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Betimi i Hipokratit

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

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

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

The Oath of Hippocrates

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

My colleagues will be my brothers.

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

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PREVALENCE, AWARENESS AND RISK FACTORS OF DIABETES AND PREDIABETES AMONG ADULT POPULATION OF TETOVO REGION IN REPUBLIC OF MACEDONIA

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ABSTRAKTI

Aim: The aim of this study was to assess the prevalence, awareness and the risk factors associated with diabetes mellitus and pre-diabetes in the adult population of the region of Tetovo.

Methods: Total of 630 subjects aged over 18 years were selected at random and constitute a representative sample of a population of 185.743 inhabitants in the region of Tetovo adjusted for age and sex. All subjects completed the modified "WHO STEPS questionnaire" and answered questions on socio-demographic data, behavioral data, disease and family history data. Biochemical analysis of cholesterol, triglycerides, HDL- cholesterol and blood glucose was estimated in fasting venous blood samples.

Results: Mean age of the population was 43.8 ± 16.01 years. Prevalence of diabetes was 9.36% (9.67% male and 9.68 % female), of pre-diabetes was 16.7% (17.09% vs. 16.25%). 35.59% of diabetics were not aware of their disease. Though not statistically significant undiagnosed diabetes was higher in females (37.93% vs. 33.33%). Logistic regression analysis showed: age, family history, serum triglycerides, body mass index and sedentary lifestyle were significantly associated with an increased risk of diabetes.

Cunclusions: Although the prevalence of diabetes and prediabetes in our sample were somewhat lower than in general in Macedonia, they remain higher than in the developed countries. This even further obliges the public health sector to undertake activities with health education programs to increase public awareness of diabetes, its risk factors and complications.

Keywords: diabetes; prediabetes; awareness; risk factors

INTRODUCTION

Diabetes mellitus (DM) as a global epidemic, represents a considerable health and socio-economic challenge growing rapidly worldwide.[1,2]. DM prevalence has doubled since 1980, estimated to further increase. If these trends continue, from 425 million in 2017, by 2045, 629 million of people 20-79 years, will have DM [3].

As one of the major contributors to cardiovascular disease, for successful management of DM and prevention of its complications, early detection is important. However, as indicated in a recent review of data from seven countries, a substantial proportion of individuals with DM remain undiagnosed and untreated, both in developed and developing countries[4]. Even in high-income countries, the proportion of undiagnosed DM is high at about 30-50% [5]. Also, a majority of people with DM are unaware of having DM complications.[6].

Early detection is also important for the population with prediabetes (with glycemic values lower than 7 mmol / L

and higher or equal to 6.1 mmol / L) which are at high risk of developing type 2 DM. Prediabetes risk factors are the same as for type 2 DM: overweight, advanced age, lack of physical activity, smoking, and family history[17,18,19]. There is reliable evidence from randomized controlled studies that intervention in lifestyle contributes to the slowing or stopping the progression of prediabetes to diabetes [20,21,22].

As indicated in a review article from 2015, in RM the estimated total DM prevalence, of both diagnosed and undiagnosed cases, in RM was around 80,000 people in 2004, whereas the estimated total DM prevalence in 2014 should be 180,180 [7]. The same report states that screening at the primary care program suggests that the prevalence of undiagnosed DM was 6.5%, which means that half of the patients with DM in Macedonia were not aware of having DM. According to recent data DM prevalence in RM was 12.2% (among highest in Europe), whereas 7.67% of them were undiagnosed. [3].

Considering some socio-economic and cultural characteristics of the Tetovo region, we thought it would be useful to estimate total DM prevalence, of both diagnosed and undiagnosed cases as well as the risk factors associated with DM of our region.

MATERIAL AND METHODS

In this study we have used the database from our earlier survey of metabolic syndrome prevalence, so the survey methodology has been described elsewhere [8]. In short, 630 participants were randomly selected from the primary health care register that represented several municipalities with the population of about 200,000 residents of the Tetovo region[10]. The study included individuals over the age of 18. For examining the subjects we used "WHO STEPS Instrument" (World Health Organization STEPwise approach to noncommunicable disease surveillance). It included the questionnaire for socio-demographic and behavioral data, physical measurements and biochemical measurements. For the determination of metabolic syndrome, we have applied the revised criteria according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII)[9].

The venous blood samples for measurement of glycemia and lipid profile were collected in the morning after overnight fasting for at least 8 hours. All samples were analyzed on the same day, using the automated biochemistry analyzer. According to American Diabetes Association (ADA)[11], criteria for the diagnosis of DM was a fasting plasma glucose (FPG) level of 7 mmol/L or higher. If the blood glucose was high for the first time, then the diagnosis of DM was made when two separate blood tests show fasting blood glucose level greater than or equal to 7 mmol/L. Criteria for the diagnosis of prediabetes was FPG level from 5.6 to 7.0 mmol/L.

STATISTICAL ANALYSIS

Statistical data processing is done in STATISTICA 7.1 and SPSS 13.0 statistical programs. The following methods have been implemented:

- In series with numerical variables, were assigned: Descriptive Statistics (Mean ± Std. Dev. ± 95.00 CI: Minimum Value, Maximum Value)
- In series with categorical variables, differences between analyzed parameters are tested with Pearson Chi-square ($\chi 2$);
- In numerical series with no deviations from a normal distribution, the difference between the two independent samples was tested by t-test for independent samples.
- The prognostic role of certain parameters analyzed as independent variables on DM as a dependent phenomenon is assigned with the application of Logistic Regression [Chi Square, WALD, Exp (B)].

RESULTS

Descriptive statistics of parameters analyzed at sample level are presented in Table1. The average age of subjects (310 men and 320 women), varies from 43.81 ± 16.01 years, ± CI 42.56 to 45.06.

The prevalence of DM in our sample was 9.36%. There was no significant difference between males and females (9.67% males and 9.06% females), (95% CI: -3.9978 to 5.2593, p = 0.7929). Table 2 and Figure 1. The prevalence of undiagnosed DM at the level of the sample (N = 630) was 3.33% (3.22% male and 3.43% female), (95% CI: -2.8011 to 3.2021, p = 0.883). The difference was not significant. Whereas, out of the total number of people with DM, 35.59% were unaware of DM. Glycemia values from 5.6 to 7.0 mmol / L, which is considered as prediabetes, had 6.59% of respondents. Even in this contingent there were no significant differences between men and women (7.4% versus 6.5%), (95% CI: -2.8104 to 5.2812, p = 0.5498).

Table1. Descriptive statistics of parameters

Parametri	Valid N	Mean	Confidence	Confidence	Minimum	Maximum	Std.Dev.
			−95,00%	+95,00%			
Glic.	630	5,41	5,27	5,56	3,70	21,80	1,86
TR	630	1,68	1,61	1,76	0,34	8,70	0,99
HDL-C	630	1,25	1,22	1,28	0,37	5,50	0,40
LDL-C	630	3,21	3,12	3,31	0,34	7,40	1,17
TC	630	5,02	4,93	5,12	1,00	9,70	1,24
Waist cir	630	93,28	92,28	94,29	58,00	161,00	12,82
SBP	630	132,22	130,45	133,99	90,00	230,00	22,58
DBP	630	82,17	81,22	83,13	45,00	140,00	12,17
Weight	630	78,31	77,33	79,30	42,00	118,00	12,59
Height	630	170,06	169,41	170,72	150,00	195,00	8,36
BMI	630	27,14	26,79	27,49	16,00	47,84	4,47

Values are mean ± SD;r; BMI:body mass index; SBP:systolic blood presure; DBP:diastolic blod presure; Glic:glicemia; serumLDL-C:low. density cholesterol; HDL-C: high-density cholesterol; TC:Total cholesterol; TR: Ttiglycerides

Table 2. The Prevalence of DM, Prediabetes and Undiagnosed DM.

Prevalence %			
	DM	Prediabetes	Undiagnosed DM
Total	9.36	6.50	3.33
Male	9.67	7.4	3.22
Women	9.06	6.2	3.43
p value	p=0.7929	p= 0.5498	p=0.883

*χ^2- Chi-square test

As expected, the prevalence of DM is related to the increase in the age group of both sexes. An important difference between the sexes was only in the age group of 70-79 years (Figure2) .

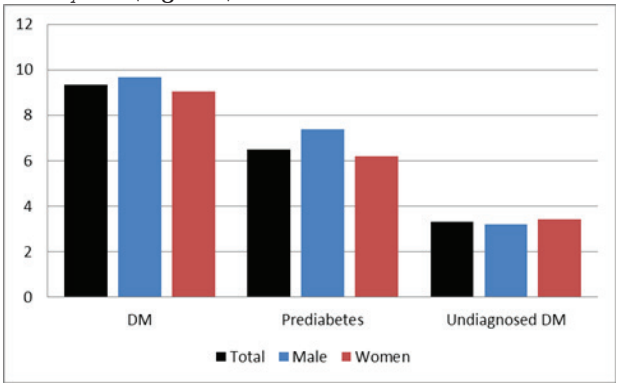

Figure1. The Prevalence of DM, Prediabetes and Undiagnosed DM

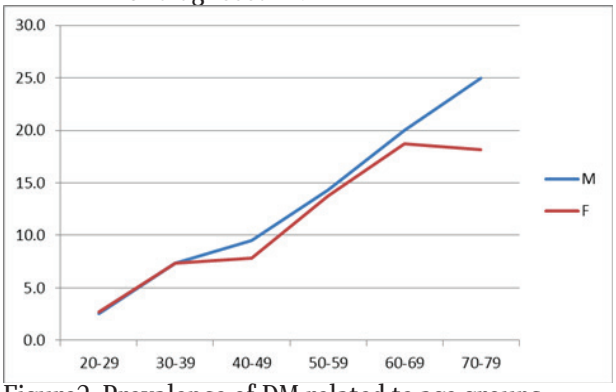

Figure2. Prevalence of DM related te age groups

By using logistic regresion analysis, the predictive role of certain risk factors as an independent variable in the occurrence of DM as a dependent phenomenon has been analyzed. The resultes showed that serum triglyceride level (95%CI 1.04-2.893, p<0.001), family history for DM (95%CI 0.122-0.538,p<0,001), older age(95%CI 1.01-1.073, p= 0.002, p<0,01), sedentary life (95%CI, 1.00-2.692, p=0.049, 0<0.05) and BMI (95%CI, 1.01-1.279, p=0.035, 0<0.05), were significantly associated with an increased risk of DM. (Table 3).

DISCUSSION

The Tetovo region in the northwest part of Macedonia has a population of about 200,000 inhabitants, representing 1/5 of the entire Macedonian population. In a previous study, we have studied the prevalence of metabolic syndrome and its risk factors for this condition [8]. Our sample consisted of 630 subjects who were representative of the population of this region. Just this contingent has also been used to determine the prevalence of DM, prediabetes and the awareness of the people of this region for diabetes mellitus.

The International DM Federation has reported a prevalence of DM in adults in Macedonia to be 12.2% [CI: 10.6-13.8] [3]. This figure is among the highest in Europe. In our sample, the prevalence rate was somewhat lower (9.36%). This difference is thought to be attributed to the socioeconomic and cultural circumstances that differ from the rest of the Republic of Macedonia. The influence of these factors on the prevalence of diabetes mellitus has been described in various studies [12-14]. Behavioral factors also play an important role in this regard [15,16]. Regarding gender differences in prevalence rates, in our study, it was slightly higher in the male population, similar to data from European countries but different

Table 3 Estimating the predictive role of age, education, Income,Family history, Smoking, Alcohol, Triglycerides, HDL-C, LDL-C, Total Cholesterol, abdominal adiposity (WC) blood pressure, and (Body mass index)BMI in Diabetes Mellitus.

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper
Sex	0.292	0.408	0.51	1	0.474	1.33	0.6	2.976
Age	0.043	0.014	9.52	1	0.002*	1.04	1.01	1.073
Education	0.047	0.26	0.033	1	0.856	1.04	0.63	1.743
Family Income	0.074	0.213	0.12	1	0.729	1.07	0.709	1.634
Family history	-1.362	0.379	12.9	1	0.000**	0.25	0.122	0.538
Smoking	0.125	0.192	0.428	1	0.513	1.13	0.779	1.651
Alcohol	0.571	0.533	1.15	1	0.283	1.77	0.623	5.03
Physical activity	0.495	0.253	3.84	1	0.049*	1.64	1	2.692
Triglyceride	0.691	0.18	14.7	1	0.00**	1.99	1.4	2.839
HDL	-0.616	0.567	1.18	1	0.277	0.54	0.178	1.639
LDL	-0.107	0.266	0.16	1	0.689	0.899	0.533	1.515
Cholesterol	0.037	0.268	0.019	1	0.892	1.03	0.613	1.755
Waist circumference	-0.015	0.023	0.414	1	0.52	0.986	0.943	1.03
Blood pressure	0.019	0.01	3.54	1	0.06	1.02	0.999	1.041
BMI	0.128	0.06	4.46	1	0.035*	1.13	1	1.279

*p<0.05, **p<0.001

from those of middle east and south America countries where prevalence to the female population was higher [3].

In our sample, more than 9 people in 100 adults had DM. Out of these, 35.59% were detected only during the survey, which means that the percentage of undiagnosed DM in our sample was quite low. It was at the level of developed countries [3]. Compared to the prevalence of non-diagnosed DM in Macedonia in general, it was significantly lower [7]. This fact remains to be explored?

The North American and Caribbean region has the highest prevalence of prediabetes (15.4%), while the Southeast Asian region has lower prevalence (3.0%). The countries with the largest number of people with IGT in 2017 were China, the United States and Indonesia [3]. In our contingent prevalence rate of prediabetes was 6.5%, slightly more pronounced among males (7.4% versus 6.2%). It was, also, slightly more than average in Europe (4.6 %).

Although this condition presents an increased risk for DM, not every person with prediabetes will have DM in the future. For this population group, there are reliable evidence that measures taken in behavior and life style, contributes to preventing of DM[20,21,21].

In our study on the multivariable logistic model, it was found that older age, family history, triglycerides, overweight and physical inactivity were all significantly associated with an increased risk of DM. While sex, smoking, alcohol, hypertension, and the social level of the population in our model did not seem to be an important factor. Our data support the evidence that overweight and obesity, in particular, are potent risk factors for type 2 DM, and a lifestyle that lacks physical activity and is rich in a fat diet are important factors of continuous increase of DM prevalence. These findings are similar to those previously reported in different populations [22]. These findings also suggest preventive interventions in the style of life which should be aimed at reducing the levels of overweight and obesity in our population.

Therefore, it is essential that health education programs within the public health sector should undertake activities to raise public awareness of diabetes, its risk factors and complications as well as to promote a healthy lifestyle for citizens, including regular health screening for early detection of diabetes, and reducing complications associated with diabetes.

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PREVALENCE, AWARENESS AND RISK FACTORS OF DIABETES AND PREDIABETES AMONG ADULT POPULATION OF TETOVO REGION IN REPUBLIC OF MACEDONIA

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ABSTRACT

Qëllimi: Qëllimi i këtij studimi ishte vlerësimi i prevalencës, ndërgjegjësimit dhe faktorëve të rrezikut të lidhur me diabetin dhe prediabetin ne popullatën adulte të rajonit të Tetovës.

Metodat: Gjithsej 630 subjekte të moshës mbi 18 vjeç u përzgjodhën në mënyrë të rastësishme dhe përbënin një mostër përfaqësuese të një popullsie prej 185.743 banorë në rajonin e Tetovës, të pershtatur për moshën dhe gjininë. Të gjitha subjektet plotësuan pyetësorin "WHO STEPS" dhe u përgjigjën pyetjeve mbi të dhënat socio-demografike, të dhënat biheviorale, sëmundjet dhe të dhënat e historisë familjare. Vlerat e profilit lipidik dhe të glukozës u përcaktuan nga mostrat e gjaku venoz të marre esell.

Rezultatet: Mosha mesatare e subjekteve ishte 43.8 ± 16.01 vjet. Prevalenca e diabetit ishte 9.36% (9.67% meshkuj dhe 9.68% femra), të prediabetit 16.7% (17.09% vs 16.25%). Numri prej 35.59% e diabetikëve nuk ishin të vetëdijshëm për sëmundjen e tyre. Megjithëse statistikisht jo signifikant, prevalenca e diabetit te pa diagnostifikuar ishte më e lartë tek femrat (37.93% kundrejt 33.33%). Analiza e regresionit logjistik tregoi se: mosha, historia familjare per diabet, trigliceridet, indeksi i mases trupore, dhe menyra sedentare e jetesës ishin shoqeruar me rrezik në rritje të shfaqjes se diabetit.

Konkluza: Edhe pse shifrat për diabet dhe prediabet në mostrën tonë ishin pakes më të ulëta se në nivel shtetëror, ato mbeten më të larta se në vendet e zhvilluara. Kjo edhe më tej e obligon sektorin e shëndetit publik që të ndërmarrë aktivitete me programet e edukimit shëndetësor për të rritur ndërgjegjësimin e publikut për diabetin, faktorët e saj të rrezikut dhe komplikimet.

Fjalekyç: diabeti; prediabeti; ndërgjegjësimi; faktoret e rrezikutKeywords: diabetes; prediabetes; awareness; risk factors

Original scientific paper

ИНИЦИЈАЛЕН ПРИТИСОК НА МИКЦИЈА- АЛТЕРНАТИВА НА LEAK-POINT PRESSURE

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АПСТРАКТ

Притисокот во момент на мокрење (leak-point pressure-LPP) е дефиниран како везикален притисок при истекување на урина за време на покачен интраабдоменален притисок, во отсуство на контракција на детрусор на мочниот меур. Истиот се мери во специфични услови, што понекогаш е многу тешко да се процени дали се испочитувани. Иницијалниот притисок на микција ги има практично истите параметри како LPP, а целта на студијата е да утврди дали постојат разлики на овој параметар кај пациентки со стрес уринарна инконтиненција, во однос на женски индивидуи без инконтиненција. Обработени се 100 пациентки (50 со СУИ и 50 контролна група), според стандардните протоколи за евалуација на уринарна инконтиненција. Во групата со СУИ средната вредност на иницијалниот притисок на микција изнесува 29,80 cmH2O, а кај контролната група 34,44 cmH2O, со висок интервал на доверба и p<0,0001. Заклучок: Иницијалниот притисок на микција е помал кај индивидуи со СУИ во однос на индивидуи без инконтиненција и е добра алтернатива на LPP во пошироки студии на проценка на уринарната инконтиненција.

