. 2015; 21(11):1350-6. doi: 10.1038/nm.3967.
7. Sugai T, Habano W, Jiao YF, Tsukahara M, Takeda Y, Otsuka K et al. Analysis of molecular alterations in left- and right-sided colorectal carcinomas reveals distinct pathways of carcinogenesis: proposal for new molecular profile of colorectal carcinomas. *J Mol Diagn*. 2006; 8(2): 193-201.
8. Nasir A, Lopez A, Boulware D, Malafa M, Coppola D. Correlation between COX-2 and APC expression in left versus right-sided human colon cancer. *Anticancer Res*. 2011; 31(6): 2191-5.

9. Kundu J, Wahab SM, Kundu JK, Choi YL, Erkin OC, Lee HS et al. Tob1 induces apoptosis and inhibits proliferation, migration and invasion of gastric cancer cells by activating Smad4 and inhibiting β-catenin signaling. *Int J Oncol*. 2012; 41(3):839-48. doi: 10.3892/ijo.2012.1517.
10. Lee HS, Kundu J, Kim RN, Shin YK. Transducer of ERBB2.1 (TOB1) as a Tumor Suppressor: A Mechanistic Perspective. *Int J Mol Sci*. 2015; 16(12): 29815-28. doi: 10.3390/ijms161226203.
11. Wu D. Quantitative real-time reverse transcription-PCR assay for the expression of Tob mRNA in human colorectal cancer. *Clin Oncol Cancer Res*. 2010; 7(5): 284-8. doi: 10.1007/s11805-010-0532-x.
12. Lin S, Zhu Q, Xu Y, Liu H, Zhang J, Xu J et al. The role of the TOB1 gene in growth suppression of hepatocellular carcinoma. *Oncol Lett*. 2012; 4(5):981-987. doi: 10.3892/ol.2012.864.
13. Lee HS, Kundu J, Kim RN, Shin YK. Transducer of ERBB2.1 (TOB1) as a Tumor Suppressor: A Mechanistic Perspective. *Int J Mol Sci*. 2015; 16(12):29815-28. doi: 10.3390/ijms161226203.
14. Jiao Y, Sun KK, Zhao L, Xu JY, Wang LL, Fan SJ. Suppression of human lung cancer cell proliferation and metastasis in vitro by the transducer of ErbB-2.1 (TOB1). *Acta Pharmacol Sin*. 2012; 33(2):250-60. doi: 10.1038/aps.2011.163.

ASSOCIATION OF TOB1 GENE EXPRESSION WITH COLORECTAL CANCER STAGE AND ANATOMICAL TUMOR LOCATION

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ABSTRACT

The *TOB1* is a tumor-suppressor gene encoding a protein which functions as a negative regulator of the receptor tyrosine-kinase ERBB2 with anti-proliferative, proapoptotic and anti-invasive effects on the cancer cells. The inactivation of *TOB1*, or a reduced gene expression, was identified in many human neoplasms. Our aim was to investigate the associations between the stage and tumor location with the *TOB1* gene expression levels in colorectal cancer patients.

A group of 42 patients with colorectal cancer was recruited for the study. A normal mucosa sample at a distance >10 cm of the tumor was collected from each patient. Total RNA was isolated, cDNA was synthetized by reverse transcription and quantitative Real-Time Polymerase Chain Reaction was used to determine the TOB1 expression.

The mean *TOB1* gene expression levels were 3.2 folds higher in patients with stage IIa than in the IIIb, as well as higher stages (p=0.038), and it was 4.9 folds lower in proximal than in the distal colon and rectum (p=0.026).

Our results suggest that *TOB1* gene expression is associated with lower stages and with a proximal colon cancer location. Our results further support the anti-proliferative role of this gene in the pathogenesis of colorectal cancer.

Keywords: colorectal cancer, stage, *TOB1* gene, expression levels, qRT-PCR

Profesional paper

KORRELACIONI NË MES TË MJEKIMIT MEDIKAMENTOZ DHE ATIJ KIRURGJIK TE POLIPOZA E HUNDËS

CORRELATION BETWEEN MEDICAMENTOUS AND SURGICAL TREATMENT IN NASAL POLYPOSIS

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REZYME

Polipoza nazale është një prej sëmundjeve kronike respiratore, që prek kualitetitn e jetës të pacientit në shumë mënyra. Nëse dështon mjekimi medikamentoz, qasje të ndryshme kirurgjikale mund të jenë të dobishme për heqjen e polipeve. Qëllimi i punimit është krahasimi i suksesit të mjekimit medikamentoz dhe atij kirurgjik. Metoda është retrospektive ku janë hulumtuar 585 pacientë të operuar në klinikën e ORL, në periudhën 2000 – 2010, ku prej tyre 102 kanë qenë të trajtuar sipas protokolit medikamentoz. Rezultatet tregonin se pacientët e trajtuar me protokol medikamentoz pre dhe postoperativ kishin sukses më të madh të mjekimit. Konkluzioni: Mënyra më e mirë e mjekimit të polipozës nazale është ajo e kombinuar – kirurgjike dhe medikamentoze.

Fjalët kyçe: Polipoza nazale, mjekimi medikamentoz, mjekimi kirurgjik, FESS.

HYRJE

Polipoza nazale është sëmundje kronike inflamatore e rrugëve të sipërme respiratore me etiologji të panjohur. Prevalenca ndryshon prej 1 deri në 5%. Në SH.B.A. polipet nazale janë prezente në 5% të popullatës joalergjike dhe vetëm te 1.5% të njerëzve me rinit alergjik. Përafërsisht 30% të pacientëve me polipozë nazale janë pozitive në testimet në alergjenet ambientale. Polipoza nazale zakonisht manifestohet pas moshës 20 vjeçare, duke prekur mashkujt dy herë më shumë se femrat. Vendi më i shpeshtë i prejardhjes së polipeve nazale është regjioni etmoidal i përparmë. Konditat tjera të asocuara me polipe nazale përfshijnë rinosinuzitin kronik, intolerancën në aspirinë dhe fibrozën cistike. Në një studim të fundit, prevalence e polipeve nazale në 211 pacientë të rritur me fibrozë cistike ishte 37% (1). Lidhur me formimin e polipeve nazale janë sugjeruar disa mekanizma. Këtu hyjnë alergjia, infeksioni, imbalanca autonomike, transporti abnormal transepitelial i joneve, abnormalitetet e mukopolisaharideve, abnormalitetet e enzimeve, obstruksioni mekanik dhe ruptura epiteliale (2). Polipet nazale përmbajnë një numër sinjifikant më të madh të eozinofileve, neutrofileve dhe plazma qelizave sesa që ka mukoza nazale (3). Te shumica e polipeve nazale, eozinofilet përbëjnë më shumë se 60% të numrit të qelizave. Në kushte normale eozinofilet në qarkullim mbesin rreth 3 dite, kurse në një kulture qelizore të polipit nazal eozinofilet kanë qenë prezente së paku 12 ditë. Mekanizmat përgjegjës për akumulimin selektiv të eozinofileve te polipet janë të panjohura.

Simptoma më e shpeshtë është obstruksioni nazal (më së shpeshti mbyllje e të dy kaviteteve të hundës) i përcjellur me rrjedhje ujore të hundëve, teshtitje, frymëmarrje

kronike me gojë, ndryshime në kualitetin e zërit[4]. Simptomat tjera janë: hipoksia, hiperkapnia, gërhitja, çrregullimet e gjumit. Polipet poashtu shkaktojnë çrregullimet e shqisës së nuhatjes- në kuptim të hiposmisë ose anosmisë[4]. Polipet nazale janë jo të zakonshme te fëmijët, prandaj prezenca e tyre duhet të nxisë dyshimin për praninë e fibrozës cistike(1).

Testet bazike (themelore) dhe ato ndihmëse (suplementare) për diagnostikimin e polipozës nazale (sipas Brook, 2007)

Testet themelore	Testet suplementare
Anamneza dhe ekzaminimi klinik	Diagnostikimi alergjik
Endoskopia e kavitetit nazal	MRI për diagnoza të caktuara
Skenimi me CT në rrafshin koronal	Citologjia nazale
dhe aksial	Biopsia nazale

Sistemet e stejxhingut janë të bazuara endoskopikisht dhe ne bazë të CT skenimit. Zakonisht përdoren dy sisteme, ai i Lund dhe Kennedy, 1995(6), si dhe ai sipas Johansson, 2003.

Objektivat e mjekimit të polipozës nazale, sipas Lildholdt dhe Mygind(7) janë: Rikthimi i kalueshmërisë së hundës dhe frymëmarrjes nazale; Zvogëlimi i simptomeve; Përmirësimi i shqisës së nuhatjes; Trajtimi i sëmundjeve koekzistuese; Përmirësimi i kualitetit të jetës; Parandalimi i komplikimeve. Polipet nazale mund të shkaktojnë obstruksionin e sinusëve, duke rezultuar me infeksion. Trajtimi i infeksionit me antibiotikë mund të parandalojë rritjen e mëtejme të polipit dhe ta zvogëlojë gjakderdhjen gjatë intervenimit kirurgjik. Kortikosteroidet kanë një spektër të gjerë të efekteve anti-inflamatore. Steroidet topikale janë medikamente të zgjedhjes për polipozën nazale. Nëse është nevoja për operim, trajtimi afatgjatë me spreje nazale kortikosteroide e zgjat kohën e paraqitjes së rekurencës. Përkundër steroideve nazale, kortikosteroidet sistemike mund të mbërrijnë në të gjitha pjesët e hundës dhe sinusëve, duke përfshirë edhe pjesën olfaktore dhe meatusin e mesëm, ashtu që përmirëson shqisën e nuhatjes më mirë se steroidet lokale. Para ndërhyrjes kirurgjike, steroidet orale ipen zakonisht 3 deri në 4 ditë me qëllim që të zvogëlohen polipet. Mjekimi medikamentoz përfshin edhe përdorimin e antihistaminikëve, imunoterapisë, antibitiotikëve.

Heqja kirurgjike e polipeve nazale indikohet te pacientët që nuk kanë reagim adekuat ndaj mjekimit medikamentoz, te ata me infeksione të vazhdueshme ose rekurente. Të gjithë sinusët e involvuar duhet të hapen, në kuptim të heqjes së polipit. Korrigjimi i obstruksionit përmirëson drenazhën dhe çon në rikthimin e ndryshimeve mukozale brenda sinusëve paranazalë. Në të gjitha qendrat e zhvilluara botërore, mjekimi kirurgjik i polipeve nazale bëhet kryesisht me metodën e FESS-Functional Endoscopic Sinus Surgery(8), edhepse në vendet ku mungon instrumentariumi dhe paisjet për FESS, operimi i polipeve nazale bëhet me metodat e vjetra. Te mjekimi si ai medikamentoz ashtu edhe ai kirurgjik është shumë me rëndësi përcjellja e pacientit ose follow-up. Qëllimet kryesore të përcjelljes janë: parandalimi i sinekieve dhe mbylljes së ostiumeve; rikthimi i patencës së kavitetit nazal dhe kavitetit të sinusëve; parandalimi i infeksionit perzistent dhe i rritjes së mëtejme të polipit; stimulimi i zhvillimit të mukozës normale për zëvendësimin e indit patologjik. Trajtimi postoperativ me steroide intranazale është i nevojshëm sepse ndihmon në ngadalësimin e paraqitjes së rekurencave.Gjatë mjekimit kirurgjik ipen edhe antibiotikë.

QËLLIMI I PUNIMIT

- Hulumtimi epidemiologjik i patologjisë së polipozës së hundës dhe sinuseve paranazalë;
- Mënyrat e mjekimit të polipozës nazale dhe krahasimi i rezultateve të mjekimit.

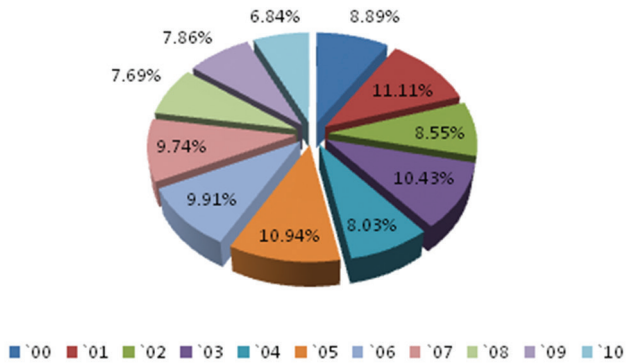
MATERIALI DHE METODAT

Ky është një hulumtim epidemiologjik – klinik, retrospektiv, duke shfrytëzuar metodologjinë e krahasimit të rasteve në Klinikën e ORL-së pranë QKUK – së ne Prishtinë. Në këte studim janë përfshirë pacientët e hospitalizuar në Klinikën e ORL-se, respektivisht në repartin e Rinologjisë, ORL-së pediatrike, Otologjisë. Materiali i grumbulluar përfshin periudhën 10 vjeqare (1 janar 2000 – 31 dhjetor 2010). Pas grumbullimit të të dhënave, ato janë sistematizuar dhe është realizuar analiza kuantitative përmes programit kompjuterik Excel, duke shfrytëzuar metodat statistikore, si janë: prezentimi tabelar dhe grafik, mesataren, përqindjen, etj.

REZULTATET

Tabela 1. Prezentimi tabelar i numrit të gjithëmbarshëm të rasteve me polipozë, sipas viteve

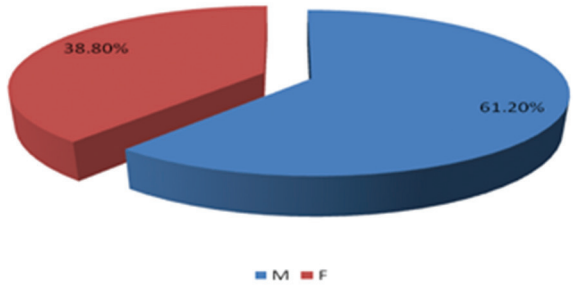
Vitet	Nr. rasteve	
	N	%
2000	52	8.89
2001	65	11.11
2002	50	8.55
2003	61	10.43
2004	47	8.03
2005	64	10.94
2006	58	9.91
2007	57	9.74
2008	45	7.69
2009	46	7.86
2010	40	6.84
Gjithsej	585	100



Grafikoni 1. Paraqitja grafike e rasteve me polipozë të hundës dhe sinusëve paranazalë , sipas viteve

Tabela 2. Rastet me polipozë të hundës dhe sinuseve , sipas gjinisë dhe viteve

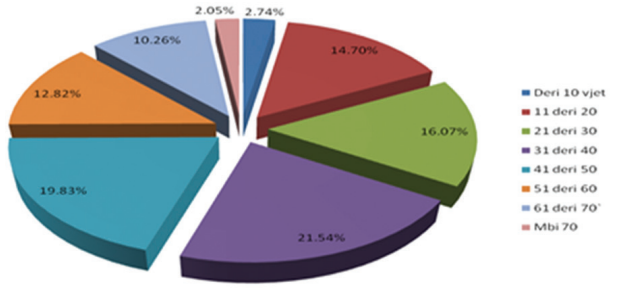
Vitet	Gjinia				Gjithsej	
	M		F			
	N	%	N	%	N	%
2000	33	9.22	19	8.37	52	100
2001	38	10.61	27	11.89	65	100
2002	23	6.42	27	11.89	50	100
2003	35	9.78	26	11.45	61	100
2004	23	6.42	24	10.57	47	100
2005	45	12.57	19	8.37	64	100
2006	35	9.78	23	10.13	58	100
2007	35	9.78	22	9.69	57	100
2008	27	7.54	18	7.93	45	100
2009	35	9.78	11	4.85	46	100
2010	29	8.10	11	4.85	40	100
Gjithsej	358	61.2	227	38.8	585	100
	X2=1.48, p> 0.05					



Grafikoni 2. Paraqitja grafike e rasteve me polipozë të hundës dhe sinusëve paranazalë , sipas gjinisë

Tabela 3. Rastet me polipozë të hundës dhe sinusëve paranazalë, sipas grupmoshës dhe viteve

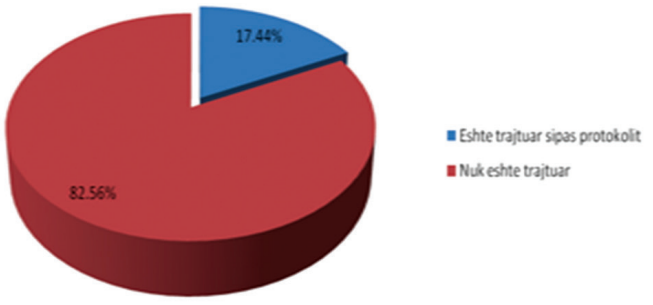
	Grupmosha																Gjithsej	
	Deri 10vjet		11 – 20		21 - 30		31 - 40		41 - 50		51 - 60		61 - 70		Mbi 70			
Vitet	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
2000	0	0	10	11.63	6	6.38	10	7.94	8	6.9	6	8	8	13.33	4	33.33	52	100
2001	1	6.25	7	8.14	13	13.83	18	14.29	8	6.9	12	16	4	6.67	2	16.67	65	100
2002	2	12.5	5	5.81	7	7.45	8	6.35	12	10.34	6	8	9	15	1	8.33	50	100
2003	5	31.25	8	9.30	13	13.83	10	7.94	9	7.76	5	6.67	11	18.33	0	0	61	100
2004	0	0	5	5.81	9	9.57	11	8.73	10	8.62	6	8	6	10	0	0	47	100
2005	3	18.75	8	9.30	7	7.45	16	12.70	11	9.48	9	12	9	15	1	8.33	64	100
2006	0	0	12	13.95	9	9.57	12	9.52	11	9.48	9	12	3	5	2	16.67	58	100
2007	0	0	8	9.3	9	9.57	13	10.32	15	12.93	6	8	4	6.67	2	16.67	57	100
2008	2	12.50	6	6.98	11	11.70	11	8.73	11	9.48	3	4	1	1.67	0	0	45	100
2009	2	12.50	8	9.30	5	5.32	10	7.94	11	9.48	6	8	4	6.67	0	0	46	100
2010	1	6.25	9	10.47	5	5.32	7	5.56	10	8.62	7	9.33	1	1.67	0	0	40	100
Gjithsej	16	2.74	86	14.70	94	16.07	126	21.54	116	19.83	75	12.82	60	10.26	12	2.05	585	100



Grafikoni 3. Paraqitja e rasteve me polipozë të hundës dhe sinusëve paranazal , sipas grupmoshave

Tabela 4. Rastet e trajtuara sipas protokolit medikamentoz, sipas viteve

Vitet	Është trajtuar sipas protokolit		Nuk është trajtuar		Gjithsej	
	N	%	N	%	N	%
2000	1	0.98	51	10.32	52	100
2001	2	1.96	63	12.75	65	100
2002	1	0.98	49	9.92	50	100
2003	6	5.88	55	11.13	61	100
2004	5	4.9	42	8.5	47	100
2005	7	6.86	57	11.54	64	100
2006	10	9.8	48	9.72	58	100
2007	12	11.70	45	11.34	57	100
2008	20	19.61	25	5.06	45	100
2009	18	17.65	28	5.67	46	100
2010	20	19.61	20	4.05	40	100
Gjithsej	102	17.44	483	82.56	585	100



Grafikoni 4. Paraqitja grafike e rasteve te trajtuara paraprakisht me kortikosteroide , sipas protokolit

DISKUTIMI

Polipoza nazale është një konditë inflamatore me etiologji të panjohur.). Hatfield (2000) studioi rreth 211 të rritur me CF dhe gjeti se incidenca ishte 37 %. Më 1968 Max Sampter i pari përshkroi triadën klinike të astmës, polipozës nazale dhe alergjisë ndaj aspirinës. Studimet e mëpastajmë kanë treguar se te pacientët me astmën dhe intolerancën e aspirinës kanë treguar një prevalencë të polipozës nazale prej 36- 95 %. Nga ana tjetër pacientë me këtë triadë kanë treguar se janë shumë më të rezistueshëm ndaj mjekimit medikamentoz. Polipoza nazale mund ta çrregullojë kualitetin e jetës të një personi më shumë se riniti alergjik perenial. Olfaksioni dhe obstruksioni nazal janë simptomet më të rëndësishme. Radenne dhe bp. gjetën se polipet nazale, përpos që shkaktojnë obstruksion nazal, hiposmi dhe infeksione rekurente, shkaktojnë çrregullim të cilësisë së jetës më shumë se riniti alergjik perennial(9). Diagnostikimi i polipozës nazale mund të bëhet me : rinoskopinë e përparme dhe të pasme, Rtg. Nativ, CT, MRI dhe me endoskopi si metoda më e mirë. Si metodë e mjekimit rekomandohet mjekimi kirurgjik, mjekimi medikamentoz ose edhe që të dyja. Sipas rasteve tona, brenda periudhës 2000-2010 janë ekzaminuar dhe operuar 585 raste me polipozë të hundës dhe sinuseve paranazalë, sipas viteve me përqindje më të madhe gjatë vitit 2001 me 11.11% dhe më së paku me 6.84% gjatë vitit 2010 (Tab.1). Në tabelën 2 janë prezentuar rastet me polipozë sipas gjinisë dhe viteve. Pjesëmarrje më të madhe kanë pasur rastet e gjinisë mashkullore me 61.2% por pa dallim sinjifikant sipas gjinisë. Poashtu sipas viteve pjesëmarrje më të madhe kanë pasë rastet e gjinisë mashkullore për vitin 2005 me 12.57%, 2001 me 10.61%, pastaj për vitet 2003, 2006, 2007 me 9.78%. Sipas tabelës 3,mosha mesatare e pacientëve të ekzaminuar ishte 39.75 vjet. Sipas grupmoshës, pjesëmarrje më të madhe ka pasur grupmosha 31-40vjet me 21.54% dhe 41-50 vjet me 19.83% dhe më së paku të grupmoshës mbi 70 vjet me vetëm 2.05%. Poashtu edhe sipas viteve ka dominuar grup mosha 31-40 vjet me 21.54% gjatë vitit 2001, me 18 raste, gjatë vitit 2005, 16 raste. Vetëm gjatë vitit 2007 pjesëmarrje më të lartë ka pasë grupmosha 41-50 vjet me 15 raste.

Sot kortikosteroidet konsiderohen si barnat më efektive për trajtimin e polipozës nazale. Sipas literaurës në 80 %

të rasteve polipet respondojnë me zvogëlim të madhësisë, përmirësim të simptomeve të asocuara dhe redukim të rekurencës postoperative. Në rastet tona të studiuara, paraprakisht me protokol të steroideve janë trajtuar vetëm 102 ose 17.44% të pacientëve të operuar (Tab.4),sipas viteve, janë trajtuar sipas protokoleve, më së shumti në vitin 2008 dhe 2010, gjë që na shtyn të përmirësojmë këtë në të ardhmen, sepse duhet të përcjellim trendet botërore në këtë aspekt.

Trajtimi kirurgjik me të cilën në botë nënkuptohet FESS-kirurgjia funksionale endoskopike e sinusëve, është një trajtim standard që jep rezultate të mira funksionale te pacientët rezistentë në terapi konzervative dhe nga ana tjetër mundëson evitimin e procedurave kirurgjike radikale. Qëllimi i FESS është të hiqet indi polipoz nga hunda dhe sinuset me ruajtje të strukturave anatomike dhe mukozës së shëndoshë. Që të ruhen rezultatet postoperative dhe të parandalohet rirritja e polipeve është e domosdoshme një kujdes agresiv postoperativ dhe përcjellje postoperative-follow-up care. Pacientët paraprakisht duhet të jenë të njohtuar lidhur me komplikimet potenciale orbitale, mundësinë e rrjedhjes postkirurgjike të lëngut cerebrospinal, gjakderdhjes së mundshme nga arteriet e afërta me sinusët dhe mundësinë e riparaqitjes së polipeve edhe pas ndërhyrjes kirurgjike.

KONKLUZIONET

1. Polipoza e hundës dhe sinuseve paranazale paraqet një proces që kryesisht ka shkaktarë të shumëfishtë;
2. Simptoma kryesore është opstrukcioni nazal progresiv;
3. Për diagnostikim më të saktë rekomandohet endoskopia nazale dhe skenimi me CT;
4. Në materialin e studiuar klasifikimi është bërë në bazë të CT skenimit dhe endoskopisë;
5. Kortikosteroidet sistemike dhe lokale i zvogëlojnë simptomat e rinitit, e bëjnë trajtimin kirurgjik më të lehtë, i parandalojnë rekurencat e polipeve pas operimit;
6. Mjekimi tjetër konzervativ përfshin përdorimin e antibiotikëve, imunoterapisë, antihistaminikëve;
7. Mjekimi kirurgjik indikohet te pacientët te të cilët mjekimi konzervativ nuk ka qenë i efektshëm dhe te rastet me komplikime;
8. Me ekscidim kirurgjik të polipeve rivendosen funksionet e hundës dhe mundësohet drenimi i sinuseve të inflamuara;
9. Përdorimi i FESS – it rekomandohet për të gjitha ndërhyrjet kirurgjike për trajtimin e polipozës nazale dhe sinuseve paranazalë;

LITERATURA

1. Hadfield PJ, Rowe-Jones JM, Mackay IS: The prevalence of nasal polyps in adults with cystic fibrosis. Clin Otolaryngol 2000, 25:19–22.
2. Coste A, Brugel L, Maitre B, et al.: Inflammatory cells as well as epithelialcells in nasal polyps express vascular endothelial growth factor. Eur RespirJ 2000, 15:367–372.
3. Denburg J: Cytokines and inflammatory cells. In Nasal Polyposis: An Inflammatory Disease and Its Treatment. Edited by Mygind N, Lildholdt T.Copenhagen: Munksgaard; 1997:78–87.
4. Limani A, Otorinolaringologjia – Kirurgjia e kokës dhe qafës, Prishtinë 2004
5. Hahnel S, Ertl-Wagner B, Tasman AJ, et al.: Relative value of MR imagingas compared with CT in the diagnosis of inflammatory paranasal sinusdisease. Radiology 1999, 210:171–176.
6. Mackay IS, Lund VJ: Imaging and staging. In Nasal Polyposis: AnInflammatory Disease and Its Treatment. Edited by Mygind N, Lildholdt T. Copenhagen: Munksgaard; 1997:137–144.
7. Lildholdt T, Mygind N: Effect of corticosteroids on nasal polyps: evidence from controlled trials. In Nasal polyposis: An Inflammatory Disease and Its Treatment. Edited by Mygind N, Lildholdt T. Copenhagen: Munksgaard; 1997:160–169.
8. Stammberger HR: Rhinoscopy: endoscopic diagnosis. In Rhinitis: Mechanisms and Management. Edited by Naclerio RM, Durham SR, Mygind H. New York: Marcel Dekker; 1999:165–173.
9. Radenne F, Lamblin C, Vandezande LM, et al.: Quality of life in nasal polyposis. J Allergy Clin Immunol 1999, 104:79–84.

CORRELATION BETWEEN MEDICAMENTOUS AND SURGICAL TREATMENT IN NASAL POLYPOSIS

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ABSTRACT

Nasal polyposis as one of severe chronic airway diseases, affects the patients quality of life.If medicamentous treatment fails,there are various surgical techniques which can be used in polyp surgery. Aim of this study was to compare success of the medicamentous and surgical treatment of nasal polyposis.Methods used were comparative ones as this was retrocpective study in which were included 585 patients operated in ENT Clinic,between January 2000 and December 2010.Also were studied number of patients treated with medicamentous protocol pre and postoperatively.Results showed that patients treated with surgery and with protocol in combination had better overall success.

Key words: Nasal polyposis, medicamentous treatment,surgical treatment. FESS.

REKURENCAT E POLIPOZËS NAZALE

RECURRENCES OF THE NASAL POLYPOSIS

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REZYME:

Objektivi: Qëllimi i punimit është vlerësimi i shkallës së përsëritjes së polipozave nazale te pacientët e operuar.

Metodat: Punimi është studim retrospektiv i realizuar te 585 pacientë të operuar prej polipozës nazale dhe të hospitalizuar në perudhën në mes viteve 2000- 2010 në Klinikën e ORL – së në Prishtinë. Koha mesatare e përcjelljes postoperative ishte 30 muaj (koha sillej prej 1 muaj deri 50 muaj).

Rezultatet: Gjatë perudhës të studimit, rekurencat u zhvilluan te 94 pacientë, me shkallë të përqindjes prej 16%.

Konkludimi: Rrezik më të lartë për paraqitjen e rekurencave të polipozës nazale pas ndërhyrjes kirurgjike kanë pacientët të cilët sëmundja është më ekstenzive e verifikuar me CT skenim dhe te pacientët që të njejtën kohë vuajnë nga astma dhe alergjia e verifikuar.

Fjalët kyçe: Polipoza nazale, rekurenca e polipozës nazale, faktorët e rrezikut për rekurencë.

HYRJE

Polipet nazale kanë qenë të njohur si çështje mjekësore qysh prej kohës së Egjiptit të lashtë(1). Prevalenca e kësaj gjendje llogaritet të jetë në mes të 1% dhe 4%(2), por disa studime raportojnë shkallë deri në 32%[(3)]. Në paraqitjen e polipeve nuk mund të implikohet asnjë gjendje e vetme predispozuese, edhe pse ato mund të shoqërohen me disa sëmundje tjera, më të njohurat si fibroza cistike, astma dhe intoleranca në aspirinë cistike të cilat kërkojnë trajtim dhe përcjellje më agresive dhe ekstenzive për shkak të shkallës së lartë të rekurencës (4). Roli i infeksionit po ashtu mendohet të jetë një shkak i rëndësishëm në paraqitjen e polipeve(5). Sidoqoftë, kur është vështirë të menaxhohen, konditat shpesh kërkojnë mjekim edhe medikamentoz edhe kirurgjikal.

Kirurgjia funksionale endoskopike e sinuseve (FESS) tash është në përdorim të gjërë për trajtimin e polipeve nazale, sidoqoftë, një incidencë e lartë e rekurencave postkirurgjike është e dokumentuar(6,7). Përdorimi i kortikosteroideve topikale konsiderohet nga disa specialistë si trajtimi më i mirë në parandalimin e rekurencave(8). Sidoqoftë, parandalimi dhe parashikimi i përsëritjeve të tyre është temë e shumë debateve ndërmjet klinicistëve dhe hulumtuesve shkencorë.

QËLLIMI

Qëllimi i punimit është hulumtimi epidemiologjik – klinik i rekurencave të polipozës së hundës dhe sinuseve paranazale pas trajtimit kirurgjik.

MATERIALI DHE METODAT

Ky është një hulumtim epidemiologjik – klinik, retrospektiv, duke shfrytëzuar metodologjinë e krahasimit të rasteve në Klinikën e ORL-se pranë QKUK –së në Prishtinë.

Në këte studim janë përfshirë pacientët e hospitalizuar në Klinikën e ORL-së, respektivisht në repartin e Rinologjisë, ORL-së pediatrike, Otologjisë. Të dhënat

janë grumbulluar nga protokoli operativ,protokolet e reparteve, historive të pacientëve

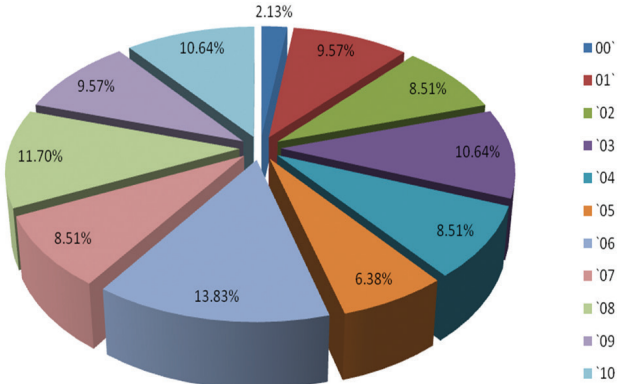
Materiali i grumbulluar përfshin periudhën 10 vjeçare (1 janar 2000 – 31 dhjetor 2010).