Клучни зборови: leak-point pressure, стрес уринарна инконтиненција, уродинамика

ВОВЕД

Притисокот во момент на мокрење (leak-point pressure-LPP) е дефиниран како везикален притисок при истекување на урина за време на покачен интраабдоменален притисок, во отсуство на контракција на детрусор на мочниот меур. Истиот може да биде предизвикан од кашлање или маневар на Valsalva, при што двата фактора физиолошки се разликуваат во однос на брзината и природата на порастот на притисокот. Иако повисоки абдоминални притисоци може да се постигнат со кашлање, leak-point pressure при Valsalva маневар е подобро контролиран и помалку променлив.[1] Општо земено, кашлањето се користи за пациенти кои не протекуваат за време на мерењето при Valsalva маневар. Притисокот при кој протекува урината може да се одреди визуелно, флуороскопски или уродинамски.

За LPP да биде валиден тест, се претпоставува дека мерниот трансуретрален катетер не ја обструира уретрата или на друг начин ја менува истата, дека маневарот не ја искривува уретрата и дека пациентката не прави пелвична релаксација или контракција. Главен недостаток на LPP е тоа што е тешко да се знае дали овие фактори се испочитувани за време на тестот. Иако концептот на LPP како метод за испитување на инконтиненција е емпириски здрав, неговата вредност е ограничена со недостаток на стандардизирана методологија. Варијации се јавуваат во типот на катетер кој се користи (трансуретрален, ректален, вагинален), калибар на катетерот, волумен на исполнетост на мочниот меур при иследувањето и позицијата на пациентката при тоа. Точната базна линија која се користи за време на тестот, исто така варира (од нулто ниво или од нивото на кое притисокот самошто почнува да расте), што може да направи разлика во вредноста на LPP. Малку податоци се достапни за големина на промената на LPP по хируршки третман на стрес уринарната инконтиненцијата(СУИ), и тоа воглавно како таа е во корелација со стапки на излекување, подобрување или неуспех на третманот. Еден општ заклучок е дека LPP, при Valsalva маневар, не се менува значително ако третманот не успее. На пример, по субуретрална слинг-операција кај 30 жени, Валсалва LPP значително се зголемил по успешна операција (просечна промена

61,1см H2O; P <0,001), но не и по неуспех (просечна промена 9,7 cm H2O, P = 0,226). [2]

Иницијалниот притисок на микција ги има практично истите параметри како LPP, со таа разлика што кај пациентките имаме униформирана состојба, а од нив бараме да започнат микција свесно, па се елиминира неконтролираната пелвична релаксација или контракција.

Целта на овој труд: е да утврди дали постојат разлики во иницијалниот притисок на микција кај пациентки со СУИ во однос на женски индивидуи без инконтиненција.

МАТЕРИЈАЛ И МЕТОДИ

Во трудот се обработени 100 пациентки и тоа:

1.група од 50 пациентки со стрес уринарна инконтиненција

2.група од 50 пациентки без инконтиненција

Од студијата се исклучени пациентки кои имале: присуство на уринарна инфекција, дијабет, состојби кои доведуваат до полиурија, невролошки заболувања (CVI, повреда на medulla spinalis, sclerosis multiplex, периферни невропатии и сл.), јатрогени фистули меѓу уринарниот и гениталниот тракт и други состојби кои би можеле да влијаат врз микцијата и нејзините параметри (нефролитијаза и сл.)

Сите пациентки се на возраст од 36-65 години со просечна возраст од 56 години за групата со СУИ и просечна возраст од 60 години за контролната група испитаници, а беа испитувани хоспитално или амбулантски. Кај пациентките од двете групи е применета стандардната дијагностичка процедура во иследувањето на уринарната инконтиненција, според протоколот за инвестигација на уринарна инконтиненција што се практикува на Универзитетската Клиника за Гинекологија и акушерство во Скопје. Притоа кај секоја од пациентките се направи: интервју, преглед на седимент на урина и уринокултура, урогинеколошки преглед, тестови за верификација на стрес уринарна инконтиненција и уродинамски иследувања во кои се вклучени: Профил на уретрален притисок (УПП), цистометрија, флоуметрија и микциона цистометрија. .

За спроведување на микционата цистометрија (по претходно направената флоуметрија, УПП и цистометрија) пациентките се поставени во седечка позиција на микционен колектор, со притисочен мерен катетер во мочниот меур, по што се бара од пациентката да ја измокри претходно наполнетата течност во мочниот меур до максимален капацитет. Притоа, се добиваат повеќе притисоци во текот на самата микција. Од кривата на протокот, со интерполација, се нотира притисокот на притисочната крива во моментот на почеток на микцијата. Податоците се обработени со статистички методи и процедури за споредба на нумерички низи и нивни средни вредности (SPSS Statistics).

РЕЗУЛТАТИ

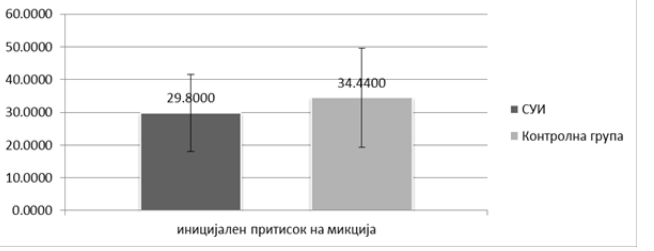
Резултатите се прикажани на Таб. 1 и Граф1.

Таб1. Иницијален притисок на микција

	N	Средна вредност ± Стандардна девијација	Стандардна грешка	p
СУИ	50	29.80±11.70	1.65	0.0001
Контролна група	50	34.44±15.14	2.14	

СУИ- стрес уринарна инконтиненција, N- број на испитаници

Анализата на податоците покажа дека дистрибуцијата на вредностите на иницијалниот притисок на микција кај СУИ е со средно помала вредност во однос на контролната група на испитаници за 4,64 cm H2O. Во групата со СУИ средната вредност на иницијалниот притисок на микција изнесува 29,80cm H2O, а кај контролната група 34,44cm H2O. Иако стандардната девијација е релативно голема, што изнесува 40,6% во групата со СУИ, а 43,9% во контролната група, стандардната грешка е мала. Статистичката анализа покажа 95% интервал на доверба за вредностите 26,47-



Граф1. Иницијален притисок на микција кај СУИ

Податоците покажуваат дека е потребно помал притисок за да се иницира микција кај индивидуи со СУИ во однос на индивидуи без инконтиненција.

ДИСКУСИЈА

Медицината базирани на докази, за употребата на

уродинамиката, открила дека постои недостаток на факти во врска со нејзината улога во предвидување на хируршкиот исход. Групата Cochrane направила преглед на литературата за уродинамика со цел да утврди дали третманот според дијагностика базирана на уродинамика, довела до клинички подобрувања во уринарната инконтиненција, во споредба со третманот базиран на анамнеза и преглед[3], но без конкретни заклучоци. Авторите препорачуваат да се спроведе голема проспективна рандомизирана студија.

Во слична анализа, Вебер и неговите колеги ги оценувале клиничките и економските последици од комплетната уродинамска евалуација, наспроти амбулантска проценка, во предоперативната припрема на пациентите со СУИ[4]. Конечно, 96% од пациентите во двете групи биле излекувани. Авторите заклучуваат дека употребата на уродинамски студии не била поддржана во рутинската предоперативна проценка на пациентите кои "веројатно" имале вистинска СУИ. Ова е контроверзно, бидејќи би било разумно да се препорача уродинамика, со цел да се види дали имало критериуми кои сигурно можеле да предвидат кои пациенти ќе имаат "вистинска" СУИ, а кои се со нестабилен детрусор. Другите напори во овој поглед, особено при употреба на стандардни прашалници, а со цел за брза и лесна дијагноза, како и предвидување на тоа кои пациенти бараат уродинамика, а кои не, имале мешани резултати [5,6,7,8,9]. Сепак, некои автори пријавиле охрабрувачки резултати. [10,11]

Во урогинеколошките кругови, добро е познат фактот: за да се одржи континенција, доволно е притисокот во уретрата да е поголем од притисокот во мочниот меур барем за еден центиметар воден столб. Ако истиот се совлада, тогаш доаѓа до истекување на урина. Најголема дискусија е околу тоа дали при инконтиненција се зголемува притисокот во мочниот меур или се намалува притисокот во уретрата. Општо е прифатено дека кај СУИ се намалени вредностите на притисокот во уретрата, а кај нестабилниот детрусор се покачени вредностите на притисокот во мочниот меур.

Податоците од студијата укажуваат на тоа дека кај индивидуи со СУИ потребен е помал притисок за да се реализира микција во однос на индивидуи без инконтиненција. Со тоа се наметнува логичен заклучок дека отпрот кој е присутен во уретрата, а се реализира преку притисокот во неа, е помал кај индивидуи со СУИ, во однос на индивидуи без инконтиненција, па според тоа и полесно се совладува. Со други зборови, потребно е присуство на помал притисок во мочниот меур за да провоцира неволно истекување на урина, што се манифестира при епизоди на покачен интраабдоменален притисок (кашлање, кивање, кревање на терет и сл.).

Индиректно, со ова се поддржува теоријата на субуретрална потпора како континентен механизам, кој го промовира македонската урогинеколошка школа[12], но и теоријата на паравагинални дефекти, која тврди дека со појава на истите во регијата на грлото на мочниот меур, се пореметува потпората, при што се манифестира СУИ[13]. Со оглед на контрверзите што го следат LPP како параметар, иницијалниот притисок на микција се наметнува како добра алтернатива во проценка на СУИ.

ЗАКЛУЧОК

- Иницијалниот притисок на микција е помал кај индивидуи со СУИ во однос на индивидуи без уринарна инконтиненција.
- Употребната дијагностичка вредност е дискутабилна, заради големата стандардна девијација
- Иницијалниот притисок на микција е добра алтернатива на LPP во пошироки студии на проценка на уринарната инкнтиненција

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Original scientific paper

ORIGINALLY MADE ANDROID GAME APPLIED IN DIFFERENT PSYCHIATRIC DISORDERS

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ABSTRACT

The potential use of modern mobile devices for medical purposes is huge. Digital mental health tools have mostly tended to use psycho-educational strategies based on treat¬ment orientations developed and validated out¬side digital health.

The aim of this study was to test availability of own original app named" Neurogame" for the evaluation reaction time in different psychiatric patients. Reaction time is strongly related to the executive brain functions.

Examined sample comprised 100 psychiatric patients (depression, general anxiety, psychosis and ADHD) compared with matched 50 healthy persons.

Obtained results showed significant difference in tested parameters depending on age and gender. Additionally, average reaction time, as well as number of hits in psychiatric patient compared with healthy people is not significantly different. However, the most important differences are found in number of hits, misses and tries in the group of depressed, psychotic and ADHD patients compared to healthy, while anxious showed pretty normal parameters.

The influence of medication in patients is not excluded, but we suppose that there is real differences between groups according the core illness.

Key words: android application, executive functions, depression, anxiety, ADHD, psychosis.

INTRODUCTION

With the expanse and advent of virtual technologies, mobile cellular devices are no longer considered only as a basic phones. Additional features in most cell phones now let phone owners' access to the Internet. On the other side, the potential for use of modern mobile devices for medical purposes is huge. In our recent publication [Pop-Jordanova et al., 2018] we evaluated the possibilities of mobile phone uses in different fields of medicine analyzing data published in Medline.

Digital mental health tools have tended to use psychoeducational strategies based on treat¬ment orientations developed and validated out¬side digital health. The group of Mohr et all. (2017) developed a suite of apps for depression and anxiety called "IntelliCare", with a focused goal and interactional style. The "IntelliCare" system is elemental, allowing individual apps to be used upon their effectiveness and utility, and it is eclectic, viewing treatment strategies as elements that can be ap¬plied as needed rather than adhering to a singular, overarching, theoretical model.

In the same context, Hung et all. (2016) published results of a smartphone application, iHOPE, used to perform daily ecological momen¬tary assessment of depression, anxiety, sleep and cognitive performance in a large sample of population. The study provides initial evidence for the feasibility of smartphone-based ecological momentary assessment in Chinese pa¬tients with depression.

In our recently published article [Loleski et al, 2018] we discussed the obtained results for healthy examinees (N=201) divided in several groups - schoolers, athletes, scientists and others. In this article we showed that reaction time is strongly dependent on age; no significant differences for both gender and type of profession

are obtained. Surprisingly, we showed that any sport activities do not influence on the reaction time. In other words, sportive activities do not influence to the reaction time. Generally, in this study we confirmed the availability and practical values of Android applications in testing attention and concentration measured by reaction time in healthy people.

The aim of this study was to test availability of our custom built android application named as "Neurogame" for the evaluation reaction time in different psychiatric patients. As it is known from neurophysiology, reaction time is strongly related to the concentration and attention in examinees, two main part of cognitive abilities, especially related to the executive brain functions.

SAMPLE AND METHODOLOGY

The research involves patients with different psychiatric disorders: depression, psychosis, general anxiety and ADHD. Total number of examinees was N=100, selected by chance, both gender included. Prior consent was obtained following Helsinki declaration (2000). All examined subjects obtained the diagnosis in psychiatric institution following DSM 4 criteria. All subjects were stable and in remission of symptoms, but still taking medications. The evaluation is performed during regular ambulatory control.

Our original Android application was used for testing reaction time, number of hits, misses and total tries following five levels of the game (very easy, easy, normal, hard and very hard). Every level has a duration of 40 sec., each next level being more difficult i.e. the ball moves faster. The client must press the start with the left thumb and as fast as he/she can to press the stop with the right thumb not allowing the ball to pass the median circle. Obtained results for all examinees are presented in tables and figures. Statistic parameters are calculated using Statistic package 8.

RESULTS

The Fig. 1 shows the screen of Neurogame.

Table 1 shows age of examinees in years, standard deviation and number of tested patients by group.

Table 1. Age and number of all examinees

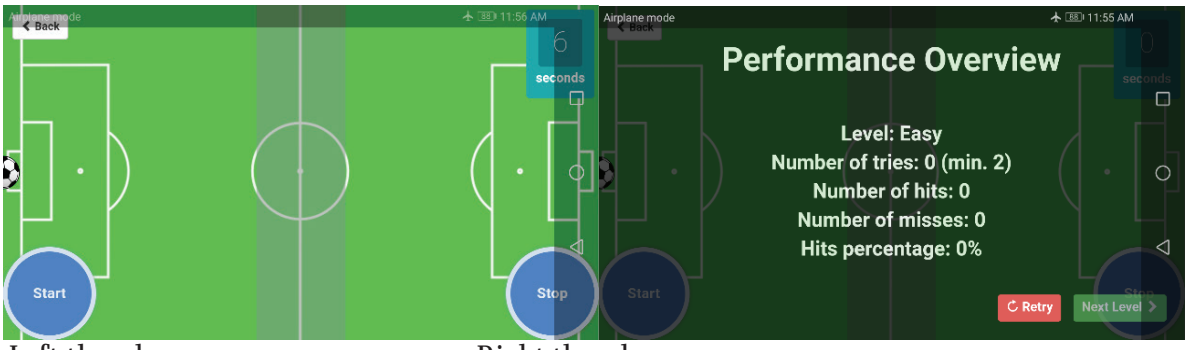
Age in years		Number	Diagnosis
31,38±16,95		35	depression
22,16±7,72		15	psychosis
24,40±15,79		20	anxiety
9,8±3,5		30	adhd
		100	total
50±1,0		50	healthy

Obtained average reaction time (t h) for all groups is presented on Fig. 2.

To clarify, t h presents average time calculated from the pressing start with the left thumb to the right thumb pressing stop. If the hit is achieved, (it means that the football is captured at the middle of the screen), the hit is positively calculated. But, in the case where the left thumb starts the ball and the right thumb selects stop option, but the ball is not captured in the middle, than the result is not recorded as a hit.

As can be seen, total reaction time is practically similar in all examinees. However, it is highest in healthy group, followed by anxiety patients, patients with depression, while the slowest reaction time was obtained for psychosis and ADHD group. Similarly, the number of hits/ msec. is also highest in healthy group, followed by anxiety, depression, psychoses, and the lowest for ADHD patients, which seems very logical.

Calculated one way ANOVA confirmed highly significant difference of all tested parameters (tT= total tries; tH =



Left thumb Right thumb

Fig 1. The "Neurogame" screens

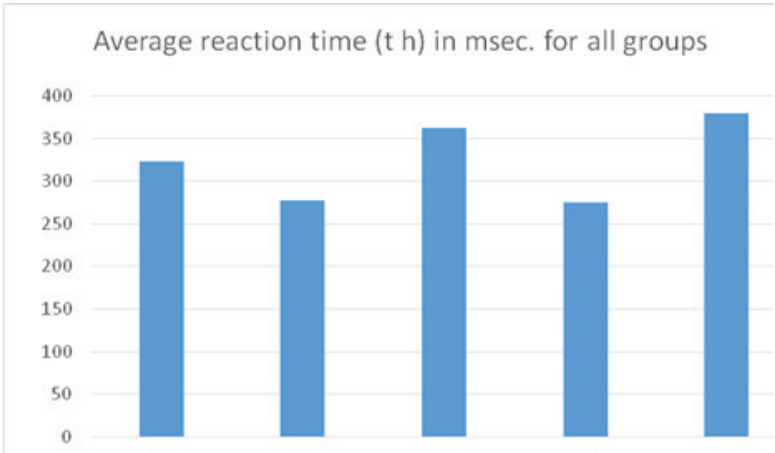


Fig. 2 Average reaction time (t h) in milliseconds in all evaluated groups compared with healthy people

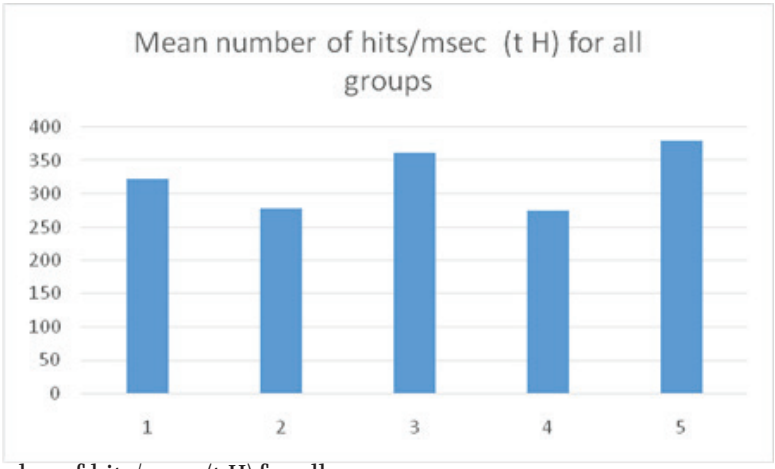


Fig.3 Mean number of hits/msec (t H) for all groups

Table 2. One way ANOVA for gender influence on tested parameters
(t T= total tries; t H = total hits; t M = total misses; t h = total time)

Effect	SS	Degr. of Freedom	MS	F	p
Intercept	672261.3	1	672261.3	2520980	0.000000
t T	14.1	57	0.2	1	0.604929
Error	4.0	15	0.3		

Effect	SS	Degr. of Freedom	MS	F	p
Intercept	668630.5	1	668630.5	3209426	0.000000
t M	14.7	56	0.3	1	0.311136
Error	3.3	16	0.2		

Effect	SS	Degr. of Freedom	MS	F	p
Intercept	623990.	1	623990.	263462	0.00000
t h	13.6	53	0.3	1	0.44206
Error	4.5	19	0.2		

Effect	SS	Degr. of Freedom	MS	F	p
Intercept	537889.	1	537889.	175366	0.000000
t H	7.7	38	0.2	1	0.895733
Error	10.4	34	0.3		

Table 3. One way ANOVA for age influence on tested parameters
(t T = total tries; t H = total hits; t M = total misses; t h = total time)

Effect	SS	Degr. of Freedom	MS	F	p
Intercept	57645.22	1	57645.22	288.4825	0.000000
t T	14800.69	57	259.66	1.2995	0.295813
Error	2997.33	15	199.82		

Effect	SS	Degr. of Freedom	MS	F	p
Intercept	47925.88	1	47925.88	171.0321	0.000000
t h	12473.93	53	235.36	0.8399	0.699746
Error	5324.10	19	280.22		

Effect	SS	Degr. of Freedom	MS	F	p
Intercept	36938.00	1	36938.00	144.3301	0.000000
t H	9096.50	38	239.38	0.9353	0.581260
Error	8701.53	34	255.93		

Effect	SS	Degr. of Freedom	MS	F	p
Intercept	54990.33	1	54990.33	195.6154	0.000000
t M	13300.19	56	237.50	0.8449	0.690782
Error	4497.83	16	281.11		

total hits; tM = total misses; th = total time) for age and gender (Table 2 and 3).

Pearson's coefficient of correlation was calculated for all four parameters between healthy vs. non-healthy patients (Fig.4) and was significantly negative, except for the total time reaction (last line).

Calculation of Student t-test give us significance of differences in mean values and standard deviation of obtained results for two groups. Comparison of healthy vs all non-healthy group is presented on Table 4. For parameters tT tH tM obtained results are significant. T-test obtained for total time for healthy vs. non-healthy group is non-significant, which is related to other results.

Calculated Student t-test for anxiety versus healthy group is not significant [t-test=-0.365 p= 0.71].

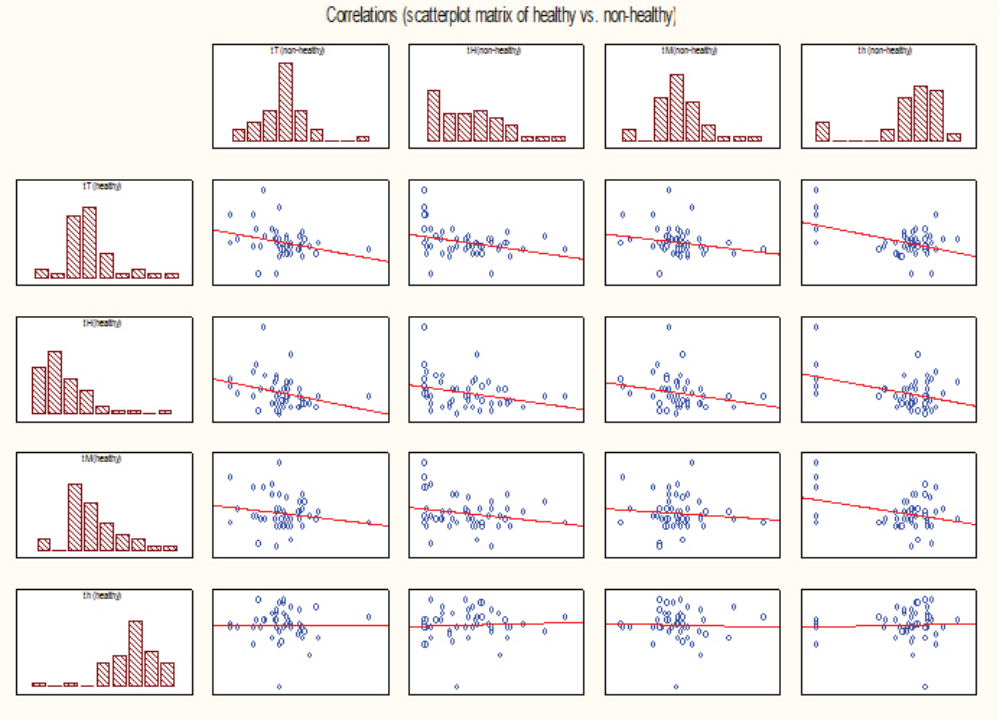


Fig. 4 Correlation scatterplot matrix (healthy vs. non-healthy)
[For the tT, tH, tM correlation is negative, while for th no correlation was obtained]

Table 4. Student t-test healthy vs. non-healthy group

	T-test for Independent Samples (healthy vs. non-healthy) Note: Variables were treated as independent samples										
Group 1 vs. Group 2	Mean Group 1	Mean Group 2	t-value	df	p	Valid N Group 1	Valid N Group 2	Std.Dev. Group 1	Std.Dev. Group 2	F-ratio Variances	p Variances
t T (healthy) vs. t T (non-healthy)	195.4792	159.5493	2.8153	117	0.005720	48	71	65.07311	70.3793	1.16973	0.572402
t H (healthy) vs. t H (non-healthy)	45.5625	31.3803	2.3621	117	0.019821	48	71	36.46561	28.8565	1.59691	0.074396
t M (healthy) vs. t M (non-healthy)	149.9167	128.1690	2.1801	117	0.031256	48	71	50.81331	55.0447	1.17348	0.564405
t h (healthy) vs. t h (non-healthy)	346.3750	321.9577	1.0647	117	0.289213	48	71	86.90754	141.7932	2.66192	0.000530

For the group with depression, only for total trial (tT) t-test is significant [t value = 2, 06 p= 0, 04].

For psychotic patients, significant t-test was obtained for total trials [t value= 2, 50 p=0, 01], as well as for total hits[t value=2, 82 p= 0,006].

This results are confirmed by one way ANOVA calculated for all parameters comparison for healthy vs. psychotic, depressive and anxious patients.

For the group of patients with psychosis vs healthy persons one way ANOVA for total tries (t T), for total hits (t H), as well as for total time (t h) was significant, except for total misses (t M) which was non-significant (table 5)

Table 5. One way ANOVA of t T, t H, t M and t h between Psychoses vs. Healthy group

Effect	ANOVA (healthy vs psychosis) SS	Degr. of Freedom	MS	F	p
Intercept	620014.5	1	620014.5	2811.857	0.012004
t T (psychosis)	75128.4	10	7512.8	34.072	0.132609
Error	220.5	1	220.5		

Effect	ANOVA (healthy vs psychosis) SS	Degr. of Freedom	MS	F	p
Intercept	57021.6	1	57021.6	12.7730	0.03744
t H (psychosis)	14205.0	8	1775.6	0.3977	0.86784
Error	13392.6	3	4464.2		

Effect	ANOVA (healthy vs psychosis) SS	Degr. of Freedom	MS	F	p
Intercept	1492267	1	1492267	372.7871	0.002672
t h (psychosis)	44419	9	4935	1.2329	0.525611
Error	8006	2	4003		

Effect	ANOVA (healthy vs psychosis) SS	Degr. of Freedom	MS	F	p
Intercept	270900.8	1	270900.8		
t M (psychosis)	42142.3	11	3831.1		
Error		0			

Table 6. One way ANOVA for parameters between Healthy vs Depression (Comparison by t T, t H, t M and t h)

Effect	ANOVA (healthy vs depression) SS	Degr. of Freedom	MS	F	p
Intercept	821334.7	1	821334.7		
t T (depression)	84646.3	17	4979.2		
Error		0			

Effect	ANOVA (healthy vs depression) SS	Degr. of Freedom	MS	F	p
Intercept	80446.82	1	80446.82	66.80242	0.014642
t H (depression)	37622.00	15	2508.13	2.08273	0.372113
Error	2408.50	2	1204.25		

Effect	ANOVA (healthy vs depression) SS	Degr. of Freedom	MS	F	p
Intercept	391851.5	1	391851.5	110.287(	0.00184
t M (depression)	38048.7	14	2717.1	0.7645	0.688846
Error	10659.(	3	3553.(		

Effect	ANOVA (healthy vs depression) SS	Degr. of Freedom	MS	F	p
Intercept	2034673	1	2034673	114.1392	0.008648
t h (depression)	191749	15	12783	0.7171	0.721677
Error	35653	2	17826		

For anxious patients one way ANOVA shows significant results for total time (t h) [F= 20901.43 p= 0,004]. All other parameters (t H, t M and t T) were similar for both groups healthy/anxious.

DISCUSSION

Psychoinformatics, a relatively a new field in medicine comprises the cooperation between the disciplines of psychology/psychiatry and computer science in handling large data sets derived from heavily used devices, such as smartphones or online social network sites, in order to enlighten a large number of psychological traits, including personality and mood (Montag et al, 2016). Digital mental health tools have tended to use psychoeducational

strategies based on treatment orientations developed and validated outside of digital health.

A pilot study of Mohr et al, (2017) presents a coach-assisted version of a system named IntelliCare and evaluate its use and efficacy at reducing symptoms of depression and anxiety. Authors explained IntelliCare apps as a very interactive, emphasizing the application of skills through in-app actions, which is different from other known app systems.

Searching in the most known database related to health (PubMed, PsycINFO, Cochrane, Scopus, Embase and Web of Science) we can found an emerging evidence that mobile phones can play an important role in health care delivery, especially in mental health. Generally, in many published articles devoted to mental health and smartphone, it was shown that text messaging was used in a wide range of mental health situations. Especially, messages are used for manage some problems such as substance abuse, schizophrenia, and affective disorders. In this context, it was identified four ways in which text messages were used: reminders, information, supportive messages, and self-monitoring procedures. Berrouiguet S. et al, (2016) showed that text messaging was especially used in the management of chronic conditions, reactive conditions, and preventative strategies for healthy or at-risk individuals.

Mobile mental health has a potential to improve the recognition and management of patients with depression (Hung S. et al, 2016). A smartphone application, named iHOPE, was used to perform daily data of depression, anxiety, sleep and cognitive performance.

Based on the knowledge that suicide is a global problem worldwide, a rapid growth in the use of new technologies such as mobile health applications (apps) to help identify and support those at risk for suicide has been noticed.

In a study of Larsen et al (2016) it was proposed two apps which provided some degree of interactive psychotherapeutic content, and another which provided postvention support for those bereaved by suicide. Both of the apps which delivered psychotherapy were based on cognitive therapy, one in the context of depression, and the other for deliberate self-harm. Both apps used thought challenging techniques: the depression app provided a tool that assisted users in identifying and challenging negative thoughts, while the other app system provided a space to think about negative thoughts and to reframe them positively.

Anyhow, many adolescents and adults do not seek treatment for mental health symptoms. Smartphone applications (apps), being more practical and available worldwide, may assist individuals with mental health concerns in alleviating symptoms or increasing understanding. In a study of Radovic et al. (2016) it was presented that the most common supported purpose for the apps was symptom relief and general mental health education. However, it was shown that these approaches for improving mental health were useful by teaching relaxation only for milder symptoms. Still, the most app descriptions did not include information to substantiate stated effectiveness of the application and had no mention of privacy or security.

Our custom Android application is used for assessing attention, concentration and reaction time in some psychiatric patients: depression, psychosis, general anxiety and ADHD. Reaction time is measured by positive total hits in the 40 second five levels games, using press on the screen of both thumbs of the preferred hand. All examined subject have diagnosis made in psychiatric institution following DSM 4 criteria. All subjects were in remission, but still taking medications.

It is known that attention and concentration are the main function of the executive brain system. In this context, our Android application indirectly measure the function of executive system in these patients. In our previous researches this evaluation we made by QEEG recording, especially by ERP's component in the EEG (Pop-Jordanova et al, 2008, 2010; Markovska-Simoska et al, 2011, 2016, 2017). However, mobile phone application seems more practical, need few time consuming, and it is portable and interesting for all examinees.

In the future research, we will ameliorate the system including possibilities to record movements, tremor and other characteristics of some neurological disorders.

CONCLUSION

The aim of this study was to test the availability of our application for evaluation of the reaction time in different psychiatric patients. Reaction time is strongly to the executive brain functions.

We showed that average reaction time, as well as number of hits in psychiatric patient compared with healthy people is not significantly different.

Significant differences are confirmed for age and gender

issues.

The most important differences are found in number of hits, misses and tries in the group of depressed, psychotic and ADHD patients, while anxious showed pretty normal parameters.

Further research in the similar direction is proposed.

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ORIGINALLY MADE ANDROID GAME APPLIED IN DIFFERENT PSYCHIATRIC DISORDERS

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АБСТРАКТ

Потенцијалот за примена на модерните мобилни телефони е голем. Дигиталните алатки во областа на менталното здравје користат психоедукативни стратегии за третмански ориентации развиени и валидизирани надвор полето на дигиталното здравје.

Цел на оваа студија беше да се тестира подобноста на оваа оригинална апликативна алатка која ние ја нарековме Неурогаме за евалуација на реакционото време кај разни психијатриски болни. Реакционото време корелира со егзекутивната функција на мозокот.

Испитуваната група ја сочинуваат 100 психијатриски болни (депресија, општа анксиозност, психоза и АДХД), споредени со 50 здрави луѓе.

Добиените резултати покажаа зна~ајни разлики во тестираните параметри зависно од возраста и полот на испитаниците. Дополнително, средното реакционо време, како и бројот на погодоци кај психијатриските болни споредени со здравата популација не се значајно различни. Сепак, најголемите разлики се најдени во бројот на погодоци, промашувања и обиди во групата на депресивни, психоти~ни и АДХД пациенти споредено со здравите, додека анксиозните болни покажаа скоро нормални резултати.

Можно е влијание на медикаментите врз добиените резултати, но ние сметаме дека сепак тие се должат на особеностите на самите болести.

Клучни зборови: андроидна апликација, егзекутивни функции, депресија, анксиозност, АДХД, психоза.

Original scientific paper

КВАЛИТЕТ НА ЖИВОТ КАЈ ПАЦИЕНТКИ СО ЦЕРВИКАЛНА ДИСПЛАЗИЈА ПРЕДИЗВИКАНА ОД ХУМАН ПАПИЛОМА ВИРУС ВО ОДНОС НА СОЦИОДЕМОГРАФСКИТЕ ФАКТОРИ

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АПСТРАКТ

Вовед: Цервикалниот карцином е еден од најчестите малигноми кој се дијагностицира кај жените. За негов развој не е доволна само перзистенцијата на Хуман папилома вирусот, туку зависи од бихејвиоралните, сексуалните и социоекономските фактори. Целта на нашата студија беше да се одреди квалитетот на живот кај пациентки со абнормална цервикална цитологија и позитивна ХПВ инфекција во однос на социодемографските карактеристики. Материјал и методи: Во испитувањето вклучени се 200 пациентки кај кои е дијагностицирана цервикална дисплазија или цервикален канцер на Универзитетска клиника за гинекологија и акушерство–Скопје. Потребните податоци собрани се со модифициран анкетен прашалник ЈОКА-2015. Од секоја пациентка беше земен податок за место на живеење, етничка припадност, степен на образование, возраст и сексуална возраст, занимање и постојан партнер/брачен другар. Резултати: Резултатите покажаа дека пациентките кои живеат на село, пациентките ученик/студент, пациентките со високо образование, пациентките кои немаат постојан партнер/брачен другар, како и невработените, имаат незначително поквалитетен живот во однос на пациентките кои живеат во град, со средно и средно стручно образование, вработените пациентки и пензионерите, кои незначително имаат помал квалитет на живот. Во однос на етничката припадност нема значајна разлика во квалитетот на животот на пациентките. Заклучок: Во нашата студија се покажа сигнификантно делување на местото на живеење, возраста и сексуалната возераст, образованието, етничката припадност, како и брачниот статус од социодемографските ризик фактори, врз квалитетот на живот.

Клучни зборови: цервикална дисплазија, цервикален канцер, HPV, демографски карактеристики, квалитет на живот.

ВОВЕД:

Карциномот на грлото на матката е трета најчеста неоплазма кај жени. На глобално ниво, ракот на грлото на матката опфаќа околу 528.000 нови случаи на рак во светот и 266.000 смртни случаи во 2012 година (1). Во развиените земји во 2012 година ракот на грлото на матката беше единаесеттиот најчест вид на рак кај жените (9,9 на 100.000 жени) и деветтата најчеста причина за смртност од рак (3,3 на 100.000)(2). Годишно инциденцата на цервикална интраепителна неоплазија (CIN) во САД кај жените кои се подложени на скрининг на рак на грлото на матката е 4 проценти за CIN 1 и 5 проценти за CIN 2,3 (3) Лезиите со висок степен обично се дијагностицираат кај жени на возраст од 25 до 35 години, додека инвазивниот рак најчесто се дијагностицира кај жени по 40-годишна возраст, обично 8-13 години по дијагностицирање на високо-степенска лезија. Хуман папилома вирус (ХПВ) инфекцијата е одговорна за преинвазивни промени на грлото на матката (цервикална интраепителна лезија), како и за цервикален карцином кај најголем број од жените. За развој на цервикалната епителијална лезија, како и за развој на цервикалниот карцином, не е доволна само перзистенцијата на ХПВ инфекцијата, туку во голема мерка зависи од бихејвиоралните, сексуалните и социоекономските фактори како фактори на ризик. (4)

Во литературата се објавени повеќе од 200 типови на ХПВ од кои 40 се одговорни за промени на аногениталната мукоза, а од нив 15 се високо ризични. (5) Високо ризичните типови на ХПВ, како што се 16 и 18, се силно поврзани со лезии со висок степен (CIN 2,3), перзистентност и прогресија на инвазивен канцер, иако што може да бидат поврзани и со лезии од низок степен. HPV 16 и 18 сочинуваат 25 % од лезиите со

низок степен, 50 до 60 % од лезиите со висок степен и 70 % од карциномите на грлото на матката (6).