Pas grumbullimit të të dhënave, ato janë sistematizuar dhe është realizuar analiza kuantitative përmes programit kompjuterik Excel, duke shfrytëzuar metodat statistikore, si janë: prezentimi tabelar dhe grafik, mesataren, përqindjen, etj.

REZULTATET

Tabela 1. Rastet e operimeve të rekurencave të polipozës së hundës, sipas viteve

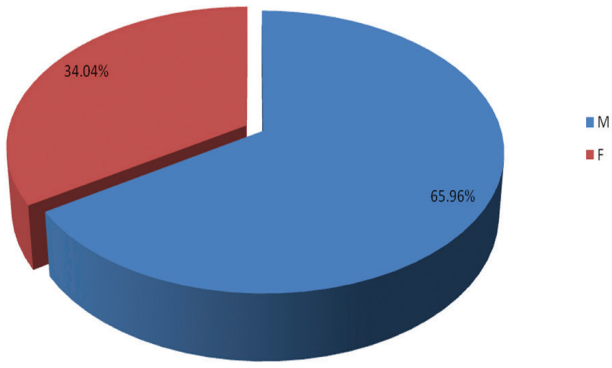
Vitet	Gjithsej	
	N	%
2000	2	2.13
2001	9	9.57
2002	8	8.51
2003	10	10.64
2004	8	8.51
2005	6	6.38
2006	13	13.83
2007	8	8.51
2008	11	11.70
2009	9	9.57
2010	10	10.64
Gjithsej	94	100



Grafikoni 1. Paraqitja grafike e rasteve me polipozë të hundës dhe sinusëve paranazalë, sipas viteve

Tabela 2. Rastet e operimeve të rekurencave të polipozës së hundës, sipas viteve dhe gjinisë

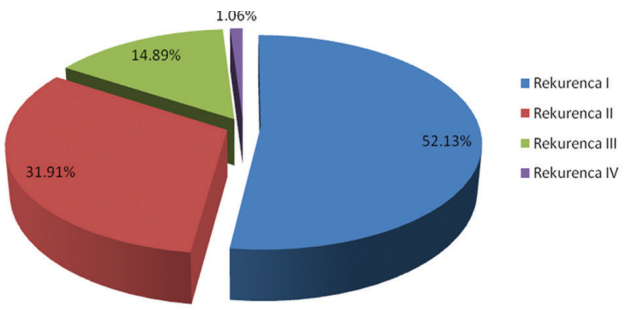
Vitet	Gjinia				Gjithsej	
	M		F		N	%
	N	%	N	%		
2000	1	2	1	3.13	2	100
2001	6	10	3	9.38	9	100
2002	4	6	4	12.50	8	100
2003	7	11	3	9.38	10	100
2004	4	6	4	12.50	8	100
2005	5	8	1	3.13	6	100
2006	9	15	4	12.50	13	100
2007	5	8	3	9.38	8	100
2008	6	10	5	15.63	11	100
2009	6	10	3	9.38	9	100
2010	9	15	1	3.13	10	100
Gjithsej	62	65.96	32	34.04	94	100
	X2=0,20, p>0.05, SHl=4					
	X2=1,32, p>0.05, SHl=1					



Grafikoni 2. Paraqitja grafike e operimeve te rekurencave të polipozës së hundës , sipas gjinisë

Tabela 3. Rastet sipas radhës së rekurencave të polipozës së hundës dhe sipas viteve

Vitet	Rekurenca e I-rë		Rekurenca e II – të		Rekurenca e III – të		Rekurenca e IV – të		Gjithsej	
	N	%	N	%	N	%	N	%	N	%
2000	1	2.04	0	0	1	7.14	0	0	2	2.13
2001	4	8.16	3	10	2	14.29	0	0	9	9.57
2002	6	12.24	0	0	1	7.14	1	100	8	8.51
2003	6	12.24	3	10	1	7.14	0	0	10	10.64
2004	5	10.20	2	6.67	1	7.14	0	0	8	8.51
2005	1	2.04	3	10	2	14.29	0	0	6	6.38
2006	6	12.24	4	13.33	3	21.43	0	0	13	13.83
2007	5	10.20	2	6.67	1	7.14	0	0	8	8.51
2008	6	12.24	5	16.67	0	0	0	0	11	11.70
2009	4	8.16	4	13.33	1	7.14	0	0	9	9.57
2010	5	10.20	4	13.33	1	7.14	0	0	10	10.64
Gjithsej	49	52.13	30	31.91	14	14.89	1	1.06	94	100
	X2=5,82, p> 0.05, SHl=8									
	X2=12,67, p< 0.01, SHl=2									



Grafikoni 3. Paraqitja grafike e rekurencave te polipazës se hundës , sipas radhës

DISKUTIMI

Ka shumë të dhëna të ndryshme lidhur me prevalencën e polipozes nazale rekurente te pacientët që janë operuar nga polipoza unilaterale ose bilaterale. Është vlerësuar se shkalla e rekurencës së polipozës sillej prej 15% deri 25%. Sipas Wynn dhe bp, faktori që ndikonte në rritjen e shkallës së rekurencës së polipozës ishte prania e sëmundjeve inflamatore të pacientit,p.sh., 80% e pacientëve me astmën që iu kishin nënshtruar FESS, kishin shkallë rekurence në krahasim me 40% të pacientëve pa astmën. Poashtu 73% e pacientëve me histori të alergjisë dhe që ishin operuar me FESS, kishin rekurencë të polipozës(9). Nëse është nevoja për operim, trajtimi afatgjatë me spreje nazale kortikosteroide e zgjat kohën e paraqitjes së rekurencës. Sipas një punimi të autorëve britanikë (2007), rekurenca është e zakonshme te 60 % të pacientëve te të cilët është e nevojshme procedura tjetër brenda 5 viteve, kurse 5-10 % të pacientëve kanë përkeqësim të sëmundjes. Polipet solitare të mëdha kanë më pak gjasa të rikthehen por pacientët me polipe dhe astmën kanë më shumë gjasa për probleme të mëtutjeshme. Në një punim tjetër janë përcjellur 41 pacientë gjatë periudhës 20 vjeçare, 85 % të tyre ende kanë vuajtur prej sëmundjes. Tetë pacientë, prej tyre 7 me intolerancë ndaj aspirinës, i janë nënshtruar 11 ose më shumë ndërhyrjeve kirurgjike gjatë kësaj periudhe. Në një punim tjetër të botuar në Medscape, gjatë periudhës 3 vjeçare të studimit, 53 pacientë janë operuar 1 herë, 26 % janë operuar 2 herë, 12

% 3 herë dhe 9 % më shumë se 3 herë. 20 % të pacientëve kishin rekurencë 1 muaj pas trajtimit kirurgjik. Koha e rekurencës sillej prej 1 muaj deri në 27 vite, me kohë mesatare prej 2.5 vitesh. Në materialin tonë kemi hasur në 94 raste të rekurencës së polipozës nazale ose 16 % prej numrit të gjithmbarshëm të rasteve, prej tyre 88 raste kanë qenë te të rriturit, kurse 6 raste kanë qenë te fëmijët nën moshën 16 vjeçare. Në tabelën 1 shihet shpërndarja e operacioneve të rekurencave të polipozës së hundës sipas viteve. Më së shumti operacione janë kryer gjatë vitit 2006 me 13.83% dhe në vitin 2008 me 11.70% ndërsa më së paku në vitin 2000 me 2.13%. Në tabelën 2 shihet se sipas gjinisë në tërësi operacionet e rekurencave të polipozës së hundës kanë qenë më të shpeshta tek pacientët e gjinisë mashkullore me 65.96 % por pa dallim sinjifikant.Për vitet 2006 dhe 2010 operacionet më të shpeshta kanë qenë tek pacientët e gjinisë mashkullore me pjesëmarrje të barabartë prej 15% , përderisa për vitet 2002 dhe 2004 pjesëmarrja ka qenë e barabartë sipas gjinisë dhe pa dallim sinjifikant sipas gjinisë. Për herë të parë të operuar kanë qenë 491 raste , për herë të dytë ose rekurenca e parë janë operuar 49 pacientë, për herë të tretë ose rekurenca e dyte janë operuar 30 pacientë, kurse më shumë se 3 rekurenca kanë qenë 15 raste. Koha e paraqitjes së rekurencës ka variruar prej 2.5 muaj deri në 18 vite. Rekurencat e polipozës së hundës janë paraqitur në tab.3 sipas rradhës së tyre dhe viteve. Numri më i madh i takon rekurencës të parë me 52.13% dhe dallim sinjifikant krahasuar me rekurencën e dytë, tretë, dhe të katërt, ndërsa sipas viteve dhe llojit të rekurencës dallimi nuk është sinjifikant.

Autori Cheng (2007) rekomandon këtë përcjellje ose follow-up:

Dita 1-2: heqje të tamponadës dhe debridement të sinusëve, këshilla për kujdes të pacientit në shtëpi, përdorim të yndyrnave lokale; Dita 4-5: inspektim dhe debridement për sigurim të kurimit të duhur; Dita 10: inspektim, debridement, fillim të mjekimit me inhaler steroid; Pas 2-3 javësh: inspektim, debridement për sigurim të kurimit komplet të mukozës nazale dhe të sinusëve; Pas 5-6 javësh: inspektim, follow-up rutinor, kujdes mjekësor. Pas 3 muajsh: e njëjtë. Pas protokolit të sipërm, follow-up në intervale 4-6 muajsh duhet të jetë i mjaftueshëm. Këto udhëzime mund të individualizohen varësisht nga progresi klinik i pacientit. Në Klinikën tonë e kemi pothuajse të njëjtën metodë të përcjelljes postoperative të pacientëve.

KONKLUZIONET

Përdorimi i FESS – it rekomandohet për të gjitha ndërhyrjet kirurgjike për trajtimin e polipozës nazale dhe sinuseve paranazalë;

Pacientët me polipozë të hundës duhet të jenë të njohtuar për shkallën e lartë të përsëritjes së sëmundjes;

Ndërhyrja kirurgjike duhet të shoqërohet me kontrolla në intervale kohore të caktuara në çdo 3 muaj, 6 muaj dhe 9 muaj;

Rekomandohet dhënia e kortikosteroideve dy javë pas ndërhyrjes kirurgjike, me qëllim të parandalimit të paraqitjes së rekurencave;

LITERATURA

1. Wright J. History of laryngology and rhinology. St Louis: Lea and Febiger, 1893; 57-9
2. Bateman N, Fahy C, Woolford TJ. Nasal polyps: still more questions than answers. J Laryngol Otol 2003; 117: 1-9.
3. Larsen P, Tos M. Origin of nasal polyps: an endoscopic autopsy study. Laryngoscope 2004; 114: 710-9.
4. Newton JR, Ah-See KW. A review of nasal polyposis. Ther Clin Risk Manag 2008; 4: 507-12.
5. Xu G, Xia JH, Zhou H, Yu CZ, Zhang Y, Zuo KJ, et al. Interleukin-6 is essential for Staphylococcal exotoxin B-induced T regulatory cell insufficiency in nasal polyps. Clin Exp Allergy 2009; 39: 829-37.
6. Becker SS. Surgical management of polyps in the treatment of nasal airway obstruction. Otolaryngol Clin North Am 2009; 42: 377-85.
7. Karakus MF, Ozcan KM, Ozcan M, Yuksel Y, Titiz A, Unal A. Changes in indications for endoscopic sinonasal surgery over 14 years. B-ENT 2008; 4: 221-5.
8. Stjärne P, Olsson P, Alenius M. Use of mometasone furoate to prevent polyp relapse after endoscopic sinus surgery. Arch Otolaryngol Head Neck Surg 2009; 135: 296-302.
9. Wynn R, Har-El G. Recurrence rates after endoscopic sinus surgery for massive sinus polyposis. Laryngoscope. 2004;114:811-813.

RECURRENCES OF THE NASAL POLYPOSIS

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ABSTRACT

Objective: To assess the rate of recurrence of nasal polyps in operated patients.

Methods: A retrospective study was conducted on 585 patients operated for nasal polyps in a hospital set-up between 2000 and 2010. The median follow-up period was 24 months (range 12 months to 50 months).

Results: During the study period, recurrences developed in 94 patients, with a rate of 16%.

Conclusion: Patients presenting with extensive disease suggested by C.T scan staging and patients associated with asthma and verified allergy are at higher risk for the development of recurrences after surgery for nasal polyps.

Key words: Nasal polyposis, recurrence of nasal polyposis, risk factors of recurrence

DO THE CHILDREN WHO UNDERWENT CARDIAC SURGERY FOR CONGENITAL HEART DISEASE HAVE FEEDING DIFICULTIES – KOSOVO

EXPERIENCE A KANË ÇRREGULLIME NË USHQIM FËMIJËT TË CILET IU NËNSHTRUAN INTERVENIMIT KARDIOKIRURGJIK - PËRVOJA NË KOSOVË

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ABSTRACT

Objective is assessing the prevalence and predictors factors of feedings difficulties in children who underwent cardiac open heart surgery in neonatal period and infancy. We address selected nutritional and caloric requirements for children after cardiac surgery and explore nutritional interdependence with other system functions.

Methods This was a retrospective study in a tertiary referral hospital, and prior approval from the institutional ethics committee was obtained. Information for 78 children (42 male and 36 female) was taken from patients charts. The presence of feeding difficulties or disorders was assessed by a questionnaire when the child was 3 years old. As a feeding disorder was defined as an inadequate food intake for age, failure of thrive or for few cases need for tube feeding. Data were analysed with descriptive statistics and logistic regression.

Results From cohort of analysed children feeding problems occurred in 23%. At the time of study, refusal to eat or poor appetite was reported as a significant problem in 19 children and subnormal height and/or weight were recorded in 11 children. Early neonatal intervention and reoperation were identified as a risk factors for latter feeding difficulties or inadequate intake. Children with feeding problems also tended to eat less than children without feeding problems. There was a trend towards more feeding problems in patients with chromosomal abnormalities or other associated anomalies.

Conclusion Feeding disorder is often and frequent long-term sequel in children after neonatal or early infancy heart surgery. Patients with chromosomal and associated anomalies who underwent multiple cardiac surgeries are at risk of developing feeding difficulties.

Key words: congenital heart defect, neonatal cardiac surgery, feeding problems, chromosomal abnormalities

What is known?

1. Children with congenital heart disease have problems with feeding caused by heart insufficiency
2. Patients with chromosomal and associated heart disease are at risk with feeding problems.

What is new?

1. Patients with complex congenital heart disease and chromosomal anomalies who underwent multiple cardiac surgeries are at risk of developing feeding difficulties.

2. As a lack of paediatric cardiac surgeries in Kosovo, children with congenital heart disease have been surgically treated in many European and North American centres.

INTRODUCTION

A feeding disorder in infancy and during childhood is a complex condition involving different symptoms such as food refusal and faddiness, both leading to a decreased food intake. It often results from abnormal feeding development. Also, adequate nutrition is crucial and challenge in children after surgery for congenital heart disease. There is a worldwide reason for attention to lesion or specific feeding problems, supplementation of trace elements and minerals, and an organized approach to pace, timing, and type of feeding are beneficial. These patients need to be selected for preventive strategies and nutritional intervention should be offered in order to increase the caloric intake of the child and to develop a sound feeding relationship in the family.

Babies with congenital heart disease often need more calories per day than babies with normal hearts, particularly if they are struggling with symptoms of congestive heart failure. Feeding can be challenging for a number of reasons, so parents and other caregivers often work closely with the baby's healthcare team to make sure the baby is getting enough calories to gain weight and grow.[1,2]

Adequate enteral nutrition may be difficult to achieve early in neonates after cardiac surgery, but it is essential for growth, wound healing, and immune function. Feeding difficulties in infancy and childhood is a complex condition involving different symptoms, such as food refusal or inadequate intake leading to a decreased food intake and malnutrition. Child's feeding development is determined by its constitution, the environment and the child's learning process.[3,4] Pathology in one or more of these components can lead to a feeding disorder. Factors of constitutional origin can be organic diseases, such as disease of organs directly related to food intake or transport, or diseases of other organ systems that disturb the child's feeding and digestion process by impacting on its general health.[5] The child's environment is defined by the parent's behaviour and the family's cultural and social background. Some children start with a purely organic problem, that is, constitutional or mixture of organic and non-organic components. Any imbalance between parental expectations and the child's feeding progress could cause an interaction problem, generating feeding disorders, such as food refusal, avoidance of aversion, on the part of the child. In most patients with feeding disorders, there are a combination of different factors that give rise to the disorder.[5,6,7]

Recent advances in cardiac surgery techniques and progress in the pre- and postoperative care of new-borns and low weighing children have substantially improved the survival of infants with CHD.[4,8] This trend is creating a growing "population at risk" for neurodevelopmental and behavioural problems as well as for the developing of feeding disorders. However feeding disorders tend to be increasingly common, since advances in technology are allowing more very ill children to survive.

Early identification of deficient oropharyngeal motor skills and vocal cord dysfunction is crucial to establish enteral nutrition safely and has been demonstrated to improve clinical outcomes. The use of prealbumin as a marker of nutritional state should be accompanied by C-reactive protein given the influence of inflammation on its levels. Insulin infusions may improve outcomes in patients with postoperative hyperglycaemia. Trace element abnormalities and early identification of immune-compromised states can aid in reducing morbidity in children after cardiac surgery. Use of feeding protocols and a home surveillance system for hypoplastic left heart syndrome improves outcomes of those children.[4,5,9]

The aim of this retrospective study was to describe the prevalence of feeding disorders in infancy and children after open heart surgery. The study included 78 children undergoing open heart surgery for congenital heart defects in neonatal period and infancy between 2005 and 2010. Study group included patients which had survived more than three years after surgery; all patients who did not survive the first 3 years of life after surgery were eliminated from the study.

Study was designed collecting data from medical records of cardiological diagnosis, reports from surgery intervention and outpatient correspondence as well as fellow and assessment 3 years after surgery from paediatrics cardiologist at tertiary level. In the lack of cardiosurgical services in Kosovo all children were sent abroad for surgery. Cardiological diagnosis from the local cardiologist were compared with diagnosis at the centre where the surgery was done and there we found full compliance. Differently from the other centres which used 2 years for reassess the feeding behaviour, we have chosen the period of 3 years as a reason that few children have been sent abroad under treatment with Prostaglandins where possibility for developing neurological consequences are much higher. Otherwise,

the period of 2 years is taken from more centres in the world as the ideal period to reassess feeding behaviour and only severe and relevant feeding disorders persist until that age and because the prevalence of the feeding disorders in the normal population has been well defined at the age of 2 years.[7,10,11]

Analysed data included pre-operative data: birth weight, type of congenital heart disease, associated anomalies and syndromes, need for giving Prostaglandins and long term of treating, based on the type of CH. The Cardiac surgery data included: the centre where the surgery was done, the type of surgery, the duration of extra-corporal circulation or the duration of the operation in off bypass operations. Post-operative data included: duration of the mechanical ventilation, total hospital stay, in-hospital feeding parameters which included the duration of tube feeding, the onset of oral food intake, and whether the child was referred to the speech pathologist on account of severe difficulties in swallowing or sucking. In the post-operative data we also have attached neurological findings documented during the routine neurological examination after the operation were labelled as neurologic abnormalities.

To simplify data of cardiac disease included in study all these were divided into two groups based on cardiological findings before the surgery and on the intra-cardiac morphology during the surgery: Group 1: "simple cardiac disease" in which an complete anatomical repair is possible by one intervention. Group 2: "complex congenital disease" in which are necessary two or three cardiac intervention to achieve on anatomical or physiological repair. Most patients of the Group 2 underwent two interventions and whereas few of them are preparing for third-stage of palliation.

Based on the age of children when they underwent surgery all patients are divided into three groups:

Group 1: Children underwent complete cardiac surgery on the neonatal period;

Group 2: Children where the first surgery was in neonatal period and the second was in infancy;

Group 3: Patients where cardiac surgery was done at the infancy period.

The questionnaire was designed to obtain information for quality and quantity of the nutrition, on feeding behaviour and food intake, whether it was appropriate for the age of 3 years old. The questionnaire include also body weight gain, needs for artificial feeding, present of gastro-oesophageal reflux and frequent respiratory infection (aspirate pneumonia).

Feeding disorder was defined as the presence of one or more of the following criteria at the age of 3 years, based on the information given from care provider.

Group 1: Child is partially or completely dependent on tube feeding;

Group 2: Feeding is not adequate for age and mostly is based on the drink or takes pureed food;

Group 3: Child manifests delays in obtaining foods, there is a failure of thrive, the body weight is under third percentile, child manifests anaemia etc.

In the absence of cardiac surgery services in Kosovo all children were sent abroad. Based on the country where surgery was done all children can be divided in four groups:

Group 1: Italy (mostly Genoa, few of them in Bergamo, Padua, Bologna and Verona) – 54/78 (69 %);

Group 2: Albania – 12/78 (15.4 %)
Group 3: Turkey - 6/78 (7.7 %)
Group 4: Other countries 6/78 (7.7 %)

STATISTICAL ANALYSIS

Data were analysed using the SPSS 15.0 for Windows statistical software. We analysed continuous variables which are expressed as the median (range) and dichotomous variables as numbers and percentage. Multivariate logistic regression analysis was performed to determine the independent influence of risk factors on abnormal feeding problems. Univariate analyses were performed using the chi square test or Mann – Whitney U-test. Also Spearman's correlation coefficient were calculated to determine the correlation between different risk factors.

RESULTS

The study group consisted of 78 patients. Median birth weight was 3.35 kilograms, with a range from 2.8 to 4.6, median gestational period was 39 weeks (range from 32 to 41 weeks). The patients underwent surgery for CHD at a median age of 16 days, ranging from 8 to 27 days (Group 1), 18 days, ranging from 12 to 31 days (Group 2) and 5 month and 16 days, ranging from three month and 22 days to 7 months and 12 days (Group 3). Clinical signs of heart failure were presented in 43/78 (55 %) patients. Open heart surgery with the use of cardiopulmonary bypass was performed in 62 patients (79 %). The most frequent surgery was resection of the aortic coarctation 21/78 (27 %), large ventricular septa defect 17/78 (22 %) and arterial switch operation for transposition of the great arteries

13/78 (16.6 %). Malformations syndromes were present in 11/78 (14 %) children. (Table 1 and 2)

Initially, feeding through the nasogastric tube was in 43/78 (55 %) children (all neonates and 6 infancies). After 3 years feeding through the nasogastric tube continued only in 3 patients. The remaining patients obtained a nasogastric tube on introduction of the anaesthesia as a routine procedure to start early feeding within the first few post-operative days. None of them needed gastroscopic tube.

Table 1. Type of congenital heart defect, number of patients and percentage

	N	%
Aortic coarctation	21	27
Ventricular septal defect	17	22
Transposition of the great arteries	13	16.6
Tetralogy of Fallot	8	10
Complete atrioventricular canal	6	7.7
Pulmonary atresia with ventricular septal defect	5	6
Total anomalous pulmonary venous return	4	5
Double outlet right ventricle	3	3.8
Double inlet left ventricle	1	1.3

Table 2. Patients with malformations syndromes and with normal feeding, feeding disorders (FD) and neurological abnormalities (NA).

	Normal	FD	NA
Trisomy 21	2	2	4
Microdeletion 22q11	2	1	0
Turner syndrome	2	0	0
Unclassified dysmorphy syndrome	0	1	1

Feeding status after 3 years

From the study group of 78 children, 9 patients (11.5 %) were diagnosed with feeding disorders. There was noted a strong relationship between the type of the surgery, duration of mechanical ventilation, age at the surgery, duration of perioperative tube feeding and centre where surgery was done (all $R > 0.8$, $p > 0.01$). Patients which undergo complex surgery (univentricular heart palliation, double outlet right ventricle), with small age at the time of surgery, and longer ventilation were more frequent in the group with abnormal feeding compared with those with normal feeding behaviour. Also patients with malformations syndromes manifested higher rate of neurological and feeding difficulties. The multivariate logistic regression analysis included the variables that were significant in the univariate analysis since there was a very high correlation between the three variables: type of CHD, age at operation and reoperation of the univentricular heart.

DISCUSSION

Retrospective analysis of the data of children underwent open heart surgery shows that feeding disorders are a relevant problem on this population. This study has not included all aspects of energy balance as we have not attempt to assess time spent and energy expended in activity, thermogenesis, or other non-resting metabolism. Using a similar definition of feeding problems and age of children at the time of study, the prevalence of severe feeding problems is much higher in population of children who underwent open heart surgery (23%) in compare with healthy children (1.42%).[4,6,12] This prevalence is almost as frequent and in correlation with age at the time of cardiac surgery and type-complexity of CHD. Cardiac diseases are a significant constitutional factor which contributes to the development diseases in other organs and systems including a secondary feeding difficulties. Simultaneously, our study shows that at the age of 3 years feeding difficulties were not depended from birth and gestational age, haemodynamics status pre and postoperatively but the greatest impact on the development of feeding disorders have general medical condition such are: age of children who go through the surgery, duration of the medical ventilation and type of surgery, reoperation. Since these three variables were strongly interrelated, only early feeding disorders and multiple surgeries remained significantly associated with feeding problems at age of three years in the multivariate regression analysis.

Besides other relevant influences on the development of feeding disorders in our study significant implication has a fact that children are treated in several different Europeans Centres, mostly in Italian's, and in some of cases cardiovascular system were affected as a consequence of that some are children have been longer treated by Prostaglandins (one 38 and the other one 36 days). From this we can conclude that severe and long hypoxemia, caused by the primary disease and long-term Prostaglandin therapy, are crucial for developing neurological and feeding abnormalities.

There was a high variability of the cardiac diagnoses in our study group. We found that univentricular repair was associated with a higher risk of feeding and neurological disorders in compare with simplex and at once corrected anomalies. This can be explained by the various degree of intracardiac mixing and volume overload, various degree

and duration of hypoxemia which is present in children with univentricular heart. These children often require palliative surgery within the first few days of life, followed by at least two other open-heart surgeries.

In our study the group the type of malformation syndromes was heterogeneous. It is known that not all syndromes are associated with feeding disorders; in our study in patients with trisomy 21 and those with microdeletion 22q11, the prevalence of feeding disorders is high, whereas in Turner's syndrome the prevalence is not present. The presence of feeding disorders in children with chromosomal and malformations syndromes is reported to be higher than in children without such syndromes due to the associated developmental delay, oral malformation and neurological comorbidity. In most children with malformation syndromes, several of the above-listed risk factors co-occur, which increases the probability of the manifestation and persistence of a feeding disorder.[13,14]

There is considerable inter-individual variability in the manifestation of feeding disorders within one and the same syndrome category. In our study group children with chromosomal abnormalities had a higher prevalence of abnormal feeding development at the age of 3 years. Also, the effect of malformation syndrome on latter feeding difficulties can be mediated by other risk factors such as more complex cardiac disease and neurological comorbidity. The association between neurological disorders and feeding problems is a well-known phenomenon.[8,15] Neurological abnormalities such as muscular hypotonia are frequent in children with congenital heart disease and are often diagnosed before cardiac surgery.[13,15] Among those neurobehavioral abnormalities there was also an absent suck or poor feeding efficiency. In our study we found that neurological abnormalities at the time of surgery were associated with abnormal feeding behaviour at 3 years of age. This association persist after correction for other factors: children with neurological abnormalities were six time more likely to manifest later feeding disorders than those without neurological problems. Thus, confirmed neurological abnormalities before the surgery can contribute to the development of feeding disorders as an independent risk factor.

CONCLUSION

Babies with congenital heart disease often need more calories per day than babies with normal hearts, particularly if they are struggling with symptoms of congestive heart failure. Feeding can be challenging for a number of reasons, so parents and other caregivers often work closely with the baby's healthcare team to make sure the baby is getting enough calories to gain weight and grow. Simultaneously, children who require cardiac surgery in neonatal period and early infancy are at increasing risk of developing a feeding disorder at 3 years of age. This is a result of a complex multi-factorial process. Independent risk-factors include severity of CHD, age of child who goes through the surgery, type of operation and re-operation, duration of mechanical ventilation, previously diagnosed neurological abnormalities and presence of malformations syndromes. These factors provide key evidence as to which children need to be referred to multidisciplinary team who will care for elimination or minimization of feeding problems on these sensitive categories. Whenever feeding problems are reported, nutritional intervention should be offered in order to increase the caloric intake of the child and to develop a sound feeding relationship in the family.

REFERENCES

1. Thommessen M, Heiberg A, Kase BF. Feeding problems in children with congenital heart disease: the impact on energy intake and growth outcome. Eur J Clin Nutr. 1992;46:457-64.
2. Moller JH, Taubert KA, Allen HD, et al; Cardiovascular health and disease in children: current status. A Special Writing Group from the Task Force on Children and Youth, American Heart Association. Circulation. 1994;89:923-30.
3. Perloff JK, Warnes CA; Challenges posed by adults with repaired congenital heart disease. Circulation. 2001;103:2637-43.
4. Lipsitt LP, Crook C, Booth CA. The transitional infant: behavioural development and feeding. Am J Clin Nutr 1985;41:485 – 496.
5. Deller SF, Hyams JS, Treem WR et al Feeding resistance and gastroesophageal reflux in infancy. J Pediatr Gastroenetrol Nutr 1993;17:66 – 71.
6. Reilly S, Skuse D, Poblete X. Prevalence of feeding problems and oral motor dysfunction in children with cerebral palsy: a community survey. J Pediatr 1996;129:877 – 882.
7. Dahl M, Sundelin C, Early feeding problems in affluent society. I. Categories and clinical signs. Acta Pediatr Scand 1986;75:370 – 379.
8. Ilona M, Beatrice L, Hilda G et all. Prevalence and predictors factors of letter feeding disorders in children who underwent neonatal cardiac surgery for congenital

heart disease, Card in the Young, 2011;21:303 – 309.
9. Bejiqi R, Retkoceri R, Zeka N, et all. Treatment of children with protein - losing enteropathy after Fontan and other complex congenital heart disease procedures in condition with limited human and technical resources. Mater Sociomed. 2014;26:39-42.
10. Dahl M, Eklund G, Sundelin C. Early feeding problems in an affluent society. II. Determinants. Acta Pediatr scand 1986;75:380 – 387.
11. Dahl M. Early feeding problems in an affluent society. III. Follow-up at two years: natural course, health behaviour and development. Acta Pediatr Scand 1987;76:872– 882.
12. Stein A. Barnes J. Feeding and sleep disorders. In: Rutter M (ed) Child and Adolescent Psychiatry, 4th edn. Blackwell Science, Oxford, 2002; 754 – 775.
13. Morris CD, Maneshe VD. 25 year mortality after surgical repair of congenital heart defect in childhood. A population based study. JAMA 1991;266:3447 – 3452.
14. Boneva RS, Botto LD, Moore CA et al. Mortality associated with congenital heart defects in the United States. Trends and racial disparities 1979 – 1997. Circulation 2000; 103: 2376 – 2381.
15. Limperopolous C, Majnemer A, Shevell MI, et al. Neurodevelopmental status of new-borns and infants with congenital heart defects before and after open heart surgery. J Pediatr 2000; 137:638 – 645.