Цервикалната интраепителна неоплазија (CIN), како и карциномот на грлото на матката може да се детектира со редовен скрининг за рак на грлото на матката, кој вклучува цервикална цитологија и тестирање за онкогени подтипови на Хуман папилома вирус (ХПВ), со што може да се редуцира карциномот на грло на матка и до 70% (7). Следење на абнормалните скрининг тестови со колпоскопија и цервикална биопсија резултира со навремена детекција на CIN и рак на грлото на матката.

Лезиите со висок степен обично се дијагностицираат кај жени на возраст од 25 до 35 години, додека инвазивниот рак најчесто се дијагностицира кај жени по 40-годишна возраст, обично 8-13 години по дијагностицирање на лезија од висок степен. Абнормалниот цитолошки наод како и наодот на ХПВ инфекција често резултира со промена на квалитетот на живот кај пациентките предизвикувајќи страв и анксиозност (8,9)

Од прегледот на досегашната литература се уште не постојат голем број на податоци за ефектот на ХПВ инфекцијата и абнормалната цитологија, врз квалитетот на живот кај жената (10)

Целта на нашата студија беше да се одреди квалитетот на живот кај пациентки со абнормална цервикална цитологија и позитивна ХПВ инфекција во однос на социодемографските карактеристики.

МАТЕРИЈАЛ И МЕТОДИ:

Во испитувањето вклучени се 200 пациентки постари од 18 години кај кои е дијагностицирана цервикална дисплазија предизвикана од Хуман папилома вирусот изведено на Универзитетска клиника за гинекологија и акушерство-Скопје (УГАК) во периодот 1.10. 2017 – 31.03.2018 година. Цервикалната дисплазија беше детектирана со помош на анализа на ПАП тест, кој беше земен од искусен гинеколог и анализиран од искусен цитолог. ХПВ детекцијата беше направена со помош на PCR (polymerase chain reaction) метода во цитогенетската лабораторија на УГАК. Потребните податоци собрани се со модифициран анкетен прашалник ЈОКА-2015 кој се состои од четири дела: социодемографски дел, генерални факти за ХПВ, ефекти кои влијаат на идната бременост, прашалник за проценка на квалитетот на живот кај пациентките. Секоја пациентка беше испитана за место на живеење, етничка припадност, степен на образование, возраст и сексуална возраст, занимање и постојан партнер/ брачен другар.

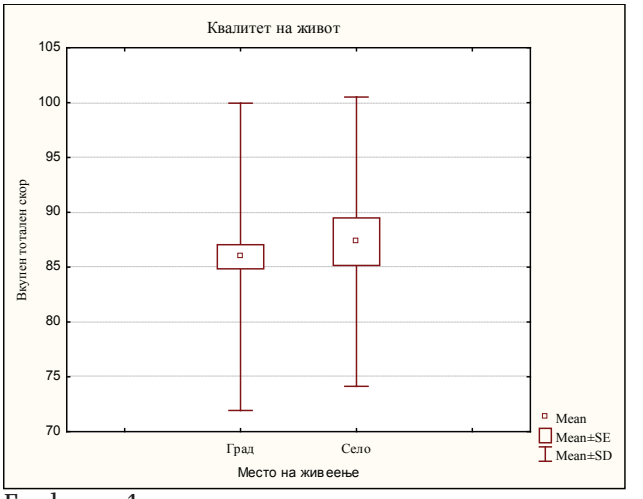
РЕЗУЛТАТИ:

1. Место на живеење

На табела 1 и графикон 1 прикажаните резултати се однесуваат на разликата во квалитетот на животот на пациентките во однос на местото на живеење. Имено, пациентките кои живеат на село имаат незначајно поквалитетен живот во однос на пациентките кои живеат во град. (p=0,59)

Табела 1. Квалитет на живот / Место на живеење

Квалитет на живот	Просек Град	Просек Село	t-value	df	p	N Град	N Село	Стд.Дев. Град	Стд.Дев. Село
Вкупен тотален скор	85,94	87,32	-0,55	198	0,59	163	37	14,01	13,18



Графикон 1

2. Етничка припадност

Резултатите кои се однесуваат на квалитетот на животот на пациентките во однос на етничката припадност прикажани се на табела 2. За F=0,83 и p>0,05 (p=0,53) нема значајна разлика во квалитетот на животот на пациентките во однос на етничката припадност.

Помеѓу просечни вредности на вкупниот тотален скор кои се однесуваат на квалитетот на животот на пациентките во однос на етничката припадност, македонска (П=85,75), албанска (П=89,32), турска (П=88,80), ромска (П=88,25), српска (П=87,75), категорија друго (П=64,00), за p>0,05 нема значајна разлика.

Табела 2. LSD Test / Етничка припадност

Етничка припадност	{1} П=85,75	{2} П=89,32	{3} П=88,80	{4} П=88,25	{5} П=87,75	{6} П=64,00
Македонска {1}		0,26	0,63	0,72	0,78	0,12
Албанска {2}	0,26		0,94	0,89	0,84	0,08
Турска {3}	0,63	0,94		0,95	0,91	0,10
Ромска {4}	0,72	0,89	0,95		0,96	0,12
Српска {5}	0,78	0,84	0,91	0,96		0,13
Друго {6}	0,12	0,08	0,10	0,12	0,13	

П / просек

3. Степен на образование

Резултатите кои се однесуваат на квалитетот на животот на пациентките во однос на степенот на образование покажуваат дека нема значајна разлика во квалитетот на животот на пациентките во однос на степенот на образование. (F=1,65 и p>0,05(p=0,15))

Табела 3. Квалитет на живот / Степен на образование

Квалитет на живот	SS Effect	df Effect	MS Effect	SS Error	df Effect	MS Error	F	p
Вкупен тотален скор	1550,60	5	310,12	36543,40	194	188,37	1,65	0,15

Резултатите од post-hoc компарацијата на просечните вредности од вкупниот тотален скор за квалитет на живот во однос на степенот на образование на пациентките прикажани се на табела 4. Пациентките со високо образование за p<0,05 имаат значајно поквалитетен живот во однос на пациентките со средно и средно стручно образование. Во останатите релации за p>0,05 нема значајна разлика во квалитетот на животот на пациентките во зависност од степенот на образование.

Табела 4. LSD Test / Степен на образование

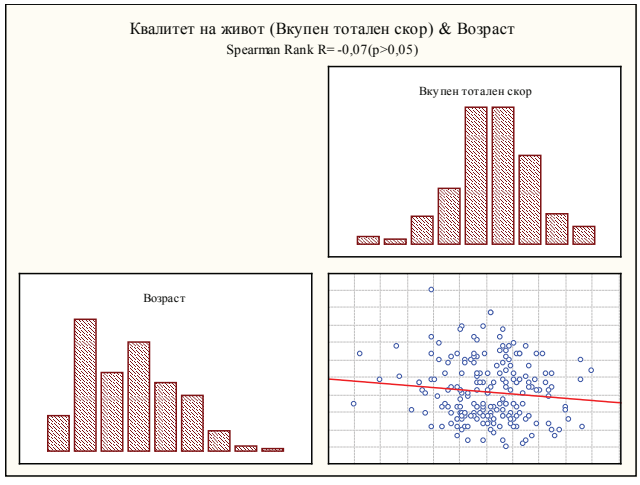
Степен на образование	{1} П=87,00	{2} П=86,49	{3} П=84,81	{4} П=80,87	{5} П=89,33	{6} П=76,00
Без образование {1}		0,97	0,87	0,67	0,87	0,49
Основно образование {2}	0,97		0,55	0,19	0,32	0,21
Средно образование {3}	0,87	0,55		0,31	0,04	0,28
Средно стручно образование {4}	0,67	0,19	0,31		0,03	0,58
Високо образование {5}	0,87	0,32	0,04	0,03		0,10
Друго {6}	0,49	0,21	0,28	0,58	0,10	

П / просек

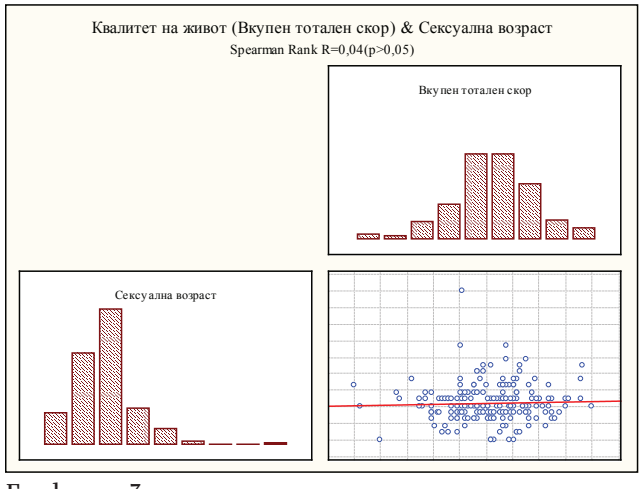
Пациентките со основно образование просечно за 0,51 (Б=-0,51), со средно образование просечно за 2,19 (Б=-2,19), со средно стручно образование просечно за 6,13 (Б=-6,13), имаат незначајно помал квалитет на живот компарирано со пациентките без образование, при непроменети вредности на останатите параметри додека пак, пациентките со високо образование просечно за 2,33 (Б=2,33) имаат незначајно поголем квалитет на живот компарирано со пациентките без образование, при непроменети вредности на останатите параметри. Како референтна категорија земена е категоријата без образование.

4. Возраст и сексуална возраст на пациентите

Резултатите покажаа многу слаба негативна незначајна корелација за возраста, (R= -0,07 и (p>0,05), како и за сексуалната возраст на пациентката (R= 0,04 и (p>0,05)) Имено, со пораст на возраста на пациентките квалитетот на животот опаѓа, меѓутоа корелацијата е незначајна. Додека пак, со пораст на сексуалната возраст на пациентките квалитетот на животот расте, меѓутоа корелацијата е незначајна што е прикажано на графиконите бр 2 и 3.



Графикон 2



Графикон 3

5. Занимање

Резултатите кои се однесуваат на квалитетот на животот на пациентките во однос на занимањето, покажаа дека постои значајна разлика во квалитетот на животот на пациентките во однос на занимањето.

(F=2,43 и p<0,05 (p=0,04)

Табела 5. Квалитет на живот / Занимање

Квалитет на живот	SS Effect	df Effect	MS Effect	SS Error	df Effect	MS Error	F	P
Вкупен тотален скор	1808,15	4	452,04	36285,85	195	186,08	2,43	0,04

Резултатите прикажани на табела 6. се однесуваат на корелацијата помеѓу тоталниот скор на квалитет на живот на пациентките и занимањето.

За R=0,22 и p<0,05 во испитаниот однос утврдена е умерено слаба значајна корелација.

Како референтна категорија земена е категоријата друго занимање.

Пациентките со занимање ученик/студент, како и невработените, просечно имаат незначајно поголем квалитет на живот компарирано со пациентките од категоријата друго занимање, додека пак, вработените пациентки и пензионерките имаат незначајно помал квалитет на живот компарирано со пациентките од категоријата друго занимање, при непроменети вредности на останатите параметри.

6. Постојан партнер/брачен другар

Резултатите покажаа дека пациентките кои немаат постојан партнер/брачен другар имаат незначајно поквалитетен живот во однос на пациентките кои имаат постојан партнер/брачен другар.

Пациентките кои имаат постојан партнер/брачен другар (1) просечно за 1,55 (Б=-1,55) имаат незначајно помалку квалитетен живот во однос на пациентките кои немаат постојан партнер/брачен другар.

Табела 6. Квалитет на живот & Постојан партнер/брачен другар / Корелација

Regression Summary for Dependent Variable: Квалитет на живот
R= 0,04; F(1,198)=0,37 и p<0,54

	Beta	Std.Err. of Beta	B	Std.Err. of B	t(198)	p-level
Intercept			87,47	2,31	37,87	0,00
Постојан партнер/брачен другар (1)	-0,04	0,07	-1,55	2,55	-0,61	0,54

Постојан партнер & брачен другар (1) / Има

ДИСКУСИЈА

Со нашата студија докажавме дека цервикалната дисплазија и ХПВ инфекцијата делува на квалитетот на живот кај жената, зависно од демографските карактеристики. Во литературата се опишани психолоши нарушувања после дијагностицирање на ХПВ инфекцијата кои делуваат на промена на квалитетот на живот и потекнуваат од неколку извори, како што се болка и срам при прегледот, анксиозност при чекање на резултати, стравот од премин во цервикален канцер или неразбирање на резултатите од тестирањето (11). Досега многу малку истражувања и внимание е посветено на психолошката состојба и квалитетот на живот со ХПВ инфекција кај жени во Македонија. Во една студија во Велика Британија каде што се испитани 84 жени со CIN1, 203 жени со CIN 2/3 и 186 со генитални кондиломи, докажано е дека ХПВ инфекцијата и преканцерозните лезии на грлото на матка имаат сигнификантно негативно влијание на психолошката благосостојба и на квалитетот на живот кај жената (12). Анксиозноста, дистресот и вознемиреноста е најмногу изразено кај жени со средна дисплазија, или во случаи каде што ризикот за премин во малигнитет е голем.

Во една студија во Кина каде што биле вклучени 2086 жени од урбана средина и 519 жени од рурална средина, потврдено е дека ХПВ инфекцијата сигнификантно делува повеќе на психолошката состојба кај жените во урбана средина, со тоа и на квалитот на живот (13). Истото беше потврдено во нашата студија во која докажавме дека пациентките кои живеат во село имаат појквалитетен живот.

Најголемо дејство има на емоционалната, социјалната и сексуалната функција кај жените. Абнормален наод на ПАП тест или позитивна ХПВ типизација иницијално е придружено со шок за некои пациентки, страв, себеобвинување, снеможеност и нервоза (14)

Во нашата студија беше покажано дека пациентките кои имаат непостојан партнер имаат поквалитетен живот. За разлика од тоа, во студијата на Wanessa Cassemiro Fernandes1 докажано е дека пациентките кои имале постојан партнер имаат подобар квалитет на живот како резултат на физичка, емоционална и психолошка поддршка од истиот (15).

Прогресијата на болеста има влијание врз сексуалното здравје на жената и квалитетот на живот. Чувството на загрозеност на здравјето зависи и од степенот на лезиите бидејќи тие бараат поинаква агресивност на третманот и следење.

ЗАКЛУЧОК

Анализата на квалитетот на живот кај пациентките во однос на социодемографските фактори укажа дека: пациентките кои живеат на село имаат незначајно поквалитетен живот во однос на пациентките кои живеат во град; нема значајна разлика во квалитетот на животот во однос на етничката припадност на

пациентките; пациентките со високо образование имаат значајно поквалитетен живот во однос на пациентките со средно и средно стручно образование; со пораст на возраста на пациентките квалитетот на животот опаѓа, со пораст на сексуалната возраст на пациентките квалитетот на животот расте; вработените пациентки и пензионерки имаат значајно помалку квалитетен живот во однос на пациентките со занимање ученик/студент и невработените пациентки; пациентките кои немаат постојан партнер/брачен другар имаат незначајно поквалитетен живот во однос на пациентките кои имаат постојан партнер/брачен другар.

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Original scientific paper

CLINICAL THERAPEUTIC EFFECTS OF USING THE CORONARY ADVANCED FLAP TECHNIQUE COMBINED WITH XENOGENEIC COLLAGEN MATRIX

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ABSTRACT

Aim of the study. To investigate the therapeutic effect of the application of the coronally advanced flap technique combined with a xenogeneic collagen matrix in the treatment of gingival recessions in a three-month observational period.

Material and methods. The survey was conducted as a prospective clinical study with 17 patients that presented single gingival recession defects Miller Class I and II in the upper jaw and who were treated with a coronally advanced flap technique combined with a xenogeneic collagen matrix (Mucograft®, Geistlich, Wolhusen, Switzerland). Before the surgical intervention and in the follow-up period of 1 and 3 months, the following clinical parameters were registered and compared for each patient: the recession depth (RD), the periodontal probing depth (PD), and the level of the clinical attachment (CAL). The postoperative status was registered with clinical photos of the treated sites and the postoperative values of these parameters at 1 and 3 months after the surgery were statistically compared to the preoperative values using the Friedman ANOVA Chi Sqr. Test.

Results. At 1 and 3 month post-treatment, mean RD was respectively 0.66 and 0.61 compared to 2.26 at the baseline ($p<0.001$); mean PD was respectively 2.34 and 2.37 compared to 2.44 ($p>0.05$), whereas the mean CAL was respectively 2.99 and 2.98 compared to 4.7 ($P<0.001$) at the baseline.

Conclusion. The combination of the coronally advanced flap with a collagen membrane has contributed to the significant reduction of the recession depth (RD), the significant gain in the clinical CAL values, and the insignificant reduction of the periodontal probing depth at 1 and 3 months after surgery, compared to the preoperative values. Anyway, a longer follow-up period is needed in order to establish whereas these results are stable in time.

Keywords: Coronally advanced flap, Collagen membrane, Mucograft, recession depth, clinical attachment level

INTRODUCTION

Gingival recessions are one of the most common aesthetic and functional problems of the oral soft tissues, but from the aspect of the aetiology and treatment, they are also one of the most complex. In general, gingival recessions are defined as the exposure of the root surface, which occurs as a consequence of the apical migration of the marginal gingiva below the level of the enamel-cement boundary1. In many cases with gingival recession, other signs of the periodontal disease are also present.

The key factors which determine the successful management of gingival recessions are the identification of its etiologic agents and their elimination, the assessment of the degree of tissue involvement and last but not least, the selection and the careful implementation of the appropriate surgical procedure in order to achieve optimal root coverage, improved soft tissue aesthetics and reduced sensitivity. Since the 1960s, a series of surgical techniques have been used for the treatment of the gingival recessions. Membrane techniques used for the treatment of the gingival recessions have proven to be quite effective in improving periodontal parameters and recession depth, but at the same time, better results are achieved when the thickness of the gingival tissue is greater.2,3 It has been proven that the recession is

three times higher in cases where the non-resorbable membranes are placed at sites with thinner gingival tissue (less than 1.5 mm) than in sites with a thicker gingival tissue. 4 According to some authors, 2,3 it is required a minimum of 1 mm of gingival thickness at the recession site in order to achieve the expected radicular coverage results. Some authors have found that in recession cases treated only with the technique of the coronally advanced flap, the initial value of the keratinized gingival tissue affects the degree of the recession reduction 5 although other authors do not support these findings. 6

The most predictable treatment, considered the "gold standard" for root coverage, is the subepithelial connective tissue graft (SCTG). However, this technique offers a disadvantage related to the morbidity to the patient, where it is necessary to remove the connective tissue from the palate area. Adverse effects reported by individuals who have undergone this technique are discomfort and postoperative pain in the palatal wound.7

Recently, a new approach that consists in the combination of the coronally advanced flap with a xenogeneic bilayer collagen matrix (Mucograft, Geistlich), has been proposed for the treatment of the gingival recessions. 8 Mucograft (CM) contains 2 functional layers: a single occlusal cell layer composed of collagen fibers placed in a compact manner that prevents cellular adhesion and acts as a barrier, and a porous layer composed of loosely packaged collagen fibers that form spaces for the formation of blood clots and invasion of osteopoietic cells, allowing regeneration.

Several studies have concluded that the collagen matrix of porcine origin has proven to be as effective and predictable as the connective tissue graft for increasing the width of keratinized gingiva and to be associated with a significantly lower patient morbidity7, 9-12.

In 2009, Sanz et al.7 conducted a randomized retrospective clinical trial consisting of 20 patients followed for 1, 3 and 6 months with regard to keratinized tissue gained through SCTG vs CM augmentation. They found a statistically significant amount of keratinized tissue achieved with both grafting materials (2.6 mm and 2.5 mm respectively) and a lower patient morbidity associated with the collagen matrix. Similarly, in one of the first clinical studies that have compared CM to SCTG, McGuire et al.8found that for both techniques, parameters such as the mean clinical attachment level, the periodontal depth and the keratinized gingiva width, improved significantly compared to baseline. All parameters tested for differences between treatment groups also showed equivalence and at 6 months, no difference could be made in regards to colour or texture.

Since the approach is relatively new and there is still lack of sufficient data to prove its effectivity, we decided to investigate the therapeutic effect of the coronally-advanced flap technique combined with a xenogeneic collagen matrix in the treatment of gingival recessions in a three-month observational period.

MATERIAL AND METHODS

The research was conducted at the Clinic of Periodontology at the Dental University Clinical Center "St. Panteleimon" in Skopje, the Clinic of Periodontology at the University Clinical Centre in Kosovo, Prishtina, as well as in the "Dens-M" Clinic in Pristina, Kosovo.

It was a prospective clinical study that included 20 patients, selected according to the inclusion and exclusion criteria as presented in Table 1.

Table 1. The inclusion and exclusion criteria for selecting the patients

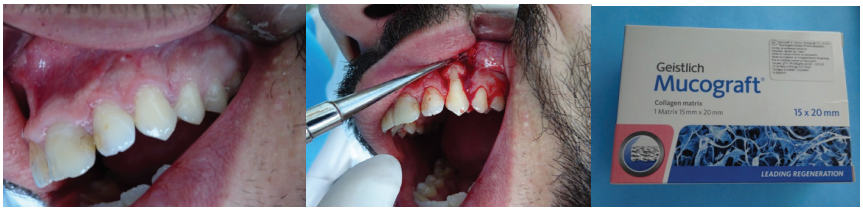
Inclusion criteria	Exclusion criteria
- Patients over 18 years of age; - Healthy individuals without systemic diseases; - The presence of single gingival recessions Miller Class I and II in the upper jaw; - Depth of recession ≤ 4 mm; - Keratinized gingival width ≥ 3 mm; - Patients with well-controlled plaque (FMPS <20%).	- Passionate tobacco smokers (more than 10 cigarettes per day). - Patients with registered systemic diseases (autoimmune, immune-compromising diseases). - The use of medicines that have the ability to compromise the wound healing; - Gravidity and lactation (in women); - Allergies to used drugs or other materials used during the research.

All patients who agreed to be included in the study, signed an informed consent form approved by the Ethics Committee of the Faculty of Medicine, University of Cyril and Methodius, and then were monitored according to a strict preoperative, operative and postoperative protocol.

At the baseline visit, immediately before the surgical procedure, and also after 1 and 3 months all subjects had the following clinical parameters being recorded by the same examiner: the recession depth (RD) measured as the distance in mm from the cement – enamel boundary of the tooth crown to the edge of the free gingiva; the

periodontal probing depth (PD) - i measured from the marginal gingival to the bottom of the gingival sulcus or pocket, at the vestibular tooth surface, with a graded periodontal probe with a protruding peak; the level of the clinical attachment (CAL) calculated as the sum of the depth of periodontal probing (PD) and the depth of the recession (RD).

After the data collection, the patients underwent the surgical intervention by two experienced specialists. The surgical intervention began with the administration of the appropriate local anaesthesia (Scandonest 3%, Septodont). The choice of the flap design was modified Widman flap. Mucograft was cut with Goldman-Fox scissors so that it could be easily adapted to the recession defect. The compact side wad placed oriented towards the outside whereas the spongy one towards the bone. Then, the flap was coronally advanced and sutured tension-free covering the membrane and the recession defect. It was sutured with a 5/0 silk suture.



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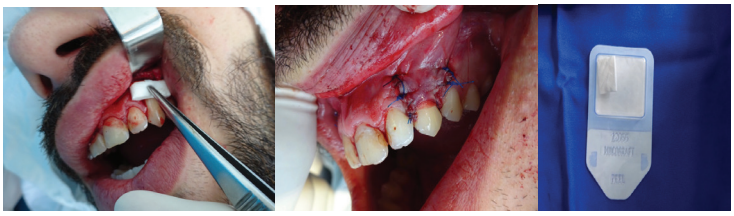

d e f

Fig.1 Surgical technique. a) Before treatment b) Flap preparation and raising c) d) Collagen membrane e) Collagen membrane adaptation f) Suturing

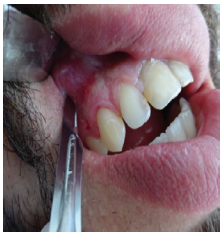

Fig.2 Postoperative result 3 months after surgery

After the intervention, all the patients received specific instructions regarding the maintenance of oral hygiene and post-operative wound care. All the participants were asked to rinse the mouth with Chlorhexidine 0.2%, 2 times a day for 2 weeks, while after 2 weeks to brush their teeth with a soft-fibres toothbrush with rotating movements. For the eventual pain and oedema, patients might receive Ibuprofen 400 mg. The sutures were removed after 10 days. Only 17 patients presented in the follow-on visits (drop-out rate 15%). The analysis of the data was performed using the statistical programs Statistica 7.1 for Windows and SPSS Statistics 17.0. Descriptive statistics were generated for both the preoperative and postoperative values and presented as means, SDs, 95% confidence intervals (CI), and Minimum and Maximum. In order to investigate the clinical effect of the treatment, differences between preoperative and post-operative values at 1 and 3 months of the analysed parameters have been tested with Friedman ANOVA Chi Sqr. / ($P<0.05$).

RESULTS

The results shown in Table 2 refer to the preoperative values of the recession depth (RD), the periodontal probing depth(PD), and the clinical attachment level (CAL). The value of the recession depth (RD) varied in the range 2.26 ± 0.86 mm, ± 95.00% CI: 1.82-2.70; the minimum value was 0.95 mm. and the maximum value was 3.76 mm.

The value of the periodontal probing depth (PD) varied in the interval 2,44 ± 0,30 mm, ± 95,00% CI: 2,29-2,59; the minimum value was 1.97 mm. and the maximum value was 3,01 mm.

The value of the clinical attachment level (CAL) varies in the range 4.70 ± 0.86 mm, ± 95.00% CI: 4.27-5.14; the minimum value was 3.23 mm. and the maximum value was 6.30 mm.

Table 2. Descriptive statistics of the analyzed parameters RD, PD and CAL, before the treatment in the examined region

Before the treatment	Valid N	Mean	Confidence -95,00%	Confidence +95,00%	Minimum	Maximum	Std.Dev.
RD	17	2,26	1,82	2,70	0,95	3,76	0,86
PD	17	2,44	2,29	2,59	1,97	3,01	0,30
CAL	17	4,70	4,27	5,14	3,23	6,30	0,86

The results shown in Table 3 refer to the values of the recession depth (RD), the depth of periodontal probing (PD) and the clinical attachment level (CAL) in the same research sample, 1-month post-treatment.

The value of the recession depth (RD) varied in the interval 0,66 ± 0,37 mm, ± 95,00% CI: 0,46-0,85; the minimum value was 0.23 mm. and the maximum value was 1.24 mm.

The value of the periodontal probing depth (PD) varied in the interval 2,34 ± 0,10 mm, ± 95,00% CI: 2,29-2,39; the minimum value was 2.12 mm. and the maximum value was 2.51 mm.

The level of clinical attachment (CAL) varied in the range 2,99 ± 0,37 mm, ± 95,00% CI: 2,80-3,19; the minimum value was 2.49 mm. and the maximum value was 3.67 mm.

Table 3. Descriptive statistics of the analysed parameters RD, PD and CAL, 1 month after the intervention in the examined region

After 1 month	Valid N	Mean	Confidence -95,00%	Confidence +95,00%	Minim um	Maximum	Std.Dev.
RD	17	0,66	0,46	0,85	0,23	1,24	0,37
PD	17	2,34	2,29	2,39	2,12	2,51	0,10
CAL	17	2,99	2,80	3,19	2,49	3,67	0,37

The results shown in Table 4 refer to the values of the recession depth (RD), the depth of the periodontal probing (PD), and the clinical attachment level (CAL) 3 months after the intervention.

The value of the recession depth (RD) varied in the range 0.61 ± 0.20 mm, ± 95.00% CI: 0.50-0.71; the minimum value was 0.32 mm. and the maximum value was 1.05 mm.

The value of the periodontal probing depth (PD) varied in the interval 2,37 ± 0,18 mm, ± 95,00% CI: 2,28-2,47; the minimum value was 2.04 mm, and the maximum value was 2.65 mm.

The value of the clinical attachment level (CAL) varied in the interval 2,98 ± 0,25 mm, ± 95,00% CI: 2,85-3,11; the minimum value was 2.58 mm. and the maximum value was 3.37 mm.

Table 4. Descriptive statistics of analysed parameters (RD, PD and CAL) 3 months after intervention

After 3 months	Valid N	Mean	Confidence -95,00%	Confidence +95,00%	Minimum	Maximum	Std.Dev.
RD	17	0,61	0,50	0,71	0,32	1,05	0,20
PD	17	2,37	2,28	2,47	2,04	2,65	0,18
CAL	17	2,98	2,85	3,11	2,58	3,37	0,25

Table 5. Differences in values of the depth of recession (RD) in patients before treatment, after 1 and 3 months of intervention

Friedman ANOVA Chi Sqr. (N = 17, df = 3) = 31,31 и p<0,001(p = 0,000)				
The depth of recession (RD)	Average Rank	Sum of Ranks	Mean	Std.Dev.
Before the treatment (RD)	4,00	68,00	2,26	0,86
After 1 month (RD)	2,09	35,50	0,66	0,37
After 3 months (RD)	1,91	32,50	0,61	0,20

The results shown in Table 5 refer to the difference between pre-treatment and 1 and 3-month post-treatment values of the recession depth (RD). The values of the recession depth (RD) 1 and 3 months (RD) post- treatment for N = 17, df = 3 and p <0.001 (p = 0.000) are significantly lower in relation to the preoperative values (Table 4).

The results shown in Table 5 refer to the difference between pre-treatment and 1 and 3-month post-treatment values of the periodontal probing depth(PD). The values of the periodontal probing depth 1 and 3 months after treatment (N = 17, df = 3) = 3.02 and p> 0.05 (p = 0.39) are lower than the pre-treatment values, but this difference is insignificant (Table 5).

Table 6. The difference in the values of the depth of periodontal probing depth(PD) in patients before the treatment, after 1 and 3 months of intervention

Friedman ANOVA Chi Sqr. (N = 17, df = 3) = 3,02 и p>0,05(p = 0,39)				
The depth of paradontal probe (PD)	Average Rank	Sum of Ranks	Mean	Std.Dev.
Before the treatment (PD)	2,88	49,00	2,44	0,30
After 1 month (PD)	2,21	37,50	2,34	0,10
After 3 months (PD)	2,62	44,50	2,37	0,18

Table 6. Difference in CAL values in patients before the treatment, 1 and 3 months of intervention

Friedman ANOVA Chi Sqr. (N = 17, df = 3) = 30,67 и p<0,001(p = 0,000)				
Clinical attachment level (CAL)	Average Rank	Sum of Ranks	Mean	Std.Dev.
Before the treatment (CAL)	4,00	68,00	4,70	0,86
After 1 month (CAL)	2,06	35,00	2,99	0,37
After 3 months (CAL)	2,00	34,00	2,98	0,25

The results shown in Table 6 refer to the difference between pre-treatment and 1 and 3-month post-treatment values of the clinical attachment level (CAL). The values of this parameter at 1 and 3 months after treatment (N = 17, df = 3) = 30.67 and p <0.001 (p = 0.000) are significantly lower than the preoperative values (Table 6).

DISCUSSION

Most of the studies concerning the treatment of the gingival recessions have been focused on the clinical effectivity of the coronally-advanced flap technique. Cortellini- Pini Prato5 confirm that the technique of the coronary advanced flap allows complete root coverage of Miller Class I and II recession defect with long-lasting and sustained results. Another study by De Sanctis-Zuccelli6 which investigated the 3-year results of the treatment of Miller Class I and II recessions with a coronally-advanced flap technique, root coverage after 1 and 3 years was 98.6% and 96.7% while the gain in the clinical attachment level was 3.65 +/ -1.10 and 3.70+/- 1.09 mm, a gain which was also accompanied with a significant increase in the width of the keratinized gingiva.

In our research, where we combined the coronally advanced flap technique with a xenogeneic collagen matrix, we found that the mean RD after 1 and 3 months (respectively 0.66 and 0.61) was significantly reduced (p<0.001) in comparison to the baseline (2.26). The technique has thus ensured a very significant reduction of the recession depth, a finding which is totally in concordance with the study of McGuire and Scheyer (2010)8, where the mean recession depth after treatment was o.52 mm and the reduction was very significant (p=0.0062).

Also, in terms of clinical attachment gain, the results from this investigation confirm the previous published results using the same xenogeneic material. In our survey, at the baseline, the mean CAL was 4.7 ±0.86, a value which was significantly reduced (p<0.001) to 2.99±0.37 mm 1 month post-operatively and 2.98±0.25 3 months post-operatively. This is an indication that, similarly with Cardaropoli et al (2012) 9- where CAL after 12 months was 2.41± 0.28 mm and the difference was significant (P<0.001)- the technique has had a significant impact in terms of clinical attachment gain. In another study of Castro and Grados (2014) 13 CAL value after 2 months was 3.17±0.98 mm, a value which is not very different from ours.

Differently from the above mentioned parameters, but still concordantly with other studies8,9, the mean of the periodontal probing depth at 1 and 3 months (respectively 2.34 and 2.37) was reduced in comparison to the preoperative value (2.44), but this difference was insignificant (p<0.05). In the studies of McGuire and Scheyer (2010)8 and Cardaropoli et al (2012)9 the values of the periodontal probing depth 6 months after the treatment were respectively 2.29 ad 2.46, but this difference was insignificant (p>0.05) compared to the pre-treatment value for both studies. Anyway, our general findings demonstrate that Mucograft used in combination with the coronally advanced flap is clinically effective in improving the compromised clinical parameters associated with the gingival recession.

Besides the improved clinical outcomes, McGuire and Scheyer (2010)8 concluded that the combination of the coronally advanced flap with Mucograft avoids the morbidity of donor graft harvest, and provides excellent aesthetic outcomes. Although not measured definitively, their observation was that Mucograft, like CTG, provided a

tissue substrate or scaffold, capable of thickening tissues, which may be a desirable attribute when treating thin tissue biotypes or managing contour deformitiesAlso, according to Cardaropoli et al. (2012), 9 the application of Mucograft in the treatment of gingival recession of the Miller Class I and II provides quite predictable results from an aesthetic aspect without the need for a second surgical procedure, which is an attractive alternative compared to conventional graft techniques. The same was reported by Sanz et al. (2009)7 who concluded that Mucograft was as effective and predictable as the SCTG for attaining a band of keratinized tissue and moreover, its use was also associated with a significantly lower patient morbidity. Castro and Grados (2014)13 also concluded in their randomized clinical trial that both techniques are useful to improve the analyzed clinical parameters: KG, CAL, PD with CMP having the advantage of avoiding a second surgical site like palatal tissues thus reducing morbidity and surgical risks. A more recent study of McGuire and Scheyer (2016) 12 which compared the long-term results (after 6 months and 5 years) of CM+ CAF and SCTG+CAF for the treatment of dehiscence-type recession defects concluded that CM + CAF appears to present a viable and long-term alternative to traditional SCTG + CAF therapy.

The improved treatment outcomes we observed in our study may also be related to the favourable tissue response that is elicited by Mucograft. According to a study by Ghanati et al. (2011)14 Mucograft successfully promoted the ingrowth of gingival tissue, reversed gingival tissue recession, demonstrated potential as a barrier for preferential tissue ingrowth, and achieved a desirable therapeutic result when applied in humans for soft tissue regeneration14. Of particular importance was also the fact that in the clinical situation no multinucleated giant cells, no granulation tissue and no evidence of a marked inflammatory response were observed.14

We think that the CAL correction 3 months after the treatment is due to the characteristics related to the application of Mucograft in the technique of a coronary advanced flap combined with a collagen membrane. In fact, Mucograft is a cell-occlusive layer composed of collagen fibers placed in a compact manner that prevents cellular adhesion and is a barrier. The other porous layer consisting of collagen fibers that are loosely packaged forming formation spaces blood coagulum and invasion of osteopathic cells allowing regeneration.