A KANË ÇRREGULLIME NË USHQIM FËMIJËT TË CILET IU NËNSHTRUAN INTERVENIMIT KARDIOKIRURGJIK - PËRVOJA NË KOSOVË

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ABSTRAKT

Qellimi i punimit është vlerësimi i prevalencës dhe faktorëve parashikues për vështirësitë në ushqimin e fëmijëve të cilët iu nënshtruan operacionit të hapur në zemër në moshën neonatale dhe foshnjëri. Në këtë drejtim janë vlerësuar nevojat ushqyese tek fëmijët pas operacionit kardiak, ndikimin dhe efektet ndërvarëse ushqyese me funksionet tjera të oragnizmit tek fëmija kardiopat.

Metodologjia Studimi është retrospektiv dhe është kryer në Qendër të nivelit terciar, me miratimin paraprak nga Komiteti Etik. Në studim janë përfshirë 78 fëmijë (42 meshkuj dhe 36 femra); të dhënat janë marr nga dokumentacioni me të cilin posedojmë për këta fëmijë. Prania e shenjave klinike e vështirësive dhe çrregullimeve në ushqyerje është vlerësuar me një pyetësor deri në moshën 3 vjeçare. Si çrregullim i të ushqyerit është marre pamjaftueshmëria e të ushqyerit për moshë, dështimi në gëlltitje ose, për disa raste, nevoja e të ushqyerit me tub. Të dhënat janë analizuar dhe përpunuar në mënyrë statistikore dhe me anen e regresionit logjistik.

Rezultatet Nga grupi i fëmijëve në studim probleme në të ushqyerit janë regjistruar në 23% të fëmijëve. Refuzimi për të ngrënë ose oreks i dobësuar është regjistruar si problem i rëndësishëm në 19 fëmijë kurse gajtësia trupore dhe/ose pesha nën vlera për moshë është regjistruar tek 11 fëmijë. Ndërhyrja e hershme kardiokirurgjike në moshën neonatale ose rioperimi është identifikuar si faktor i rrezikut për vështirësitë e të ushqyerit ose marrjes së pamjaftueshme të ushqimit. Është regjistruar një trend i rritur për pengesa ne ushqim tek fëmijët me çrregullime kromozomale apo me anomali shoqëruese.

Përfundim Çregullimet në ushqim janë të shpeshta dhe me sekuela të rënda tek fëmijët pas intervenimeve kardiokirurgjike në moshën e hershme neonatale ose në moshën e foshnjërisë. Në rrezik jane posaqërisht fëmijët me ndryshime kromozomale ose ata më anomali tjera shoqëruese.

Fjalët kyçe: anomalitë e lindura të zemrës, kardiokirurgjia neonatale, problemet e të ushqyerit, anomalitë kromozomale

Review

S100B EARLY BIOCHEMICAL MARKER FOR BRAIN INJURY AT CHILDREN

С100Б РАН БИОХЕМИСКИ МАРКЕР ЗА МОЗОЧНА ПОВРЕДА КАЈ ДЕЦА

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ABSTRACT

Birth asphyxia results in a significant percentage of neonatal morbidity and mortality. A key factor in the management of this complication is the early and accurate detection of brain damage following asphyxia. The identification of early noninvasive biochemical markers of disease is a crucial issue of the current scientific research, particularly during the first period of life, since it could provide useful and precocious diagnostic information when clinical and radiological signs are still silent. The ideal biomarker should be practical and sensitive in the precocious identification of at risk patients. Brain damage and sepsis are common causes of severe morbidity with poor outcome and mortality during the perinatal period. The measurement of brain constituents, such as S100B protein, may be an alternative and a direct indicator of cell damage in the central nervous system when clinical and laboratory results remain unclear to the end. The purpose of this research is to determine the kinetics of S100B protein in the biological fluids at an early stage of a circulatory disorder. This will make possible the monitoring of certain events even at the earliest stage of a brain damage, such as neurodegenerative diseases, cerebral tumors, cerebral traumas and cerebral diseases. Measuring blood levels of this protein as a marker for brain trauma is the easiest and most widely used in laboratories worldwide.

Key words: S100B protein, brain-specific biological marker, hypoxic-ischemic encephalopathy, cerebral hemorrhage, asphyxia

INTRODUCTION

Biomarkers are molecules released by or specific to a particular organ, can give a glimpse into the physiologic or pathologic status of that specific organ Biomarkers can be obtained from the blood, urine, cerebrospinal fluid (CSF), or any other bodily fluid. In neonates with brain injury, biomarkers may be able to predict the degree and location of injury shortly after the injury occurs (1). The use of noninvasive laboratory biomarkers has become a key element in clinical practice throughout the last decades. The research of new biological markers enabling a precocious identification of neonates at risk of neonatal diseases, allowing a close monitoring of the disease and providing information about prognosis, represents a strategic objective of several current researches (1,2). A "biomarker" is a characteristic which is objectively measured and evaluated as an indicator of physiologic biological processes, pathogenic processes, or pharmacologic responses to a therapeutic treatment. The development of a biological marker starts with the discovery and identification of a new biomarker, is followed by a close evaluation of its accuracy, and, thereafter, evaluates the impact of the marker on clinical outcomes(3,4). Therefore, the identification of early biochemical markers of disease is a crucial issue of the current scientific research, since it could provide useful and precocious diagnostic information when clinical

and radiological signs are still silent. Extensive research has focused on biomarkers in an attempt to solve this matter (5,6,7). Recent data marked serum elevation of the S100B protein as an established peripheral biomarker for detection of brain injury including traumatic head injuries and brain damage following cardiac arrest and stroke. In the past decade, a substantial number of studies illustrated the potential use of S100B testing in order to detect brain damage in asphyxiated newborns.(8,9). This review summarizes the available data regarding the use of S100B as a biomarker of brain damage following birth asphyxia.

MATERIAL AND METHODS

32 patients from Intensive Care Unit of the University Children Hospital from the time 2014-2017 year. The patients were asphyxiated full-term neonates, with HIE gr.1, 2 or 3 according to SarnatSarnat classification, with an Apgar score below 5, with or without the need for mechanical ventilation. A serum blood sample was obtained from each patient at 24h after admission: 4th and 7th S100B levels were measured using ECLIA (Electro-Chemi-Luminiscence Immuno Assay) method. We analysed neonates with chronic brain injyry due to intrapartum suffering of the brain according to S100B protein.Asphyxiated full-term neonates were supposed to meet the criteria of the International Classification of Diseases, and the World Health Organization, Revision 10. In the first minute the Apgar score ranges from 0 – 3, with a need for resuscitation (severe asphyxia), or in the first minute the Apgar score ranges from 4 to 7 (intermediate asphyxia), with or without the need for mechanical ventilation.

RESULTS

Differences in the three measurements of S100B protein in the group of asphyxiated full-term neonates

As the results in the first two measurements do not meet the criteria for ANOVA for PM, the Friedman test is used instead.

Table 1. Tabular representation of the results of the Friedman test

Measurement	N	Arithmetic mean	Standard deviation (SD)	Min	Max	Mean rank
Day 1	32	0,642	0,352	0,100	1,350	1,40
Day 4	32	0,680	0,414	0,090	1,900	2,07
Day 7	32	1,078	1,001	0,020	4,300	2,53

The value of the Friedman test is $\chi 2$ (2; N = 32) = 19.33, $p < 0.001$, which indicates that there is a significant difference between the three measurements.

Table 2. Tabular representation of the results from theWilcoxon test

Values for the Wilcoxon test	Day 4 – Day 1	Day 7 – Day 4	Day 7 – Day 1
Z Asymp. Sig. (2-tailed)	-1.983(a) 0.047	-2.881(a) 0.004	-3.179(a) 0.001

a Based on negative ranks
b Wilcoxon Signed Ranks Test

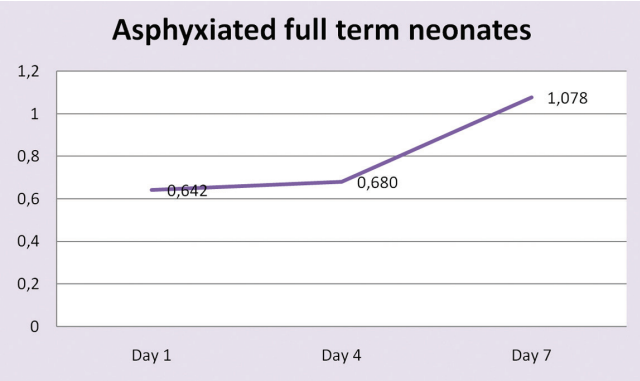

Chart 1. Average values of S100B protein in asphyxiated full-term neonates

The Wilcoxon test shows a significant difference in the values of S100B protein in asphyxiated full-term neonates between Day 1 and Day 4 (on level 0.05, where the value is greater on Day 4), between Day 7 and Day 4 (on level 0.005, where the value is greater on Day 7) and between Day 7 and Day 1 (on level 0.001, where the value is greater on Day 7).

Results of the average values of S100B protein in all measurements as a function of mechanical ventilation in the subgroup of asphyxiated fullterm neonates

Table 3. S100B protein in the subgroup of asphyxiated full-term neonates on mechanical ventilation

Measurement	N	Arithmetic	Standard devidation (SD)	Min	Max	Main rank
Day 1	3	1,733	1,086	0,990	2,980	1,67
Day 4	3	1,620	1,504	0,220	3,210	2,00
Day 7	3	1,890	1,904	0,300	4,000	2,33

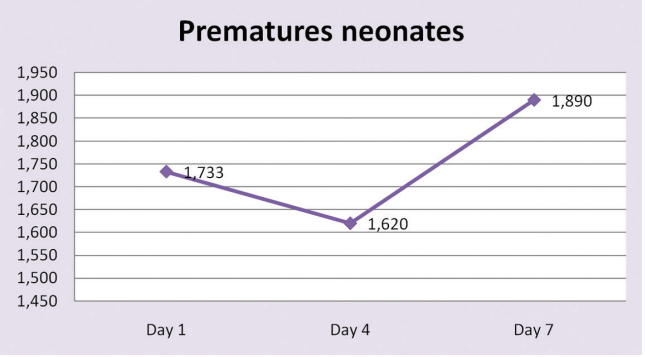

Chart 2. Average values of S100B protein in all measurements in the subgroup of asphyxiated full-term neonates with and without mechanical ventilation

The multivariate analysis of variance was conducted in order to assess whether there is a difference between the subgroup of asphyxiated full-term neonates that are on mechanical ventilation and the subgroup of asphyxiated full-term neonates that are not on mechanical ventilation, on a linear combination of the average S100B protein in all three measurements. The value of the Pillai's Trace test is statistically significant: Pillai's Trace = 0.314, $F(3, 25) = 3.808$, $p = 0.022$, $\eta 2 = 0.314$ and shows that there are statistically significant differences in the three measurements with higher values of S100B protein in the children without mechanical ventilation.

DISCUSSION

Hypoxic-ischemic encephalopathy (HIE) is a condition with a huge impact on the newborn. As a result of perinatal asphyxia, several organs could be affected, and there is a possibility for development of certain conditions such as cerebral palsy, epilepsy and mental retardation (10, 11). Its clinical signs are the progressive involvement of neurological functions, which also includes a breathing problem, a reflexes disorder, a change in consciousness and convulsions. According to the literature, the incidence of HIE varies from 0.1-0.4% of births (12,13). The central nervous system reacts differently depending on the gestational age, the type of injury and treatment. Premature neonates are known to have deeper periventricular injuries, in comparison with the full-term neonates whose injuries are located in the cortico-subcortical area (14, 15). Depending on a complex biochemical cascade, different forms of neuronal death can occur. Several changes in anaerobic metabolism occur in the event of a decrease in blood-brain circulation, such as glycolysis, elevated concentrations of inorganic phosphates and lactates (16, 17). What is crucial is the brain's ability for autoregulation, which is maintained by the cerebral flow that should be stable with regard to the changes in the cerebral perfusion pressure by adjusting the cerebral vascular resistance. As a key protective mechanism, the autoregulation function protects the brain from ischemia and hypoxia during hypotension or from hemorrhage and edema during hypertension. On the one hand, in the stage of reduction of the cerebral flow, autoregulation depends on the ability of the cerebral circulation for vasodilatation. On the other hand, the high level of neural activity requires a high level of basal circulatory flow (18). Unwanted neurological complications in newborns with hypoxic-ischemic encephalopathy (HIE) are strongly associated with poor cerebral perfusion in the first hours after birth (van Bel et al. 1993), which increases the possibility of exacerbation of the brain injury (Osborn et al. 2003). Similarly, it has been shown that after the initial recovery and restoration of the cerebral blood flow, there is a transient secondary fall in cerebral pressure, and this has been confirmed in numerous experimental studies (Conger & Weil, 1995).

Its duration and speed correlate with the severity of the brain injury (Karlsson et al. 1994; Huang et al. 1999). The importance of this delayed hypoperfusion lies in the fact that it occurs because of the unrepaired primary damage to the endothelial tissue, thus extending the primary ischemic brain injury (Hossmann, 1997; Ten & Pinsky 2002). At the same time, it reflects the decreased metabolic demand, oxygenation and activation of certain mediators (Michenfelder & Milde, 1990; Gold & Lauritzen, 2002). However, in certain areas of the brain tissue there is an increase in oxygen consumption and a decrease in the cerebral metabolism as a result of the reduced cerebral pressure that initiates lipid peroxidation, which is suggestive of severe oxidative stress. In this context, an experiment on sheep demonstrated that abruption of the carotid artery results in a fall in blood pressure after 30 min., but it is gradually restored after 6 hours (19,20). In the same study it is described that in full-term sheep, the return of the cerebral pressure, after primary damage, occurs after 12 hours, while in pre-term sheep in the first few hours. This depends on the differences in maturation and severity of the insult.Based on previously published results, there is evidence that oxygen consumption is reduced during secondary hypoperfusion following asphyxia or ischemia in newborn and fetal sheep (Rosenberg, 1986; Gunn et al. 1997), and there is no change in cerebral oxygen extraction (Gunn et al. 1997).

There is evidence of a significant increase in cytochrome oxidase after 30 minutes of hypoxia and hypercapnia in a newborn sheep, along with reduced oxygen utilization by the brain during this stage (Shadid et al. 1999). This evidence for reduced oxygen utilization is associated with increased cortical local tissue PO2 utilization, which is a real and direct proof of tissue oxygenation during secondary hypoperfusion. These results indicate that in the postasphyctic stage of hypoperfusion cerebral flow is related to the suppressed cerebral metabolism, but it is all regulated under physiological conditions that are characteristic only of the brain, while their real ratio is dependent on the strength and magnitude of neural activity (Thompson et al. 2004). Findings that cortical tPO2 was increased suggest that cerebral flow is not reduced as much as metabolism, which is constant. Additional factors contribute to hypoperfusion, such as the increased activity of the sympathetic nervous system (Quaedackers et al. 2004) or the increased number of free radicals (Rosenberg et al. 1989; Shadid et al. 1998). This mechanism of reduction of the cerebral metabolism after asphyxia is either a passive function of the cerebral hypoxic injury or an active regulatory inhibition which could facilitate the recovery. Potential inhibitory neuromodulators are known to be elevated, including GABA and others (Nguyen et al. 2004). Recent studies give hope that by administering alpha-adrenergic receptor antagonists shortly after asphyxia, secondary hypoperfusion of other affected organs is prevented in the asphyxia in both full-term and preterm fetal sheep. This kind of treatment is also associated with the prevention of early postasphyctic convulsions (Quaedackers et al. 2004). This means that the transient suppression of cerebral metabolism may actively and timely be regulated if detected at an early stage, thus protecting the brain from further damage. All these mechanisms are mentioned in favour of the introduction of a possible biological marker that can provide longitudinal and early information on adverse events in the brain. In asphyxiated full-term neonates, the early increase in S100B protein was found to be predictive of HIE and subsequent adverse neurologic outcomes (20,21). As it is known that the ischemia-reperfusion injury is pathophysiologically a major complication in newborns, the increased blood value of S100B protein has been indicated as an index of brain injury in patients undergoing surgical procedures (22) and premature neonates with respiratory distress who are subjected to high-frequency ventilation or ECMO - extracorporeal membrane oxygenation (23,24). The next step in brain neuroprotection is the identification of biomarkers that can facilitate clinical decisions. Biomarkers will help clinicians identify neonates that will respond to hypothermia and those that will need other new neuroprotective interventions. If clinicians are able to stratify patients using biomarkers, neonates will be protected from exposure to unnecessary, ineffective therapies. Furthermore, these same infants may benefit from other specific therapies more tailored to their biological profile. Biomarkers will be a key feature of future neuroprotective trials and will help gage the intervention's short- and long-term efficacy. Based on the results of this research, it was established that the serum level of S100B protein increased significantly on the first day in the subgroup of neonates with asphyxia, which is an early signal of a potential danger of developing cerebral palsy. In addition, serum S100B protein facilitates the early differentiation of the subgroup of premature neonates who display signs of intracranial hemorrhage. The early application of the hypothermia principle, especially on the calvaria, would produce a beneficial effect in these subjects.