CONCLUSION

From our findings, we can conclude that the combination of the Mucograft with the coronally advanced flap technique has contributed to the significant gain of the CAL, the significant reduction of the recession depth and to an insignificant reduction of the periodontal probing depth after 1 and 3 months of treatment, compared to the pre-treatment values. Anyway, we acknowledge the need for a longer follow-up period in order to establish whereas these results are stable in time.

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Profesional paper

МЕХАНИЧКИ ПОВРЕДИ НА ОЧНИОТ БУЛБУС

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АБСТРАКТ

Механичките повреди на органот за вид се урегентни состојби во офталмологијата. Афекција на очното јаболко може да има значајни реперкусии на видната острина, но и на виталноста и перзистентноста на самиот булбус.

Цел на трудот е преку категоризација на клиничките случаи, аплицирајќи ја BETT терминологијата, да се направи анализа на механичките повреди на очнотот јаболко на клиничките болни и да се елаборира начинот на лекување.

Пациенти и методи: На Клиниката за Очни болести во периодот од две години (2016/17) се лекувани 285 пациенти, кои се вклучени во оваа студија.

Кај сите пациенти беше одредена видна острина на прием, директна аферентна пупиларна реакција, преглед на биомикроскоп, индиректна офталмоскопија, преглед со лупа 78D, Rtg на орбита и ехографија кај повреди со тапа траума, направена КТМ на орбити и MRI.

Кај отворените повреди беше аплицирана антитетанична заштита, парентерална антибиотска терапија и извршен оперативен зафат (примарна обработка на рана), а ако е присутно страно тело парс плана витректомија (PPV) со инсталација на силиконско масло.

Класификација на повредите правена е според BETTs (Brimingham Eye Trauma Terminology Sistem)

Резултати: Сите 285 пациенти се поделени во две групи, од кои 250 беа затворени повреди на очите и 35 со отворена повреда. Пациентите се класифицираа во зависност од видот на повредата, механизамот на настанувасње и потребата за третман. Од отворените повреди 7 беа руптури со локализација на корнеа од кои 2 со трауматска катаракта, додека 28 беа лацерации и тоа 11 на корнеа, 8 на корнеосклера и 9 на склера. Имено 11 беа перфорантни повреди, 1 пенетрантна и 8 со интраокуларно страно тело, сите хируршки обработени.

Заклучок: Окуларните механички повреди се честа патологија во офталмолошката пракса кои можат да имаат значајно влијание на функцијата на органот за вид, како и на неговата морфологија, дури и опстанок. Воглавно е афектирана помлада популаија што го истакнува значењето на проблематиката.

Повредите на органот за вид, а приори треба да се сватат сериозно, да се проследат муниционо сите мандаторни дијагностички испитувања и превземат адекватни тераписки процедури. Особено повредите на очниот булбус, макар и наизглед незагрозувачки, потрено е да се следат подолготрајно, заради можни касни компликации.

Во време на нови технолошки достигнувања, напредокот во витреалната хирургија и можностите во реконструкција на изразено тешки лацерантни повреди на очното јаболко, прогнозата во однос на функцијата и морфологијата на органот е значајно поизгледна.

Клучни зборови: механички повреди, лацерација, контузија, руптура

ВОВЕД

Механичките повреди се ургентни состојби во очната пракса и се однесуваат на повреда на сите структури на органот за вид, како очното јаболко така и аднексите и очниот нерв. Чести се во офталмолошката патологија и некогаш се од безазлен карактер, како при настанување на самата повреда така и во подоцнежниот перод. Меѓутоа голем број од трауматските повреди можат да имаат значајни реперкусии на органот за вид и неговата функција.

Траумата на очното јаболко, заради оштетување на нејзините окуларни ткаења во корелација со

механизмот и типот на повредата, може да резултира со намалување на видот, дури и да доведе до губиток на самото очно јаболко.

Статистички епидемиолошки податоци истакнуваат дека со траума се афектирани воглавно млади луѓе, но не се поштедени жените и децата. Најчесто се работи за тапи повреди (USEIR 31%; HEIR 45%), но и повреди со остар предмет завземаат значаен процент. Важно во превенцијата е дека повредите во голем процент се случуваат на работа (USEI 21%; in the HEIR 27%) (2) Фактот дека се работи воглавно за млади работоспособни луѓе, што може да има реперкусија на нивната работна продуктивност и одраз во начинот на животниот стил, од значење се сознанијата за оваа патологија на окото.

Цел на трудот е аплицирајќи ја интернационалната класификација за повреди на око (BETT), да се анализираат клиничките случаи на повреди на очното јаболко и да се елаборира начинот на третман кај тие повреди.

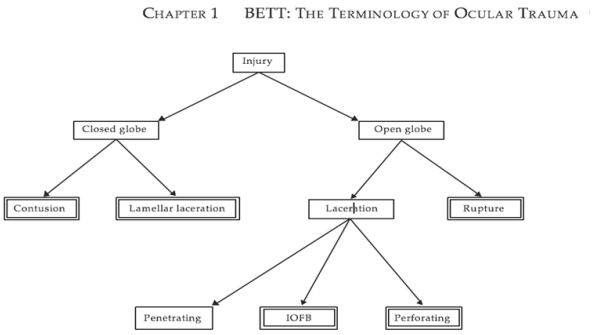
МАТЕРИЈАЛ И МЕТОДИ

На Клиниката за Очни болести во периодот од две години (2016/17) се лекувани 285 пациенти, кои се вклучени во оваа студија.

Кај сите пациенти примени на клиничко лекување спроведени се мандаторни испитувања со детално земање на анамнезата, за начинот и текот на повредата. Имено одредена е видна острина на прием, директна аферентна пупиларна реакција или консензуална, преглед на биомикроскоп, индиректна офталмоскопија, преглед со лупа 78D, Rtg на орбита и ехографија кај повреди со тапа траума или каде не била евидентна лацерантна рана на предниот дел на обвивките на очното јаболко, како и одредување на очниот притисок. При некои случаи индицирана и направена е КТМ на орбити и MRI.

Кај отворените повреди е аплицирана антитетанична заштита, парентерална антибиотска терапија и извршен оперативен зафат (примарна обработка на рана и ако е присутно страно тело парс плана витректомија (PPV) со инсталација на силиконско масло)

Класификација на повредите правена е според BETTs (Brimingham Eye Trauma Terminology Sistem) (Kuhn F., 2002) прикажани на дијаграм во Сл.1



Сл. 1 BETT Терминологија за окуларна траума (во двојна рамка се дијагнозите кои најчесто се применуваат во клиничката пракса)
Извор: Kuhn F. et all. 2002

РЕЗУЛТАТИ

Во периодот 2016/17 беа прегледани и третирани вкупно 285 пациенти со конузија на очното јаболко. Пациентите беа поделени во две поголеми групи, зависно од типот на поврдата, механизмот на нејзино настанување како и потребата за понатамошно хируршко лекување на истата.

Во првата група затворени контузиони повреди се вкупно 250 пациенти, 164 мажи на возраст (20-80 год.), 51 жени (на возрст 23-76 год.) и 35 деца (2-19 год.) (Таб. 1)

Кај 227 очи е утврдена чиста контузиона повреда од кои со засегање на периокуларните меки ткива и/или структурите на предниот очен сегмент 198, со присутно интравитреално крварење 6, и двајца пациенти со макуларен едем. (Сл. 2)

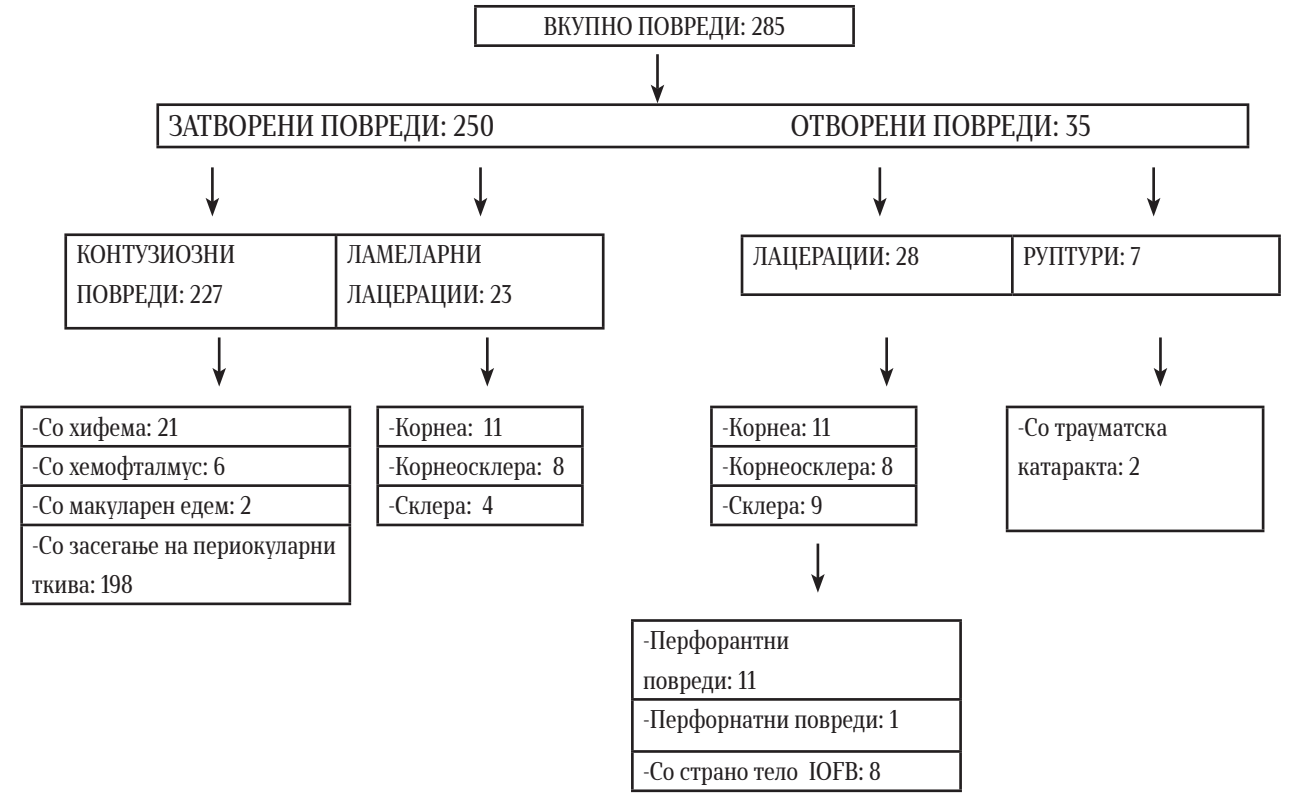
Кај 198 случаи при затворените контузии повредите беа локализирани на периокуларните меки структури (хематоми на очните капаци, и лацерантни рани на околината со или без индикација за хируршки понатамошен третман). (Сл.2)

Присутни ламеларни лацерации кај 23 очи и тоа на корнеа 11 очи, од кои кај 8 пациенти како последица на јачината на ударот беше присутна и хифема во предната комора, кај еден иридодијализа и еден случај хифема со сублуксирање на природната интраокуларна леќа.

Лацерантни корнео-склерални повреди имаше кај 8 пациенти (од кои кај 7 со пропратна хифема во предна комора). На склера ламеларни руптури беа 4; во 6 случаи беше присутно интавитреално пост контузионо крварење, а кај 2 случаи беше дијагностициран Берлингов макуларен едем (Сл.2)

Во групата на отворени контузиони поврди беа опфатени вкупно 34 пациенти. (Таб. 2) Од нив 28 лацерации и 7 руптури (од кои 2 беа корнеални со постртауматска катаракта). Лацерации на корнеа беа присутни кај 11 пациенти, на склера 9 и корнео-склерални 8 пациенти. Пенетрантни повреди беа утврдени кај 19, перфоративна повреда само кај еден, додека во 8 од`случаите беше утврдено и присуство на интраокуларно страно тело (во предна комора или во витреус).

Видната острина по повредата е во зависност од типот и механизмот на настанувањето на повредата, во корелација со видната острина на прием. (Таб.3)



Сл.2 Дијаграм на повреди класифицирани според BETT класификацијата (Kuhn F., 2002)

Patients	Gender	Range	Average	No
250	Male	(20-80)	50	164 (65, 6%)
	Fem.	(23-76)	49.5	51 (20, 4%)
	Ch	(2-19)	10.5	35 (14, 0%)

Таб. 1 Приказ на демографски карактеристики затворени контузиони повреди на очно јаболко

Sharp object	eyes	Blunt trauma	eyes
Penetrative	19	Rupture	7
Perforative	1		
IOFB	8		

Place of injury	
At home	62
At work	223

Таб. 2 Табеларен приказ според типот на повредата и местото на настанување на повредата

VA	Patients
0,6-1,0	184
0,5-0,6	34
0,2-0,4	21
0,1	18
0,05	11
Counting fingers	14
L+-P	3

Таб. 3 Табеларен приказ на видната острина

ДИСКУСИЈА

Механичките повреди се значаен сегмент во очната патологија, често проткаени со голем број дилеми. Еден дел од нив е надминат, во смисла на клсификацијата на повредите и нивна дистинкција, со примена на интернационалната терминологија за траумите на око (BETTS) (1).Впрочем, механичките повреди на очното јаболко, според сретството и начинот на повредата, се сведуваат на повреди со тап предмет или силен удар и повреди со остар предмет.

При повреда со остар предмет или мал остар објкет со голема кинетичка енергија, настануваат нарушувања на обвивките на очното јаболко. Според споменатата терминологија во колку постои комплетно раскинување на обвивките, зборуваме за целосни лацерантни повреди и некогаш тие се здружени со присуство на страно тело во некој од сегментите на очниот булбус. Кај лацерантни повреди разликуваме пенетрантни повреди каде при повреда настанува една влезна рана, или перфоративни, кога заради големата кинетичка енергија на движечкиот објект постои влезна и излезна рана.

Во групата на лацерантни повреди спаѓаат и повреди со присуство на страно тело во очното јаболко, состојба која веќе носи нови опасности и предизвици.

Меѓутоа, оштетувањето на очните обвивки со создавање на нивен расцеп може да настане и кај тапа траума, при која заради нагло зголемување на притисокот во окото при негова компресија во анетропостериорен правец, може да дојде до пукање на сепак тенка и фрагилна склера на нејзините слаби места (инсерцијата на правите надворешни мускули, екваторот или на местата на лузни од оперативни интервенции). Секако ова е пратено со оштетување на внатрешните две очни обвивки на окото и витреалното тело. Се работи за многу тешки повреди кои најчесто имаат лоша прогноза. Кај овој тип на расцепи, терминолошки зборуваме за руптури на очниот булбус.

Освен категоризација според типот на повредата за поегзактно дефинирање на проблемот на повредата, BETTs терминологијата ја инкорпорира и тежината на повредата одредена според виднта острина, реакцијата на пупилата, како и зафатеноста на окуларните структури од повредата, односно дали се однесува на оштетувања на предниот дел на окотодо иридоленталната мембрана или го афектираат задниот дел на окото, или и двете. Ова се однесува кај тапите повреди како и повреди со остар предмет.

Пристапот на болен со траума на око е доста специфичен. (2) (3) Од значење се анамнестичките податоци за начинот на повредата, но воедно при пристап на таков болен многу е важно да се испитаат повредите на другите делови од главата и телото бидејќи може да бидат животно загрозувачки. Имициング техниките кај трауматските нарушувања се од големо значење.

Повредите на окото бараат детален и внимателен преглед без дополнителна траума од притисок при прегледот. (4)(5)

Видната острина при првиот преглед е од посебно значење, и има прогностичка вредност, но секако типот и тежината на повредата се несомнено есенцијални за исходот.

Во пракса, значаен дел од повредите отпаѓа на контузионите повреди на очното јаболоко. При контузионите повреди со помала јачина страдаат деловите на предниот сегмент на очното јаболко пратени со суфузии на конјуктивата со можни лацерации, иако треба да се биде претпазлив и во однос на подлабоките структури.

Поголеми крварења на конјуктивата и еписклералното ткаење со поизразена хемоза и евентуално содржина на пигмент, алармираат на поголема траума, која ги инволвира очните обвивки и бара експолорација на окото. Ерозии на епителот на роговицата, иако се пратени со изразени симптоми и болка, се релативно беззначајни бидејќи зацелуваат во краток временски рок и дури без потреба на апликација на терапевтски агенс. Секако потребна е блиска опсервација.

Кај позначајни контузиони повреди на роговицата можна е појава на стромален едем, локално или дифузно присутен, заради оштетување на ендотелните клетки. Сепак иако ретко кај силните тапи повреди можна е руптура на стромата. Овие состојби на едем на роговицата се терапевтски решливи, но она на што овој тип на повреда упатува е повреда на структурите на предната комора односно коморниот агол и ирисот, кои би требало муниционо да се обсервираат.

Повреди со остар предмет на роговица можат да се состојат од парцијална лацерација и во колку е флапот ориентиран и прилегнува, локален антибиотик и контактна леќа се доволен третман. Секогаш кај овој тип на повреда треба да се тестира херметичноста на

предната комора.

Кај отворенитите повреди на окото најчесто се повреди на роговицата, а потоа доаѓаат корнеосклералните и склерални лацерации. Склералните лацерации се обично потешки повреди каде скоро секогаш се инволвирани и внатрешните структури на окото со можен пролапс, а некогаш се поврзани со присуство на интраокуларно страно тело.

Оваа состојба бара доследно спроведување на дијагностичките процедури кои ќе овозможат да се утврди обемноста на повредите на предниот, но и на задниот сегмент на окото, евентуално присуство на страно тело и менаџирање на повредата од офталмолог кој е искусен во хирургијата на задниот сегмент на окото.

Цел на хируршкото решавање на лацерантните рани на рогвицата и склерата е обновување на интегритетот на окото, спречување на инфекција и хипотонија, а притоа да се создаде што помала лузна и астигматизам. Потребно е да се ослободат прираслици и создадени фибрински мембрани. Полабираните окуларни структири во колку се работи за ирис кој е мацериран и дезинтегриран, би требало да се отстранат. Истото се однесува и на пролабирано витреално тело и деструирана леќа. Напротив тоа не е случај на ткаењето на постериорниот дел на увеата или кај пролапс на ретината кои би требало внимателно да се репонираат.