CONCLUSION

The discovery of neonatal brain injury biomarkers is a key step in neonatal neuroprotection. Biomarkers may enable the clinician-scientist to screen infants for brain injury, monitor the progression of disease, identify injured brain regions, and assess the efficacy of neuroprotective strategies procedures in clinical trials. In addition, large-scale validation of the potential biomarkers is required, because the potential confounders (especially for biomarkers that are non-organ specific such as inflammatory mediators). Currently, clinicians do not routinely use biomarkers to care for neonates with brain injuries. This review will examine potential biomarkers the bedside clinician-scientist may use to hone the treatment of neonates with hypoxic-ischemic encephalopathy. S100B protein is a good indicator for establishing an onset of brain damage in full-term and premature neonates, especially in the first 24 hours after the delivery, which makes it a good indicator for an early intervention as well. Therefore, S100B protein should be measured immediately after birth, within the first 24 hours, as a biochemical screening marker for fetal distress, and at the same time for HIE in neonates with asphyxia and in premature neonates with CNS hemorrhage.

REFERENCE

1. Gazzolo D, Vinesi P, Geloso MC, Marcelletti CF, Iorio FS, Marianeschi SM, et al. S100 blood concentrations in children subjected to cardiopulmonary by-pass. Clin Chem 1998 ; 44 : 1058 1060.
2. M. Douglas-Escobar and M. D. Weiss, "Biomarkers of brain injury in the premature infant," Front Neurol, vol. 3, article 185, 2013.
3. D. Gazzolo, R. Abella, E. Marinoni et al., "New markers of neonatal neurology," Journal of Maternal-Fetal and Neonatal Medicine, vol. 22, supplement 3, pp. 57–61, 2009.
4. M. Rickmann and J. R. Wolff, "S100 protein expression in subpopulations of neurons of rat brain," Neuroscience, vol. 67, no. 4, pp. 977–991, 1995.
5. Gazzolo D, Vinesi P, Bartocci M, Geloso MC, Bonacci W, Serra G, et al. Elevated S100 blood level as early indicators of intraventricular hemorrhage in premature neonates. Correlation with cerebral Doppler velocimetry. J Neurol Sci 1999; 170:32-35.
6. Gazzolo D, Di Iorio R, Marinoni E, Masetti P, Serra G, Giovannini L, et al. S100B Protein is increased in asphyxiated term neonates developing intraventricular hemorrhage. Crit Care Med 2002;30:1356-1360.
7. Nagdyman N, Komen W, Ko HK, Muller C, Obladen M. Early biochemical indicators of hypoxic-ischemic encephalopathy after birth asphyxia. Pediatr Res 2001;49:502-506.
8. Gazzolo D, Masetti P, Vinesi P, Meli M, Abella R, Marcelletti C, et al. S100B blood levels correlate with rewarming time and cerebral Doppler in pediatric open heart surgery. J Card Surg 2002; in press.
9. Gazzolo D, Masetti P, Meli M, Grutzfeld D, Michetti F. Elevated S100B protein as an early indicator of intracranial haemorrhage in neonates subjected to extracorporeal membrane oxygenation. Acta Paediatr 2002;91:218-221.
10. Volpe JJ. Hypoxic-ischemic encephalopathy: clinical aspects. Volpe JJ eds. Neurology of the neonate1995:314-370 WB Saunders Philadelphia. .
11. Leviton A, Pagano M, Kuban KC, Krishnamoorthy KS, Sullivan KF, Allred EN. The epidemiology of germinal matrix hemorrhage during the first half - day of life. Dev Med Child Neurol 1991;33:138-145.
12. Paneth N, Pinto-Martin J, Gardiner J, Wallenstein S, Katsikiotis V, Hegyi T, et al. Incidence and timing of germinal matrix/intraventricular hemorrhage in low birth weight neonates. Am J Epidemiol 1993;137:1167-1176.
13. Pezzani C, Radvanyi MF, Relier JP, Monod N. Neonatal electroencephalography of the neonate during the first twenty-four hours of life in full-term neonate neonates. Neuropediatrics 1986 ; 17 : 11-1.
14. Rennie JM, South M, Morely CJ. Cerebral blood flow velocity variability in neonates receiving assisted ventilation. Arch Dis Child 1987 ;62:1247-1251. Ilves P, Talvik R, Talvik T. Changes in Doppler ultrasonography in asphyxiated term neonates with hypoxic-ischaemic encephalopathy. Acta Paediatr 1998;87:680-684.
15. Shortland DB, Gibson NA, Levene MI, Archer LN, Eveans DH, Shaw DE. Patent ductus arteriosus and cerebral circulation in premature neonates. Dev Med Child Neurol 1990 ; 32 : 386 393.1. Rufo-Campos M.
16. Palencia - Luaces R. Encefalopatia hipóxico-isquémica del recien nacido a término: recientes avances, marc a d o res de hipoxia y opciones terapêuticas. Rev Neurol 2000;31:617-623.
17. Volpe J. Neurology of theneonate, unit III, 4th edition, chapter 6-9, 2001. 15. Ferriero DM. Neonatal brain injury. N Eng J Med 2004;351:1985-1995. 16. Macaia A. Muerte celular en la hipoxia-isquemia neonatal. RevNeuro l 2000;31:784-789.
18. G rowJ, Barks JDE. Pathogenesis of hypoxic-isquemic cerebral injuryin the term infant: current concepts. Clin Perinatol 2002;29:585-602.
19. Gazzolo D, Bruschettini M, Lituania M, Serra G, Bonacci W, Michetti F. Increased urinary S100B protein as an early indicator of intraventricular hemorrhage in premature neonates: correlation with the grade of hemorrhage. Clin Chem 2001;47:1836-1838.
20. Distefano G, Gurreri R, Betta P, et al. Serial protein S100B serum levels in preterm babies with perinatal asphyxia and periventricular white matter lesions. Am. J. Perinatolog. 2002: 19: 317-22.
21. M. Mussap, A. Noto, F. Cibecchini, and V. Fanos, "The importance of biomarkers in neonatology," Seminars in Fetal and Neonatal Medicine, vol. 18, no. 1, pp. 56–64, 2013.
22. Distefano G, Gurreri R, Betta P, et al. Serial protein S100B serum levels in preterm babies with perinatal asphyxia and periventricular white matter lesions. Am. J. Perinatolog. 2002: 19: 317-22.
23. Schrnechel D, Marangos PJ. Brightman M. Neuron-specific enolase is a molecular marker for peripheral and central neuroendocrine cells. Nature 1978; 276: 834-6.
24. Freeman JM, Nelson KB. Intrapartum asphyxia and cerebral palsy. Pediatrics 1988 ; 82 : 240 249.

С100Б РАН БИОХЕМИСКИ МАРКЕР ЗА МОЗОЧНА ПОВРЕДА КАЈ ДЕЦА

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АБСТРАКТ

Породилната асфиксија резултира со сингнификантен процент на неонатален морбидитет и морталитет. Клучен фактор во понатамошниот третман на оваа компликација е рано и навремено дијагностицирање на мозочно оштетување предизвикано од асфиксија. Идентификацијата на рани неинвазивни биохемиски маркери за болеста се клучно прашања за моменталните научни истражувања, особено во првиот период од животот, кога всушност и е можно да се обезбеди корисна и навремена дијагностичка информација кога клиничките и радиолошките знаци се сеуште латентни. Идеалниот биомаркер треба да биде практичен и сензитивен за навремена идентификација кај ризичните пациенти. Раната дијагноза може да доведе до поголем терапевтски прозорец и да го подобри неонаталниот исход. Мозочното оштетување и сепсата се заеднички причинители на тешки морбидитети со лош исход и морталитет уште во перинатален период. Мерењето на мозочните конституенти, како што е С100Б протеинот, може да биде алтернативен и директен индикатор на клеточно оштетување во централниот нервен систем кога клиничките и лабораториските резултати остануваат нејасни на крај. Целта на оваа истражување е да се утврди кинетиката на С100Б протеин во биолошките течности во раната фаза на циркулаторното пореметување. Оваа ќе овозможи мониторирање на одредени настани дури и при рана фаза на мозочното оштетување, како што се невродегенеративните заболувања, церебрални тумори, церебрални трауми и церебрални заболувања. Мерењата на серумските нивоа на овој протеин како маркер за мозочна траума е најлесен и најшироко користен во лабораториите во светот.

Клучни зборови: С100Б протеин, мозочно-специфичен биолошки маркер, хипоксично-исхемична енцефалопатија, церебрална хеморагија, асфиксија.

ИНТРАВИТРЕАЛНАТА ТЕРАПИЈА КАЈ ДИЈАБЕТИЧЕН МАКУЛАРЕН ЕДЕМ : АКТУЕЛЕН ТРЕТМАН

INTRAVITREAL INJECTIONS AND DIABETIC MACULAR EDEMA: ACTUAL THERAPY

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АБСТРАКТ

Цел: Да се прикаже ефикасноста од актуелната терапија за дијабетичен макуларен едем (DME), како примарна монотерапија преку интравитреалната апликација на Авастин (Bevacizumab), и во комбиниран третман со ласер фотокоагулација.

Вовед: Досега применуваната фокална ласер фотокоагулација останува стандарден третман, но студии ја потврдуваат апликабилноста и значењето од дополнителната терапија за DME, како примената на анти-VEGF препаратите и интравитреалното аплицирање на кортикостероиди, кои ветуваат подобрување, односно стабилизација на видната острина.

Материјал и методи: Ретроспективна, обсервациона, не-компаративна серија со вклучени 51 око со DME, третирани со 0,04 ml/1.25 mg Bevacizumab по принципот "по потреба" (PRN), а сепарирани во одделени групи во зависност од примарниот третман. Пациентите беа анализирани по период од 12 месеци, со направени редовни комплетни офталмолошки анализи.

Резултати: Првата група, само со интравитреална апликација покажа значително подобрување на VA за 0,22 ± 0,1. Во втората група, со комбиниран третман, VA се подобри за 0,17± 0,08; а групата само со ласер, покажа подобрена VA за 0,16±0,04

Во однос на OCT анализите, во првата група има намалување на централната макуларна дебелина (CMT) за 82,69 μm, по примени 3,42 инекции во просек. Во групата со комбиниран третман, со во просек по една ласер фотокоагулација и примени 3,52 инјекции намалувањето изнесува 123,73 μm, а кај третата група, пациенти само на ласер има намалување за 1,71 μm.

Заклучок: Интравитреалната апликација на Bevacizumab е ефикасен третман во подобрувањето на видната острина кај пациентите со DME, но придобивките се ограничени, во времетраење во одреден временски интервал.

Комбинираниот третман резултираше со значително намалување на потребата за интравитреална апликација на инјекции потребни за регресија на едемот.

Клучни зборови: Дијабетичен макуларен едем (DME), Bevacizumab (Авастин), Оптичка кохерентна томографија (OCT), Ласер фотокоагулација (LFC), Централна макуларна дебелина (CMT), видна острина (VA).

ВОВЕД

Дијабетес мелитус (DM) е хронично заболување со ефект на различни целни органи, вклучувајќи ја и мрежницата.

Дијабетична ретинопатија се јавува речиси кај сите индивидуи со долготраен дијабет. По 20 години боледување, 60% од лицата со тип 2 дијабет и речиси

100% од лицата со тип 1 ќе манифестираат некој облик на ретинопатија. (1)(2)

Неквалитетната контрола на шеќерот во крвта го зголемува ризикот од дијабетичната ретинопатија и дијабетичната нефропатија. (3) Системската хипертензија е фактор на ризик за развој на двата вида дијабетична ретинопатија и дијабетичен макуларен едем, а хиперлипидемијата го зголемува ризикот од протекување на ретиналните крвни садови и појава на ексудативни депозити во макулата. (4)

Имено вкупната преваленца изнесува 34,6% за било кој облик на ДР, 7,0% за пролиферативна ДР, околу 6,8% за ДМЕ и 10,2% за слепило. (5)

Причините за високата инциденца се комплексни и инволвираат повеќе фактори, како лоша компензираност на дијабетот, недоволна здравствена и офталмолошка едукација, ненавремено дијагностицирање на болеста, поставување на индикација за ласер третман и изведување на истиот кога ефектите се значајно ограничени. (6-10)

Неодамнешна студија проценува дека 93 милиони луѓе во светот имаат дијабетична ретинопатија од кои 17.000.000 (-18%) имаат пролиферативен облик на дијабетична ретинопатија, 21.000.000 (-23%) имаат дијабетичен макуларен едем и 28.000.000 (-20%) опасност по загуба на видот.(5)

DME е последица на микро-васкуларни промени на ретината кои доведуваат до акумулација на течност во интраретиналните структури, на 1 диск дијаметар од фовеата, и е присутна кај околу 9% од дијабетична популација.(5,6)

Главен предуслов за промените е развојот на ангиогенезата која претставува ослободување на определени ангиогенетски вазопролиферативни фактори кои се ослободуваат во рамки на хипоксијата и исхемичната ретина и реципрочно инволвираат механизми на ендотелна пролиферација, инвазија и миграција за развој на патолошки крвни садови. (11)

Цел на студијата е да се прикаже ефикасноста на интравитреалната апликација инхибитори на VEGF, Bevacizumab пред се како примарен третман на перзистентен дијабетичен макуларен едем (DME)

МАТЕРИЈАЛ И МЕТОДИ

Трудот претставува ретроспективна, обсервациона, не-компаративна серија на случаи, со вклучени 51 око кај 41 пациент (7 жени и 34 мажи; со просечна возраст од 58 ± 2 год.) со перзистентен дијабетичен макуларен едем, третирани со 0,04 ml инјекција која содржи 1.25 mg на Bevacizumab, по принципот “pro re nata“ (PRN), а сепарирани во одделени групи во зависност од видот на третман.

Морфолошки DME се клаасифицираше според класификацијата на Otani et al., како дифузен макуларен едем, цистоиден макуларен едем и серозна ретинална аблација, со или без тракција. (12)

За мерење на централната макуларна дебелина се користеше калипер (macula thickness caliper-CMT, изразена во μm).

Првата група се 17 очи со DME, третирани со интравитреална апликација на Bevacizumab, пациенти со просечна возраст од 62 (SD ± 3) со аплицирани 3, 42 инекции. Втората група ја сочинуваат исто така 17 очи третирани со комбиниран третман, претходно направена најмалку по еден ласер третман, а дополнително е вклучен анти VEGF препарат-Bevacizumab, во просек по 3, 52 инјекции. Третата група се 17 очи, само со ласер фотокоагулација редовно контролрани без дополнителни иследувања.