Една од најчесто присутните манифестации при повреди, било кај тапи повреди или кај лацерации, е појава на крварење во предната комора, односно хифема.

Резултат е на раскинување на крвните садови на големиот атреријален циркулус на ирисот, но и од грнките на цилијарното тело, крвните садови на пупиларниот раб или аголот на ирисот. Самата хифема иако значајна повеќе индицира на повредите на структурите на ниво на иридоленталната мембрана и цилијарното тело, со последични состојби на секундарен глауком или уште потешка за решавање и погубна за функцијата на окото и самиот булбус, хипотонијата на булбусот. Третманот на хифемата се состои од ординирање на мирување со оклузија на окото, ординирање на кортикостероиди локално, некогаш и системски, циклоплеици и антифибинолитици. (6) Воглавно има поволен тек во колку не се работи за особи со пореметени фактори на коагулација или српаста анемија, или кај случај со рецидивантна хифема.

Во колку е зголемен интраокуларниот притисок се ординира антоглаукоматозна терапија. Во случај каде интраокуларниот притисок е зголемен и не рагира на медикаментозен третман, би требало хируршки да се интервенира. Исто така каде притисокот е зголемен над 50 mmHg повеќе од пет дена, или поголем од 30 mmHg повеќе од 7 дена или пак здружен со речиси целосна хифема, како и присутен нелизирачки фибрински згрутчувања подолго од 10 дена, потребно е да се направи хируршко отстранување на крвта или коагулумот од предната комора.

Леќата е често инволвирана кај траумите на окото и овие повреди се однесуваат на нејзината положба или транспарентност. Треба да се истакне дека тежината на решавање на трауматските повреди на леќата не се споредливи со катарактата која се јавува кај други состојби, бидејќи постојат голем број на ризици заради оштетувања на самата леќа, нејзината капсула, како и на околните ткаења предизвикани од траумата.

Хируршкото решавање во овие случаи бара големо искуство. Предострожноста во "тајмингот" на операцијата на повредената леќа како и избраниот метод се многу важни бидејќи според статистичките податоци кај повреди кои ја афектираат леќата постериорниот дел на окото е инволвиран во дури 51%,што веќе индицира комплексно решавање на повредата.

Во принцип леќата кја е фрагментирана набабрена и предизвикува пупиларен блок би требало да се отстрани. Искуството на хирургот според позитивниот наод го диктира методот на оперативниот зафат. Ова е од значење во превенција на можни грешки и консекутивни компликации на задниот сегмент на окото.

Повредите на постериорниот дел на окото најчесто не се изолирани, но овие повреди се и најчесто причина за намалување на видот или губиток на органот.

Тапите повреди на очното јаболко во постериорниот дел често се пратени со крварење во витреалното тело како резултат на повреда на цилијарните крвни садови. Поради големиот антеро-постериорен притисок можна е појава на расцепи на хороидеата и Бруховата мембранаа со појава на субхороидални крварења кои особено можат да бидат значајни.

Истите антеропостериорни сили доведуваат до оштетување на базата на витреалното тело и ригидната ретина кадепокрај комоцијата и контузијата на ретиналното ткаење можна е дијализа на ретината во пределот на ора серата, но и тракциони потковичести руптури и гигантски руптури на ретината. Ова се комплексни состојби кои бараат оперативно решавање преку сложени витреоретинални процедури.

Бидејќи траумата со екстравазација на крв и оштетено ткаење на ретината и ретиналниот пигментен епител доведуваат до брзи фибропролиферативни реакции дури и при рана интервенција можни се компликации во смисла на изразен PVR (пролиферативна витреоретинопатија) кој може да резултира со лош исход.

Особено тешки механички повреди се оние со лацерации на овивките на очното јаболко. Тие можат да бидат и здружени со присуство на страно тело, што од своја страна носи изразени ризици за инфекција како и во случај на метални страни тела, опасност од неповратно уништување на рецепторните клетки. (7)

Овој тип на повреди бара хируршки третман кој во зависност од оштетувањата на ткаењата и состојбата на окото и пациентот, може да бара решавање во повеќе акти. Според повеќе автори се опишуваат таканаречени три временски прозорци за обработка на рана, што има свое оправдување од повеќе аспекти.

Примарната обработка на раната има за цел да ја спречи инфекцијата, да воспостави интегритет на очните обвивки и нормализација на тонусот на очното јаболко. При обработката се отстранува деструираното ткиво и страното тело.

Од круциелно значење во смисла на подоцнежни компликации е секундарната обработка, која се состои од комплетна витректомија со особено внимание на витреалната база и на местата на повредата и местата на поминување на страното тело. Со оваа процедура се ослободуваат инкарцерираните внатрешни обвивки и се воспоставуваат анатомските односи на булбусот. Постапката би требало да се изведе во оквир од 7-14 дена (8) (9) (10)

Терциелната обработка се изведува накнадно, кај веќе формирани окуларни фибропролиферации, а има за цел ослободување на оптичкиот простор.

Комбинираните повреди на предниот и задниот сегмент заради тежината на повредата бараат тимска работа на хирурзи од преден и заден сегмент, адекватни услови за рабта и искуство. Воведувањето на кератопротезите има значаен придонес во реконструкција на окото кај овие тешки повреди. Никогаш не би требало да се отстапи од санација на повредата на очниот булбус освен ако се работи за изразено деструирано око, конквасација, каде што очното јаболко се сведува на "остаток"(7)

ЗАКЛУЧОК

Окуларните механички повреди се честа патологија во офталмолошката пракса.

Заради можни реперкусии на видната функција и губитокот на органот за вид, за секоја повреда е важно а приори да се свати сериозно и да бидат превземени сите можни дијагностички и терапевстски методи. Кај сите трауми на око, дури и ако изгледаат банални и лесни, потребно е подолгорочно следње заради можни подоцнежни компликации од здобиената траума. Во времен ан витреална хирургија и усвојување на нови техники и осовременување на технологијата, тешките лацерантни повреди на очното јаболко имаат поповолна прогноза во однос на видна функција на органот, и неговата морфологија и виталност.

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МЕХАНИЧКИ ПОВРЕДИ НА ОЧНИОТ БУЛБУС

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ABSTRACT

Aim: Mechanical eye injuries are urgent conditions in the field of ophthalmology. Affection of the eye globe can have repercussion on the visual acuity, as well as organ vitality and the persistence of the eye globe.

The goal of the study was to categorize all the clinical cases based on BETT terminology, to analyze mechanical injuries of the eyeball and to elaborate the way of the treatment.

Patients and Methods: On the University Eye Clinic for the period of one year (2016/17), 285 patients were treated. This was a retrospective study. In all patients visual acuity was determinate, direct afferent papillary reaction, slit-lamp examination, indirect ophthalmoscopy, fundus examination with 78D, Rtg orbit imaging and ultrasonography in patients with blunt eye trauma, CTM and MRI preformed. In the patients with open globe injury antitetanic prophylaxis was administrated, intravenous antibiotic therapy and surgical procedure was performed (primary wound sanation), and if foreign body was present pars plana vitrectomy with insertion of silicon oil was done.

The eyeball injury classification is done according BETTs (Birmingham Eye Trauma Terminology System).

Results: All 285 patients were divided in two groups, 250 with closed eye injury and 35 with open eye surgery. All patients were further divided depending on type of injury, mechanism and the need for surgical treatment. From the open globe injuries 7 were located

on the cornea (of which 2 with traumatic cataract), 28 lacerations 11 corneal, 8 corneoscleral and 9 scleral. Perforative injuries were 11, one penetrative, 8 with intraocular forign body. All injuries were surgicaly treated.

Conclusion: Mechanical ocular injuries are very often in the ophthalmic pathology, they can have influence on the eye function, morphology or even its preservation as an organ. Mainly the younger population is affected which gives significance to the meaning of the pathology. Eyeball injuries should be considered seriously, all the necessary diagnostic procedures must be done and adequate procedures for treatment should be taken. Injuries of the eyeball may not be significant on first sight but over a prolonged period can cause possible complications later. Today thanks to the new achievements in technology and vitreoretinal surgery, the possibilities for eye reconstruction and preservation of visual function are fare better than before.

Key words: mechanical injuries, laceration, contusion, rupture

Profesional paper

GENETIC PROFILING OF A PATIENT WITH A COMPLEX PHENOTYPE REVEALED VARIANTS IN THE CPT2 GENE

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ABSTRACT

Objective: A next generation sequencing analysis was conducted on a deceased 9 months old baby with numerous symptoms as classical Tetralogy of Fallot, Meckel's diverticulum, micro vesicular steatosis and hypotrophy of liver, mild s-shaped scoliosis with right thoracic convexity, hypotonia, hypoxemic spells, ventilator support requirements, continuous positive airway pressure dependence, failure to thrive etc. Clinical diagnosis could not be determined precisely and it included a possibility of Noonan syndrome, a congenital genetic disorder that prevents normal development of many areas of the body.

Methods: The performed genetic analysis on the DNA from the index patient was by targeted next generation sequencing of 4186 genes by the TruSight One gene panel (Illumina).

Results: No mutations were found in the genes associated with the Noonan syndrome, or in the 118 genes associated with inborn anomalies of the heart and cardiomyopathies. The variants of most importance for the patient's phenotype were in the CPT2 gene where one novel p.Leu71Pro and a known p.Met342Thr variant were detected. The patient was also a heterozygote for dominant pathogenic mutations with later onset in the genes PKD1: p.Arg324Leu and REEP1: c.*43G>T, a heterozygote for the recessive pathogenic variants in the genes NAGA:p.Glu325Lys, HEXB:p.Ser62Leu and MPO:p.Met251Thr and a heterozygote for the variants connected to reaction to drugs in the genes NAT2: p.Ile114Thr, p.Arg197Gln, p.Lys268Arg and CYP2C9: p.Ile359Leu.

Conclusions: Genetic profiling by next generation sequencing provided additional information that could help the diagnosis of this patient with an overall complex phenotype.

Key words: Tetralogy of Fallot; Noonan syndrome; genes; sequencing; CPT2.

INTRODUCTION

The index patient was born with heart malformation - Tetralogy of Fallot (TOF, OMIM 187500), a complex, rare congenital heart defect that comprises four main features: ventricular septal defect, pulmonary stenosis, right ventricular hypertrophy and an overriding aorta. This feature as well as others like hypotonia, poor feeding, failure to thrive, hepatomegaly, chest deformities etc. found in our patient and present in patients with Noonan Syndrome, lead clinicians to indicate Noonan Syndrome as a possible diagnosis that at the time could summarize the symptoms found in the patient. Noonan syndrome (NS, OMIM 163950) is autosomal dominant genetic disorder that affects various parts of the body causing a range of clinical features as short stature, typical face dysmorphology and congenital heart defects [1]. Pulmonic stenosis, septal defects, hypertrophic cardiomyopathy

occur most commonly although other cardiovascular defects can be noted [2].

The patient was directed to us for genetic analysis by next generation sequencing. The aim was to provide information for the genetics of the patient that can furthermore help clinicians. The parents of the infant also planned future pregnancies and wanted to determine if there was a genetic basis of their first child's condition. The genes connected to 99% of cases of Noonan as PTPN11 (58%), SOS1 (23%), BRAF (5%), MEK2 (5%), RAF1 (5%), CBL (3%) [3] were inspected, as well as other genes included in a comprehensive panel targeting disease-associated regions of 4813 genes with known associated clinical phenotypes. Because of involvement of a human participant, all performed procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

METHODS & MATERIAL

Clinical procedures were performed according to the standards for clinical examination of the hospitals where the patient was examined.

Genetic analysis by next generation sequencing was ordered prior to death but analyzed afterwards. After informed consent from the parents, blood was taken from the patient and DNA was extracted using a commercial kit (Qiagen). Sequencing was performed on a MiSeq® sequencing platform (Illumina, San Diego, CA) by targeted next generation sequencing with sequencing panel for 4813 genes with known associated clinical phenotypes included in TruSight One gene panel (Illumina, San Diego, CA). Sequencing data was analyzed by Softgenetics NextGene Software (ver 2.3.3). Alignment was to the Human reference sequence (GRCh37/hg19) and annotation and filtering of variants was done using the VariantStudio Software. A list of variants was formed and variants in candidate genes that were of importance for the diagnosis were confirmed by Sanger sequencing.

RESULTS

Clinical report of the index patient when 8 months old stated that the patient was haemodynamically stable, pulmonary blood flow quite balanced with O2 saturation of about 80-85%. Experts that reviewed computed tomography (CT) of the chest concluded that the changes of the chronic lung disease were not too severe, the left lung hypoplasia was quite moderate, the cardiac appearance was compatible with Tetralogy of Fallot with right modified Blalock-Taussig Shunt (mBTS) and branch pulmonary arteries of good calibre with no focal narrowing. The left lung was hypoplastic with associated dysmorphism of the chest wall. The apparent mild s-shaped scoliosis with right thoracic convexity related to the known hypotonia. There was no other evidence of primary lung disease. All findings could not explain what caused prolonged ventilator support requirements, the continuous positive airway pressure (CPAP) dependence and failure to thrive. There was quite significant chest and vertebral deformity suspicious of neuromuscular disorder, but it was ruled out by experts after multiple investigations. It was difficult to summarize the neurological condition of the brain and the neuromuscular system. The prognosis and the unifying condition remained unclear.

The results from immunology investigations ruled out certain immune deficiency. Only IgG were quite low, 2.89g/L. She was starting to gain weight and the muscle hypotonia has improved. The trials off CPAP were of varying success with the maximum time off nasal CPAP being 24h. The patient had hypoxemic spells. The operation of total repair of the pulmonary artery branches was postponed so that the child can gain weight in order to reduce the risk of postoperative complications.

However, the child died two weeks later, less than 9 months old. The patient's weight was only 3894g and length 55cm. The autopsy and morphological investigation revealed Tetralogy of Fallot with pulmonary atresia corrected with an operation with a systematic pulmonary shunt between right pulmonary artery and truncus brachiocephalicus, pulmonary stenosis, overriding aorta, ventricular septal defect and right ventricular hypertrophy. Furthermore, the autopsy reported Meckel's diverticulum, microvesicular steatosis in liver and hepatomegaly. The thrombosis of the shunt with pulmonary and brain edema, subdural bleeding and severe venous stagnation in the internal organs were pointed out as a direct reason for death.

The genetic analysis did not confirm the diagnosis of syndrome of Noonan. The panel does not include the RIT1 gene that can be cause for Noonan syndrome. No known pathogenic variants were detected in the exons of the 118 genes associated with inborn anomalies of the heart and/or cardiomyopathies (list upon request).

The variants of significance found in the patient are presented in the Table 1.

Table 1. Variants detected by NGS in the patient.

Type of variant	Gene	Mutation	Hetero/homo/ hemizygote
Pathogenic variants	PKD1 REEP1	Chr16:g.2168022C>C/A,NM_001009944.2:c.971G>T, NP_001009944.2:p. Arg324Leu, rs199476099 Chr2: g.86444180 C>C/A, NM_001164730.1:c.*43G>T, rs377637314	heterozygote heterozygote
Likely pathogenic variants	CPT2 CPT2	Chr1: g.53666450T>T/C, NM_000098.2:c.212T>C, NP_000089.1:p.Leu71Pro Chr1: g.53676371T>T/C,NM_000098.2:c.1025T>C, NP_000089.1:p.Met342Thr, rs144658100	heterozygote heterozygote
Pathogenic variants not expressed when heterozygous	NAGA HEXB MPO	Chr22:g.42457056C>C/T,NM_000262.2:c.973G>A, NP_000253.1:p.Glu325Lys, rs121434529 Chr5: g.73981270T=, NM_000521.3:c.185C>T, NP_000512.1:p.Ser62Leu, rs820878 Chr17:g.56356502A>A/G,NM_000250.1:c.752T>C, NP_000241.1:p.Met251Thr, rs56378716	heterozygote heterozygote heterozygote
Variants connected to reaction to drugs	NAT2 NAT2 NAT2 CYP2C9	Chr8: g.18257854T>T/C, NM_000015.2:c.341T>C, NP_000006.2:p.Ile114Thr, rs1801280 Chr8: g.18258103G>G/A,NM_000015.2:c.590G>A, NP_000006.2:p.Arg197Gln, rs1799930 Chr8: g.18258316G>G/A,NM_000015.2:c.803G>A, NP_000006.2:p.Arg268Lys, rs1208 Chr10:g.96741053A>A/CNM_000771.3:c.1075A>C NP_000762.2:p.Ile359Leu, rs1057910	heterozygote heterozygote heterozygote heterozygote

Molecular analysis of the 2nd and 4th exon of gene CPT2 of the DNA from the parents by Sanger sequencing is presented in the following heredogram (Figure 1):

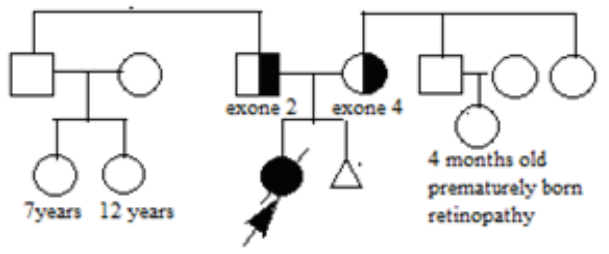

Figure 1. Segregation analysis of 2nd and 4th exon of gene CPT2

DISCUSSION

The variants that are probably of most importance for the patient's phenotype are in gene CPT2: p.Leu71Pro and p.Met342Thr described as likely pathogenic (according to functional predictors). First variant has not been described in literature so far and the second is listed as very rare and with unknown significance The CPT2 gene location is in chromosome 1p32 and consists of 5 exons with approximately 20 kb of DNA [4].

The variant p.Leu71Pro is located in exon 2 and p.Met342Thr in exon 4 (Figure 2).

The gene CPT2 codes the mitochondrial enzyme carnitine palmitoyltransferase 2 (CPT2, OMIM 600650), crucial for fatty acids oxidation that happens in mitochondrias. Acyl-CoA molecule reacts with carnitine under the influence of a CPT1 on the outer aspect of the mitochondrial inner membrane, generating free CoA and acylcarnitine that enters the inner membrane and reacts with CoA catalysed by CPT 2 on the inner face of the inner membrane where it enters oxidation [5]. Fatty acids are the main source of energy for the heart and muscles and when the organism starves, are also an important source of energy for the liver and other tissues. When the enzyme is deficient, long chain fatty acids cannot be used for energy production.