Пациентите се обработени за пероод по 12 месеци, со комплетни офталмолошки анализи, вклучувајќи најдобро корегирана видна острина, мерење на очниот притисок, биомикроскопија, фундоскопија, мерење на централна ретинална дебелина со компаративни контролни анализи на оптичката кохерентна томографија (OCT) на задниот сегмент на окото, центрирани на макула.

РЕЗУЛТАТИ

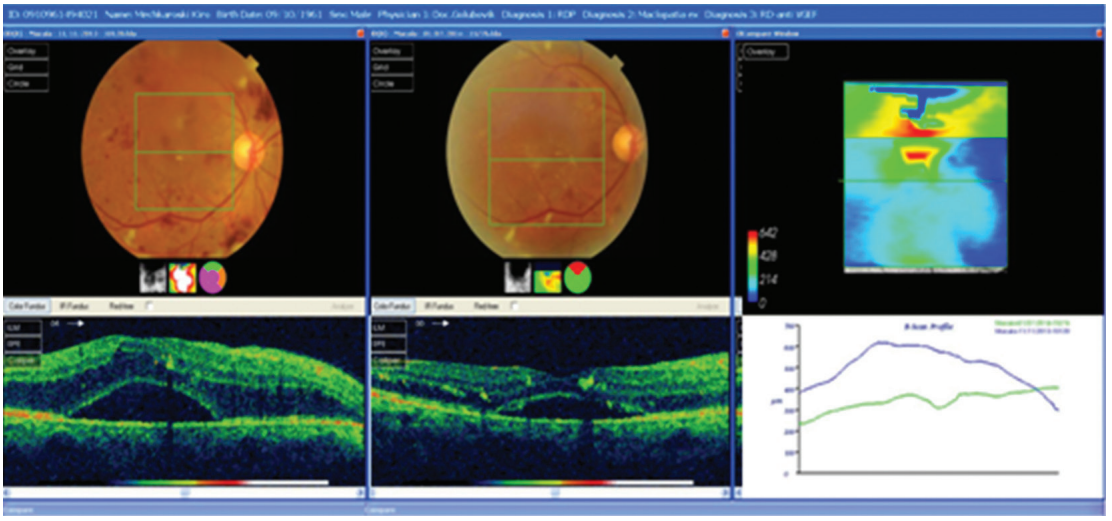
Првата група, очи третирани само со интравитреална апликација на Bevacizumab, покажаа значително подобрување на видната острина (VA) од 0,22 ± 0,1 за период од 12 месеци од третманот. (Фиг.1)

Во втората група, со комбиниран третман на терапија, видната остина се подобри за 0,17± 0,08 , а групата само со направен ласер, има VA подобрена за 0,16±0,04. (Фиг. 2, 3)

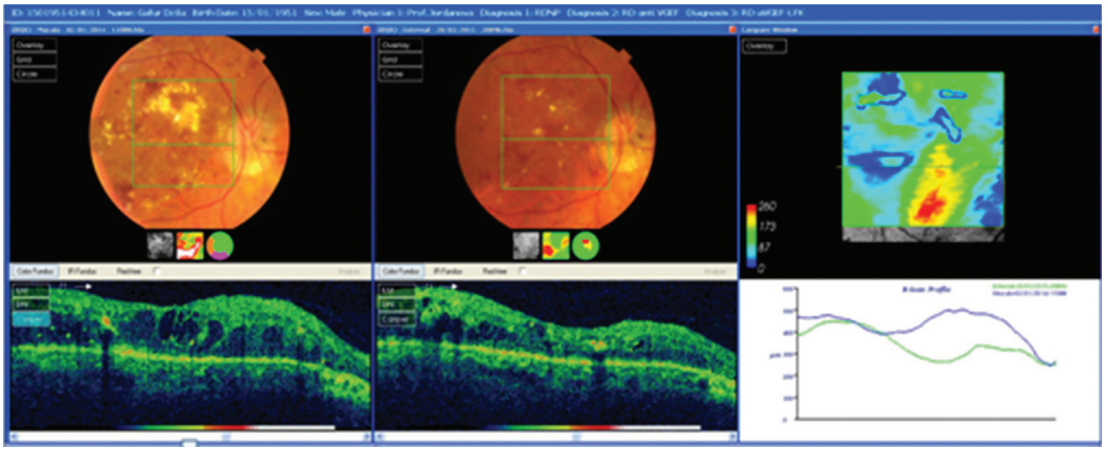
По направената анализа и мерењата утврдени со контролните OCT анализи, во првата група има намалување на централната макуларна дебелина (CMT) за 82, 69 μm, со примени 3,42 инекции во просек.

Во групата со комбиниран третман со во просек по една

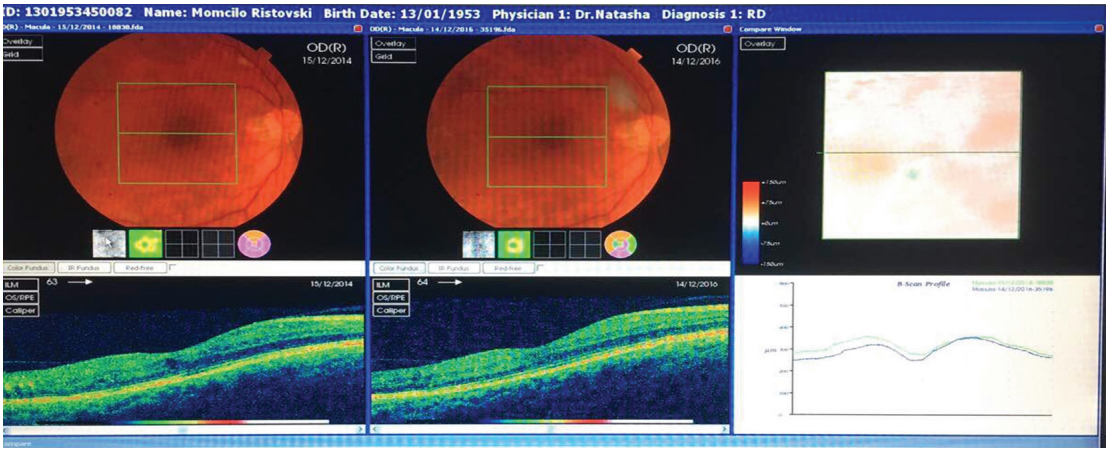
ласер фотокоагулација и примени 3,52 интравитреални апликации намалувањето изнесува 123,73 μm а кај третата група каде се пациенти само со ласерски третман има намалување за 1,71 μm, што речиси е без сигнификантно намалување на постоечкиот DME, т.е. со стагнација на состојбата. (Фиг.4, 5)



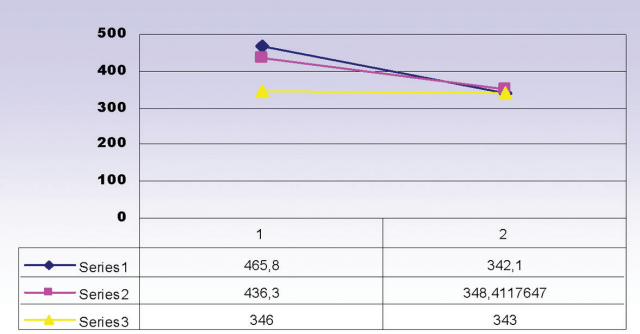
Фиг.1 Приказ на промените на DME преку OCT наод; пациент со монотераписки третман, гр.1 пред и по третман / аплицирани 3 дози на Bevacizumab iv.



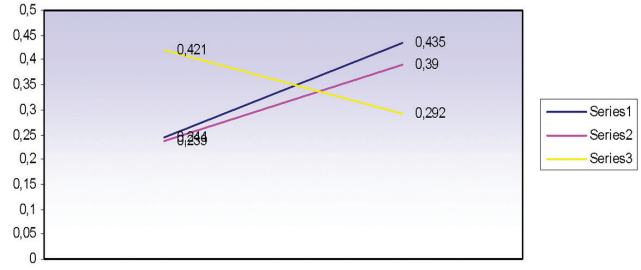
Фиг.2 Приказ на промените на DME преку компаративен OCT наод; пациент со комбиниран третман, гр.2 направен ласер и секундарно аплицирани 2 дози на Bevacizumab iv



Фиг.3 Приказ на промените на DME преку компаративен OCT наод; пациент само на ласерски третман, гр.3 пред и по направен ласер третман



Фиг.4 Графички приказ за регресијата на DME во однос на CMT (μm) кај сериите пациенти



Фиг.5 Графички приказ за промените на VA според Snellen chart кај сериите пациенти

Важно е да се напомене дека при обработка на податоците се потврди дека пациентите со комбиниран третман, кои примарно добиваа Авастин, а секундарно се изведе ласерфотокоагулацијата покажаа поголема регреија на макуларниот едем посебно анатомски, но и функционално наспроти примарно направена ласерфотокоагулација, но поради нехомогеноста на подгрупите не се анализираа.

ДИСКУСИЈА

Дијабетичната ретинопатија (DR) е невро-васкуларно заболување на ретината каде ретинални абнормалности се резултат на микроваскуларни промени, т.е се јавува зголемена вазопермеабилност со нарушување на хематоретиналната бариера (BRB) која вклучува многубројни фактори меѓу кои и регулација на факторите на раст (VEGF) и менувањето на витреоретиналниот интерфејс.

Оштетувањето на крвните садови игра примарна улога, а долгорочната хипергликемија доведува до задебелување на базалната мембрана, не-ензимска гликозилација, формирање на слободни радикали и губиток на перицити, а тоа резултира со васкуларна дилатација, зголемување на капиларниот хидростатски притисок и формирање на микроаневризми.(11)

Акумулацијата на течност е во надворешниот плексиформен слој, во интерплексиформниот или до надворешната лимитна мембрана што прави деструкција на ткивото, создавење на цистични простори и оштетување на слојот на рецепторните клетки, кое реципрочно влијае врз квалитетот на централната видна остраина. (11-14)

Но, не секогаш падот на видот е во корелација со клинички сигнификантниот едем. Факторите, како хроницитет на едемот, типот и интензитетот на истиот, како и присуството на фовеоларни тврди ексудати и макуларна исхемија имаат влијание врз крајниот исход. (12)(15)

Нормално, минимална клеточната пролиферација на ендотелните клетки се случува во ретината. Хипоксијата е почетен стимулс, индуктор, што предизвикува зголемување на бројот на факторите за раст, интегрините и протеиназите, кои понатаму вршат пролиферација и миграција, регулирајќи ја VEGF mRNA во ретинална ендотелните клетки, RPE клетки, перицитите, Милеровите клетки и ганглиските клетки. (16)

Зголемување на плазматските концентрации на VEGF најпрво биле пронајдени кај пациенти со дијабет, и тоа највисоко ниво кај пациенти со препролиферативната и пролиферативната форма на дијабетична ретинопатија.(17)(18)

Студии прикажуваат дека главниот патофизиолошки процес се состои од акутни воспаленија и васкуларна дисфункција во ретиналното и хороидалното ткиво што доведува до хипоксија, VEGF се зголемени, заедно со воспалителните медијатори, и тоа како најчесто интерлеукин (IL) -1b, IL-6, IL-8, TNF-α, интерферон гама-рамноза протеини (IP) -10, и моноцити хемоатрактант протеини (MCP) -1. (16) VEGF-A има доминантна улога и активира два рецептори на тирозин-киназа VEGF R-1 и VEGF-R2. (19-22)

Bevacizumab, е рекомбинантно хуманизирано моноклонално антитело, имуноглобулин со молекулот тежина од 149 KD но, се уште со “off label “приемена во офталмологијата.

Паралелно со конзервативниот третман е и еволуцијата на технолошките достигнувања. Оптичката кохерентна томографија на задниот сегмент овозможува објективна, морфолошка проценка на DME, давајќи

напречни пресеци на ретиното ткиво и внатрешниот интерфејс, како и компаративни контролни сумирања кои даваат морфолошки и нумеролошки приказ за централната макуларна дебелина. (Фиг.1-3)

ЗАКЛУЧОК

Интравитреалната апликација на Bevacizumab (Авастин) е ефикасна во подобрувањето на видната острина кај пациенти со примарен DME, но придобивките се ограничени во времетрење во одреден временски интервал.

Комбинираниот третман резултираше со значително намалување на потребата за интравитреална апликација на инјекции потребни за регресија на едемот. Третманот со монотерапија или во комбинација со ласер фотокоагулација е ефикасен за дијабетичен макуларен едем наспроти конвенционален ласер метод.

Нашиот период на следење е премногу краток за да обезбеди специфични препораки за третман, но овие краткорочни резултати охрабруваат натамошни проспективни студии со различни групи третман и подолго следење.

Модерните ставови базирани на бројни клинички студии ја потврдуваат потребата за континуиран комбиниран третман на оваа таргетна група во корелација со добрата метаболна контрола.

REFERENCES

1. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy: II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. Arch Ophthalmol.1984; 102:520-526.
2. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. N Engl J Med. 2000; 342:381-389.
3. Gardner TW, Antonetti DA, Barber AJ, LaNoue KF, Levison SW. Diabetic retinopathy: more than meets the eye. Surv Ophthalmol. 2002; 47(suppl 2):S253-S262.
4. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. Nat Med. 2003; 9:669-676
5. Wong TY, Klein R, Islam FM. Diabetic retinopathy in a multi-ethnic cohort in the United States. Am J Ophthalmol 2006; 14:446-55
6. Ding J, Wong TY. Current epidemiology of diabetic retinopathy and diabetic macular edema. Current diabetes reports 2012; 12(4):346-54 10.1007/s11892-012-0283-6.
7. Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of diabetic retinopathy. XIV. Ten-year incidence and progression of diabetic retinopathy. Archives of ophthalmology 1994; 112(9):1217-28
8. Klein R, Knudtson MD, Lee KE, et al. The Wisconsin Epidemiologic Study of Diabetic RXXII the twenty-five-year progression of retinopathy in persons with type 1 diabetes. Ophthalmology 2008; 115(11):1859-68 10. 1016/ j. ophtha. 2008. 08. 023
9. Klein R, Knudtson MD, Lee KE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXIII: the twenty-five-year incidence of macular edema in persons with type 1 diabetes. Ophthalmology 2009; 116(3):497-503 10.1016/j.ophtha.2008.10.016
10. Cikamatana L, Mitchell P, Rochtchina E, et al. Five-year incidence and progression of diabetic retinopathy in a defined older the Blue Mountains Eye Study. Eye (Lond) 2007; 21(4):465-71 10.1038/sj.eye.6702771.
11. Boyer D.S.The pathophysiology of Macular Edema Retina Today, September 2011 supplement available at http: //bmctoday/net/retinatoday/2011/09/
12. Panozzo G, Gusson E, Parolini B, Mercanti A. Role of OCT in the diagnosis and follow up of diabetic macular edema. Semin Ophthalmol 2003; 18:74-81.
13. Pelosini L, Hull CC, Boyce JF, McHugh D, Stanford MR, John Marshal J : Optical Coherence Tomography May be used to Predict Visual Acuity in patients with macular edema. IOVS available at: http: //www.iovs.org/content/52/5/2741.full
14. Koleva-Gjorgjieva D: Optical Coherence Tomography Findings in Diabetic Macular Edema
15. Antcliff RJ, Marshall J. The pathogenesis of edema in diabetic maculopathy. Semin Ophthalmol. 1999; 14(4):223-232.
16. Jonas JB, Jonas RA, Neumaier M, Findeisen P. Cytokine concentration in aqueous humour of eyes with diabetic macular edema. Retina. 2012; 32:2150-2157.
17. Hicklin DJ, Ellis LM. Role of vascular endothelial growth factor pathway in tumour growth and angiogenesis. *J Clin Oncol*. 2005; 23:1011-1027
18. Adamis AP, Miller JW, Bernal MT, et al. Increased vascular endothelial growth factor levels in the vitreous of eyes with proliferative diabetic retinopathy. *Am J Ophtalmol* 1994; 118:445- 450

19. Zhang S, Wang JJ, Guoguan G et al Pigment epithelium derived factor downregulateds Vascular Endothelial Growth Factor (VEGF) expression and inhibits VEGF-VEGF receptor 2 binding in diabetic retinopathy Journal of molecular Endocrinology 2006; 37; 1-12
20. Am J Patrol. 1995 May; 146(5):1029-39. Vascular permeability factor/vascular endothelial growth factor, microvascular hyperpermeability and angiogenesis. Dvorak HF1
21. Endocr Rev. 2004 Aug; 25(4):581-611. Vascular endothelial growth factor: basic science and clinical progress, Ferrara N.
22. Ciulla TA, Amador AG, Zinman B. Diabetic retinopathy and diabetic macular edema: pathophysiology, screening, and novel therapies. Diabetes Care. 2003; 26(9):2653-2664.

Легенда на кратенки:

DR – diabetic retinopathy / дијабетична ретинопатија
DME – Diabetic macular oedema / Дијабетичен макуларен едем
VEGF - Vascular endothelial growth factor
CMT - Central macular tickness / централна дебелина на макула
BCVA- Best corrected visual acuity / најдобро корегирана видна острина
OCT – Optical coherence tomography / Оптичка кохерентна томографија
LFC – Laser photocoagulation / Ласер фотокоагулација
VA- Visual acuity / видна острина
PRN – pro re nata regimen / третман по потреба
BRB – hematoretinal barrier / хематоретинална бариера

INTRAVITREAL INJECTIONS AND DIABETIC MACULAR EDEMA: ACTUAL THERAPY

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ABSTRACT

Aim: To show the effectiveness of current treatment for diabetic macular edema (DME), the primary monotherapy for intravitreal administration of Avastin (Bevacizumab), and combined treatment with laser photocoagulation.

Background: Laser photocoagulation remains the standard treatment, but numerous studies confirm the applicability and benefits of additional therapy for DME as the application of anti VEGF and intravitreal administration of corticosteroids, which promise improvement of visual acuity.

Material and Methods: Retrospective, observational, noncomparative series of cases, involving 51 eyes, with DME treated with 0, 04 ml / 1, 25 mg Bevacizumab according "pro re nata regimen", and separated into groups indicted by the primary treatment. Patients were reviewed for 12 months, underwent complete eye examination.

Results: The first group with intravitreal administration of Bevacizumab, showed significant improvement of VA for 0, 22 ± 0, 1. In the second group, with combined therapy, improved VA to 0, 17± 0, 8 and the third group with laser, the VA for 0,16 ± 0, 04

After the measurements of the control OCT analysis, in the first group there is a decrease in CMT for 82, 69 μm, received injections 3.42 on average. In second group with an average of 1 laser and intravitreal applications received 3, 52, decrease is 123, 73 μm and in the third group CMT decreased by 1, 71 μm.

Conclusion: Intravitreal administration of Bevacizumab is effective in improving VA in patients with DME, but the benefits are limited to a certain range. Combined treatment resulted in a significant reduction in the need for intravitreal administration to control edema.

Key words: Diabetic macular oedema (DME), Bevacizumab (Avastin), Laser photocoagulation (LFC), Optical Coherence Tomography (OCT), Central macular thickness (CMT), Visual acuity (VA)

ATYPICAL HEMOLYTIC-UREMIC SYNDROME

SINDROMI UREMIK HEMOLITIK ATIPIK (AHUS)

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ABSTARCT:

Background: A typical hemolytic-uremic syndrome is a disease that primarily affects kidney function. This condition, which can occur at any age, causes abnormal blood clots (trombi) to form in small blood vessels in the kidneys. Atypical hemolytic- uremic syndrome is characterized by three major features related to abnormal clotting: hemolytic anemia, thrombocytopenia and kidney failure

Case report: We present 6 year old male child with two hospitalizations in the period from 2012 to 2016. The patient presented a high grade fever (38°C), vomiting, diarrhea and abdominal pain. There was a past history of sore throat and fever. He was managed with transfusion of erythrocytes and plasma, the vital signs and the renal function were monitored. Verotoxin was not found. Genetical testing showed no significant mutations.

Conclusion: Taken together, all the results and the relapsing nature of the illness, this disorder is described as atypical hemolytic syndrome caused by unknown predisposing factors.

INTRODUCTION

Hemolytic uremic syndrome (HUS) as the name suggests is characterized by hemolytic anemia, thrombocytopenia and in most cases with kidney failure, although due to the nature of the disease it can target other organs as well.

It is categorized as atypical because in the typical HUS, the pathogenesis of the disease is due to the "shiga-toxin" from bacterias such as Escherihia coli (and others); whereas in the atypical HUS the pathogenesis is mainly genetic with a genetic penetrance of around 50%, so triggering events such as environmental factors play a role.

The disorder occurs most frequently in children under the age of 5 years, as compared with an overall incidence of 1 to 2 cases per 100.000.(1) approximately 10% of the cases with hemolytic uremic syndrome are classified as atypical, since they are not caused by either STX-producing bacteria or streptococci.(2)

CASE REPORT

A 3 year old male was admitted to the Hospital with diarrhea, vomiting and high grade fever (39°C). The patient appeared pale, weak, with loss of appétit, with dark stool and dark urine. There was a previous history of upper respiratory infection treated with antibiotics (amoxicillin). The examination revealed hepatosplenomegaly, edema in both lower extremities with hematomas.

The blood investigations showed low hemoglobin level (HGB=62 g/L), low red blood count (RBC =2.4 x 10^{12}/L), low platelets (PLT=34 x 10^{9}/L), low hematocrit (Hct=15.3 %;) high urea (36.2 mmol/L) High Creatinin (157 umol/L), high bilirubin (65umol/l.). Liver enzymes were elevated : AST 764 U/l; ALT 434 U/l; LDH 3869 U/l; GGT12 U/l. Total proteins (52 g/L). The blood smear showed schystocytes.

The urine analysis showed albumin (+++), 10-12 Red blood cells; 2-3 White blood cells and hyaline casts.

The verotoxin test in the stool was negative.

Ultrasonography showed hepatosplenomegaly, the both kidneys appeared enlarged and hyper echogenic with out clear corticomedullary differentiation.

Due to the clinical presentation and the laboratory results, a presumptive diagnosis of typical hemolytic uremic syndrome was assumed. At this point the patient was treated with fresh frozen plasma and filtered erythrocytes.

After the treatment the child appeared clinically better. The renal function, the blood investigations including the platelets were normalized and the patient was discharged in good clinical condition.

Three years later the patient was back and presented with diarrhea, vomiting, high grade fever (38°C) and abdominal pain. Four days before hospitalization he presented again with upper respiratory infection and was treated with antibiotics (amoxicillin). The laboratory results were similar to the first hospitalization .The blood investigations showed low hemoglobin level (HGB=69 g/L), low red blood count (RBC =2.53 x 10^{12}/L), low platelets (PLT = 53 x 10^{9}/L), low hematocrit (Hct = 18.7 %;) high urea (19.8 mmol/L) high creatinin (124 umol/L), high bilirubin (29,7 umol/l.) slightly elevated AST (53 U/l), normal ALT (22 U/l), normal GGT (17 U/l), elevated LDH (1955 U/l) and total proteins (52 g/L).

The urine analysis showed albumin (++), 8-10 red blood cells, 2-4white blood cells and hyaline casts. SDS- PAGE was done and showed nonselective glomerular with incomplete tubular proteinuria. Ultrasonography showed no abnormalities. The test for verotoxin was repeated and once again was negative, which definitely excluded the suspicion for typical hemolytic-uremic syndrome.

The presumed differential diagnosis were: aHUS, thrombotic thrombocytopenic purpura (TTP) and other tromboticmicroangiopathic related diseases.

Due to the unlikelihood of the repeating nature of typical Hemolytic uremic syndrome thorough biochemical and genetic testing was required for the establishment a correct clinical diagnosis (Semmelweis University, 3rd Department of Internal Medicine, ResearchLaboratory). Informed consent was obtained from the parents. The results of the analysis of the complement and related proteins are presented in the table 1.

Table 1.

ADAMTS13 activity	77% (67- 147%)
Classical pathway Hemolytic test	75 CH50/ml (ref range 48-103 CH50/ml)
Total complement activity, alternative pathway (WIELISA-Alt):	95 % (reference range 70-105%)
Complement C3:	1,06 g/L (reference range 0,9-1,8 g/L)
Complement C4:	0,25 g/L (reference range: 0,15-0,55 g/L)
C1q antigen:	80(60-180 mg/L)
Factor H antigen:	686 (reference range 127-447 mg/L)
Complement factorIantigen:	103 % (reference range 70-130%)
Complement factorBantigen:	156 % (reference range 70-130%)
Anti- factor H IgG autoantibody:	negative (43 AU/mL, ref <110)
SC5b-9 (terminal complement complex)	314 ng/mL (ref 110-252)
C3a anaphylatoxin	118 ng/mL (ref 70-270)

During the awaitfor the results, the patient was treated with fresh frozen plasma and filtered erythrocytes. After the treatment, the blood investigations and the renal function were normalized with a persistent microhematuria. All in all, the patient was dischargedin good clinical condition.

The biochemical and genetic results which arrived later, demonstrated that the patient was found to carry a heterozygous mutation in CFHR5 (K144N). This variant may or may not be considered as disease causing for aHUS. In addition, the patient is heterozygous carrier of two aHUS risk SNPs in CFH (the Q672Q and E936D), and 1 risk haplotype in MCP (MCPggaac). Finally, the patient is also carrier of a protective aHUS variant (V62I) of CFH.

Collectively, these variants cannot be considered as causative genetic predisposing factors for aHUS in this patient, however, some of them can be considered as aHUS risk increasing (or decreasing) variants only.

Taken together, based on the negative testing for verotoxin and on the relapsing nature of HUS, the disease can be classified as *atypical HUS*. Since normal complement profile and negative genetic analysis do not exclude aHUS, this patient can be classified as aHUS, with unknown predisposing factors.

DISCUSSION

The clinicalpresentation of aHUS is consisted of three main signsmicroangiopathic hemolytic anemia, thrombocyteponia and acute renal failure. Through the diagnostic process typical HUS and TTP should be excluded.(3)

Hemolytic uremic syndrome is divided in to two entities based on the pathogenesis of the disease: typical and atypical hemolytic uremic Syndrome

Typical HUS (Shiga-Toxin Associated) is the most common type of HUS.(4) It is defined with exact pathogenesis and clinical course.(4) The most frequent etiology in typical HUS areshiga-toxin producing bacteria such as Escherichia coli and Shigelladysenteria type 1.(5) Most of the cases with typical HUS(95%) have an excellent prognosis and relapses are uncommon.(4)

Atypical HUS (Non-Shiga-toxin Associated) consists a diverse group of patients, where theshiga toxin producing bacteria are not the main etiology.(2) Genetic, acquired or idiopathic factors can be the cause for atypical HUS.(5) Furthermore in several studies the genetic predisposition was affirmed with demonstrating the regulation of the alternative pathway of the complement system (factor H, CD46 or MCP for membrane cofactor protein, factor I, factor B and C3) whose main purpose is the creation of the alternative C3-convertase.(6) A connection with CFH dysfunction due to anti- CFH auto antibodies has been appointed as a possible reason for acquired HUS.(6) In the development of the disease very common are the triggering factors.(6) Triggering factors are: nonenteric infections, viruses, drugs, malignancies, transplantations, other underlying medical conditions like SLE.(3)

In our case prior to the aHUS episode the patient had an upper respiratory infection, treated with antibiotics (amoxicillin). Taken together patients with aHUS have a poor outcome. End stage renal disease or irreversible brain damage can be developed in more than 50% of the cases, and 25% of the cases end up fatally.(1) The resemblance between HUS, aHUS, and TTP make differential diagnosis crucial.(7) In order to diagnose an aHUS case, the possible diagnosis of TTP (with deficiency of ADAMTS13) and STX-HUS (with positive verotoxin) should be eliminated.(8) In our case TTP was excluded by the normal activity of ADAMTS13 77% (67- 147%). Typical HUS was excluded by the negative testing of verotoxin and by the relapsing nature of aHUS.

The treatment of aHUS is very restricted. The first choice of treatment is the plasma exchange and it should be given as soon as possible. In patients with CD46 kidney transplantation is advised. Eculizumab is new treatment with monoclonal antibodies that block the cleavage of C5 and stop the complement cascade. The only downside is the expensive price of this drug. Fluid maintenance, electrolyte balance, control of the blood pressure and prophylactic antiepilectic therapy are essential for control of the disease.

CONCLUSION

Although it is thought of as a very rare disease, the incidence of this disease is increasing .The diagnosis of aHUS is clinical, so finding no mutated gene does not exclude the diagnosis.

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REFERNCES:

1. Noris M, Remuzzi G: Atypical Hemolytic–Uremic Syndrome. *The New England Journal of Medicine* 361;17: 1676-1687, 2009
2. Noris M, Remuzzi G: Hemolytic Uremic Syndrome. *J Am SocNephrol* 16: 1035-1050, 2005
3. Gulati S, Gupta N, Chhonker D, Jain R, Sehgal S, Vasudev A, Uttam R. Atypical Hemolytic Uremic Syndrome: A case report and review of literature. *Journal of International Medical Sciences Academy* 27;1: 33-35, 2014
4. Kaplan B, Meyers K, Schulman S. The Pathogenesis and Treatment of Hemolytic Uremic Syndrome. *J Am SocNephrol* 9;16: 1126-1133, 1998
5. Fallahzadeh A, Fallahzadeh K, Derakhshan A, Shorafa E, Mojtahedi Y, Geramizadeh B, Fallahzadeh H. A Case of Atypical Hemolytic Uremic Syndrome. *Iranian Journal of Kidney Diseases* 8;4: 341-343, 2014
6. Loirat C, Noris M, Fremeaux-Bacchi V. Complement and the atypical hemolytic uremic syndrome in children. *PediatrNephrol* 23: 1957-1972, 2008
7. Benz, Kerstin, Amann, Kerstin. Tromboticmicroangipathy: new insights. *Current Opinion in Nephrology and Hypertension* 19;3: 242-247, 2010
8. Campistol J, Arias M, Ariceta G, Blasco M, Espinosa L, Espinosa M, Grinyo J, Macia M, Mendizabal S, Praga M, Roman E, Torra R, Valdes F, Vilalta R, Rodrguez de Cordoba S. An update for atypical hemolytic uremic syndrome: Diagnosis and treatment. A consensus document. *Nefrologia* 35;5: 421-447, 2015

SINDROMI UREMIK HEMOLITIK ATIPIK (AHUS)

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ABSTRAKTI

Sindromi uremik hemolitik atipik është një sëmundj e që kryesisht prek funksionin e veshkave. Kjo gjendje, e cila mund të ndodhë në çdo moshë, shkakton ngjyzje të gjakut në abdomen (tromb) të cilat pastaj shkojnë e shtresohen në enët e vogla të gjakut në veshka. Sindromi uremik hemolitik atipik karakterizohet nga tri tipare kryesore që lidhen me koagulimin e gjakut: anemia hemolitike, trombocitopeni dhe dështimi i veshkave.

Prezentimi i rastit: Ne paraqesim rastin e një fëmije 6 vjeçar mashkull që ka patur dy shtrime në spital në periudhën prej vitit 2012 deri në vitin 2016. Pacienti paraqitet me temperaturë të lartë (38 °C), të vjella, diarre dhe dhimbje barku. Nuk kishte anamnezë me dhimbje të fytit dhe ethe. I është administruar transfuzioni me eritrocite dhe plazmë dhe janë monitoruar shenjat vitale dhe funksioni renal. Verotoksinë nuk u gjet. Testi gjenetik nuk tregoi mutacione të rëndësishme.

Përfundim: Të marra së bashku, të gjitha rezultatet dhe natyra e sëmundjes, është përshkruar si sindromi uremik hemolitik atipik shkaktuar nga faktorë të panjohur predispozues.

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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).