Variants in the CPT2 gene cause an autosomal-recessive mitochondrial disease called carnitine palmitoyltransferase II deficiency associated with three clinical phenotypes: a myopathic (mild), stress induced form with adult onset (type 1, OMIM 255110), a severe life-threatening infantile/juvenile form with hepatic, muscular and cardiac involvement (type 2, OMIM 600649) and a fatal neonatal form with organ abnormalities (type

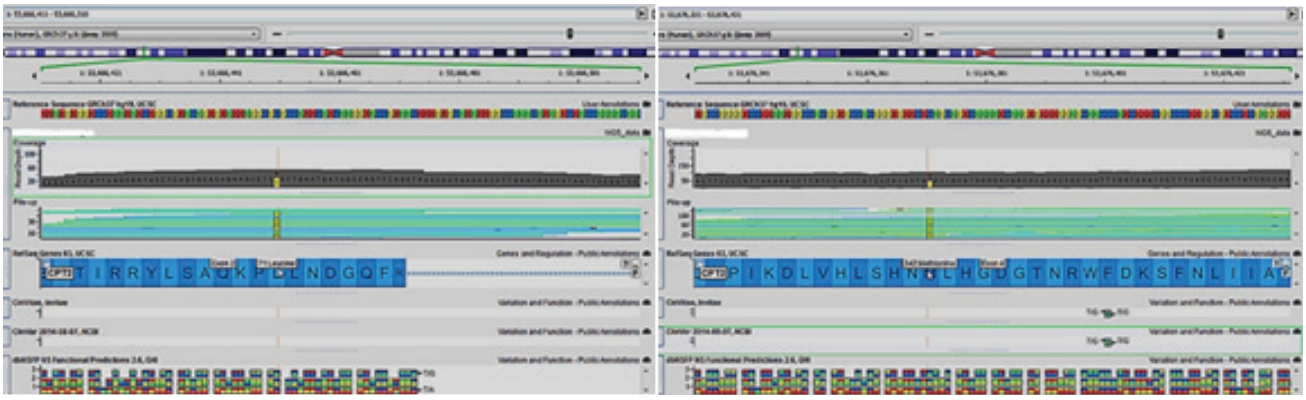

Figure.2. Exone 2 and 4 of gene CPT2 of the patient. The substituted nucleotides are marked.

3, OMIM 608836). Our patient was not screened for CPT2 function before the death, so the laboratory parameters remained unknown.

Infantile hepato-cardio-muscular form of CPT2 deficiency usually begins between 6 months and 2 years of age with recurrent attacks of seizures, hepatomegaly and liver failure, a weakened and/or inflamed heart, low blood sugar, abdominal pain, headache, muscle weakness in the arms and legs, irregular heartbeat which can result in sudden death during infancy. Symptoms are triggered by fasting, stress or infection. Some of the symptoms relate to our patient. Hepatomegaly with steatosis seen in our patient has been reported in a similar case of a boy who suddenly died at 10 months of age during an acute illness and was later diagnosed as type 2 CPT II [6].

Variant p.Leu71Pro found in our patient has not been described so far in literature. The second mutation p.Met342Thr is very rare and it has been detected only as heterozygous. According to prediction software both variants can be expected to disrupt the proteins function. The analysis by sequencing of the exone 2 and 4 of the parents showed that they are both heterozygous, each one only for one of the variants so, in the patient the variants are on different of the homologous chromosomes. Since CPT2 deficiency is an autosomal recessively inherited disorder, heterozygotes should not have symptoms. However, in a study where rigorous mutation analysis was done, 6 of 13 individuals identified with CPT2 mutations as heterozygotes displayed corresponding clinical symptoms and decreased CPT activity observed in muscle or leukocytes samples [7]. In our case the patient could be a manifesting carrier because of manifestation of only one of the variants in CPT2 or because of the both variants. Furthermore, heterozygous variant in other genes that were detected and listed above, could compound with the CPT2 gene defect to produce symptoms. The variant in the REEP1 gene might play such role since it is widely expressed and localizes to mitochondria [8]. Mitochondrial morphology in patient with mutant REEP1 is highly tubular compared with control cells because of inhibition of mitochondrial fission protein, DRP1 caused by impaired interactions between mutant REEP1 and mitochondrial phosphatase PGAM5 [9].

The other known autosomal-dominant pathogenic mutations with later onset that the patient was heterozygote for were:

- PKD1: p.Arg324Leu. The PKD1 gene codes an integral membrane protein that regulates the flow of calcium channels, modulates the G protein signal transduction and has a meaning in development of the kidney's tubules. Pathological variants of that gene are a cause for adult kidney polycystosis [10].
- REEP1: c.*43G>T. A variant detected in patients with a form of spactic paraplegia type 3, a heterogeneous disease that affects the upper motor neurons. The mutation changes the conserved sequence recognized by micro RNA in 3χ UTR and alters the translation [8].

The patient was a heterozygote for known autosomal-recessive pathogenic variants not expressed when heterozygous in genes:

- NAGA (p.Glu325Lys) – The NAGA gene codes for enzyme Alpha-N-acetylgalactosaminidase. The variant causes Kanzaki's disease and Schindler's disease type I and III [11].
- HEXB (p.Ser62Leu). The HXEB gene codes for the enzyme hexozaaminidase B. The mutation causes the disease of Sandhoff [12].
- MPO (p.Met251Thr). The mutation causes form of mieloperoxidase deficiency.

The patient was a heterozygote for variants connected to

reaction to drugs:

- NAT2: p.Ile114Thr; p.Arg197Gln; p.Lys268Arg – The NAT2 gene codes for the enzyme N acetyltransferase 2. Polymorphic variants of the enzyme are connected "fast" and "slow" acetylation's phenotype. Three heterozygous variants, all connected to lowered enzymatic activity, were detected in our patient so phenotype of "slow" acetylation is probable.
- CYP2C9: p.Ile359Leu. The studied allele is called CYP2C9*3 and is with lowered enzymatic activity. In our patient no second variant was detected, so it was expected to have normal phenotype (fast metabolism).

CONCLUSION

The results elucidate the usefulness of application of next generation sequencing in establishing genotype–phenotype correlations in patients and families affected by complex disorders thus contributing to a proper diagnosis and prognosis determination.

DISCLOSURE STATEMENT

The authors declare that they have no conflict of interests regarding this paper.

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Profesional paper

EVALUATION OF NASAL CAVITY BY ACOUSTIC RHINOMETRY AND COMPUTED TOMOGRAPHY FOR DIAGNOSIS OF NASAL SEPTAL DEVIATIONS

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ABSTRACT

Introduction: For more than 30 years, physicians have attempted to use different diagnostic methods to demonstrate nasal septal deviation objectively. CT of the sinuses and acoustic rhinometry are two diagnostic tools that can be used to demonstrate deviated nasal septum (DNS).

Material and Methods: Sixty-nine patients were examined in this prospective study. All patients were evaluated by AR (acoustic rhinometry) and CT (computed tomography). Septal deviations determined by CT coronal view and acoustic rhinometry in 2 locations corresponded roughly to minimal cross-sectional area MCA1 and MCA2.

Results: Analyzes of MCA1 and MCA2 values after decongestion of nasal mucosa and CT1 and CT2 readings with Binomial test showed statistical consistence of septal deviation in 60 (87%) and non-consistent in 9 (13%) patients ($p<0.05$). The Spearman's correlation test between CT scan readings and percentage difference values between the two sides for MCA1 was $r = 0.856$ and for MCA2 $r = 0.741$ ($P < 0.001$). The overall sensitivity and specificity of AR readings in detection of anterior septal deviations according to CT findings were found to be 67% and 79%, respectively.

Conclusion: Acoustic rhinometry as a diagnostic modality is useful in identifying DNS in anterior region of the nasal cavity. CT imaging is a reliable method for obtaining necessary anatomic information of nasal cavity. AR is better to be used because it is quicker and does not involve radiation. AR and CT are correlated to each other, but their accuracy is limited compared with that of the clinical diagnosis.

Keywords: nasal septum, acoustic rhinometry, computed tomography

INTRODUCTION

Septal deviation is a common anatomic variation in healthy adults. However, there are no standard criteria to determine when a deviated septum is clinically relevant. The diagnosis is usually based on patient symptoms and anterior rhinoscopic findings. Presently, selection of patients for septoplasty is mainly based on clinical examination, which is prone to observer bias and may lead to unsuccessful treatment (1).

For more than 30 years, physicians have attempted to use different diagnostic methods to demonstrate nasal septal deviation objectively. Patients with septal deviation usually have nasal congestion. However, these patients rarely have only anatomic deformities. They also have other problems that affect their nasal mucosa, including vasomotor diseases, infections, and autoimmune diseases. In each case, the physician must use his or her judgment to understand the contribution of any of these diseases to patient symptoms. Consequently, any nasal function test that will be used for evaluation of these patients should give information about reversible mucosal congestion as well as bony and septal deviations (2).

CT of the sinuses and acoustic rhinometry (AR) are two diagnostic tools that can be used to demonstrate DNS. Although the main purpose of obtaining a CT scan is to evaluate the paranasal sinuses, this method should

be used only rarely for the diagnosis of DNS. It is an expensive method for evaluating septal deformity and will expose patients to unnecessary radiation. CT scans and AR measurements of the nasal airway have been shown to correlate well with each other, especially in the anterior portion of the nose (3).

Acoustic rhinometry (AR) is a method based on reflection of acoustic waves and is a useful tool for measuring the dimensions of the nasal cavity. By comparing the incident acoustic wave with waves reflected from the walls, it is possible to determine changes in cross-sectional area within the nasal cavity Acoustic rhinometry measures cross-sectional area as a function of the distance from the nostril (4). Acoustic rhinometry is a quick, painless, noninvasive, reliable method that can be performed easily with minimal patient cooperation. These features explain why the technique has been widely accepted in a short time. Acoustic rhinometry has been used for characterizing the geometry of the nasal cavity, for assessing the dimensions of nasal obstructions, and for evaluating surgery results and patient response to medical treatment. Computed tomography (CT) have been also used for this purpose in clinical trials. Hilberg et al. were the first to use CT to assess the accuracy of AR measurements in a single cadaver head. They found a significant correlation between CT and AR findings when the imaging was obtained perpendicular to the acoustic wave direction (5). Clinical studies on human subjects have documented significant correlations between cross-sectional areas in the anterior part of the nasal cavity measured by various imaging modalities and AR (6, 7). However, with the exception of the study by Terheyden et al., in all previous studies on human subjects the plane of the CT and MRI slices has been perpendicular to the floor of the nose, and the images have been obtained at various distances from the anterior nasal spine or the tip of the nose (8).

The aim of this study was to assess whether CT findinngs were consistent with cross-sectional areas obtained by acoustic rhinometry in predicting nasal septal deviations.

MATERIAL AND METHODS

Sixty-nine patients were examined in this prospective study. All patients were evaluated by AR (acoustic rhinometry) and CT (computed tomography). Initial physical examination (anterior rhinoscopy and endoscopy) were used to designate a patient's septum as having no deviation or being mildly, moderately, severely, or very severely deviated. The age of the patients ranged from 11 to 46 years (mean 24.7+9.1 years). All of the interventions were based on clinical criteria.

Septal deviations determined by CT coronal view in the ranking were graduated from 1 to 4 according to the degree of deviation at the following locations: at the nasal valve - the smallest part in the nasal cross-sectional area in nasal meatus and at the anterior end of the inferior turbinate. These 2 locations corresponded roughly to MCA1 and MCA2. The graduations of septal deviations were represented as mild, moderate, severe and very severe subsequently from 1 to 4. In reading the CT scans, only shift of the septum from the midline was taken into account. Deviations to the left were labeled with negative values, deviations to the right were labeled with positive values, and no deviation was labeled with the number 0.

Acoustic rhinometry (Acoustic Rhinometer A1; GM Instruments, U.K.) was used according to the guidelines defined by the Standardization Committee. Both nasal cavities were decongested with 2 puffs of 0.05% oxymetazoline after 15 minutes of rest. The measurements were performed before and 15 minutes after decongestion. The mean value of three measurements was calculated. Unilateral minimal cross sectional area MCA1 (the smallest part in the nasal cross-sectional area in nasal meatus – nasal valve) and MCA2 (the anterior part of inferior turbinate) were measured with acoustic rhinometry. The 2 valleys were identified and noted for their respective locations according to their distance from the tip of the nosepiece. The measurements were taken at 2-2,5 cm for MCA1 and at 4-4,5cm for MCA2. The percentage difference in area before and after decongestant and the percentage difference in area between the right and left sides after decongestant were calculated.

The CT readings were compared with the percentage difference values in area between the right and left sides after decongestant. ROC analysis assesses the accuracy of a diagnostic tool by calculating sensitivity and specificity. Correlation data are not sufficient for assessing the utility of a diagnostic tool in clinical practice. Sensitivity and specificity are affected by a threshold level that sets the critical point from which results are considered positive or negative. This threshold point can be chosen arbitrarily. However, on the basis of normative data from the senior author's previous article, we chose a 24% difference between each side as the threshold value. This was based on the average percentage difference in non-DNS patients. A difference in area between the two sides

of 0% to 24% and a zero reading from the CT grading were both taken to indicate no DNS. ROC analysis provides us with predicted specificity values as the sensitivity values change. The AR measurements and CT scans were compared for each MCA, with the clinical diagnosis used as the standard.

The mean differences of MCA1 and MCA2 before and after decongestion were calculated in all 69 patients and in the cohort of patients with deviated and non-deviated nasal septum. The mean differences in area between the right and left sides and in area between the deviated and wider sides after decongestant were also calculated in all 69 patients and in the cohort of patients with deviated and non-deviated nasal septum.

STATISTICAL ANALYSIS

Statistical assessments were performed using the SPSS software (SPSS version 18). ROC analysis was used to predict specificity and sensitivity values change for AR and CT findings. The Spearman's correlation coefficients and P values were determined between the CT values and the percentage differences in area (obtained from AR) between the right and left sides after decongestion of nasal mucosa. Binomal test was used to assess whether CT findings were consistent with cross-sectional areas obtained by acoustic rhinometry in predicting the nasal septal deviations.

RESULTS

According to CT readings, 23 patients showed nasal septal deviation at the level of the nasal valve (CT1); 3 of these had minimal, 6 had moderate, 11 had severe and 3 very severe deviated nasal septum. At the level of the anterior end of the inferior turbinate, which corresponds to CT2, 32 patients had nasal septal deviation; in 3 it was minimal, in 10 moderate, in 13 severe and in 6 very severe. Nine of the patients had DNS at all 3 levels; 5 of them had DNS at the level of anterior end of both, the inferior and middle turbinates.

Table 1. Distribution of MCA values in DNS and non DNS patients.

MCA	DNS patients		Non DNS patients	
	non decongested	decongested	non decongested	decongested
1. MCA1	55	28	14	41
2. MCA2	50	41	19	28
3. Mean	52	35	16	35

According to predecongestion MCA1 values of AR measurements, 55 patients showed nasal septal deviations and 14 were classified as patients with non-deviated nasal septum, but the number of patients with non-deviated septum increased to 41 after decongestion of nasal mucosa and the number of patients with deviated septum decreased to 28. According to predecongestion MCA2 values of AR measurements, 50 patients showed nasal septal deviations and 19 were classified as patients with non-deviated nasal septum, but the number of patients with non-deviated septum increased to 28 after decongestion of nasal mucosa and the number of patients with deviated septum decreased to 41.

Analyzes of MCA1 and MCA2 values before decongestion of nasal mucosa and CT1 and CT2 readings with Binomial test showed statistical consistence of septal deviation in 55 (80%) and non-consistent in 14 (20%) patients. Binomial test (test of proportions = 0.05) showed statistical consistence of septal deviations after decongestion in 60 (87%) and non-consistent in 9 (13%) patients ($p< 0.05$).

Table 2. Side-to-side differences of MCA1 and MCA2 between larger and smaller side after decongestion

Cohort of patients	Mean difference (cm2)	
	MCA 1	MCA 2
1. DNS patients	0.06	0.68
2. Non DNS patients	0.15	0.88
3. Difference (DNS-Non DNS) patients	-0.09	-0.20

The non-DNS patients had a larger average difference in area of MCA1 and MCA2 than in the DNS patients (Table 2).

Table 3. Percentage difference of MCA1 and MCA2 before and after decongestion between wider and narrow (deviated) sides.

Cohort of patients	Mean difference (cm2)	
	MCA 1	MCA 2
1. DNS patients	51.8	179.2
2. Non DNS patients	15.5	244.9
3. Difference (DNS-Non DNS) patients	36.3	-65.7

The difference between the percentage change in area before and after decongestant values of the two sides in the DNS patients for MCA1 was much larger than that in the non-DNS patients. The difference between the percentage change in area before and after decongestant values of the two sides in the DNS patients for MCA2 was much smaller than that in the non-DNS patients. The average percentage difference for MCA1 between the two sets of patients was 36%, and for MCA2 it was 66% (Table 3).

The CT scans and AR readings were compared by means of ROC analysis. When compared with clinical diagnosis as the gold standard, both the CT and the AR readings were reasonably close to the clinical diagnoses in terms of sensitivity and specificity (Figs 1-2).

Figure 1. CT versus AR for MCA1 (Binomal ROC Curves)

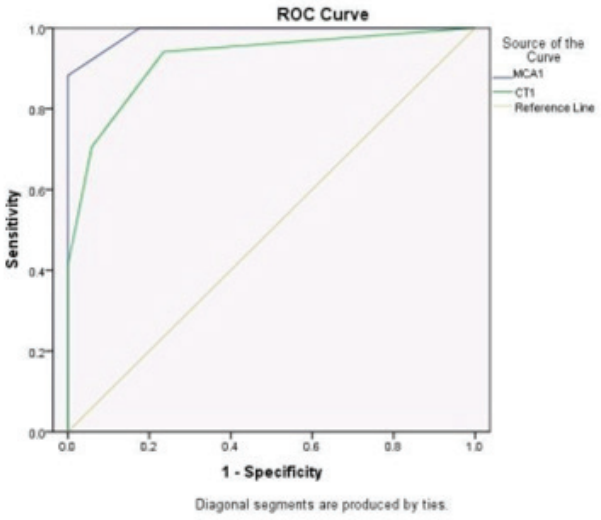
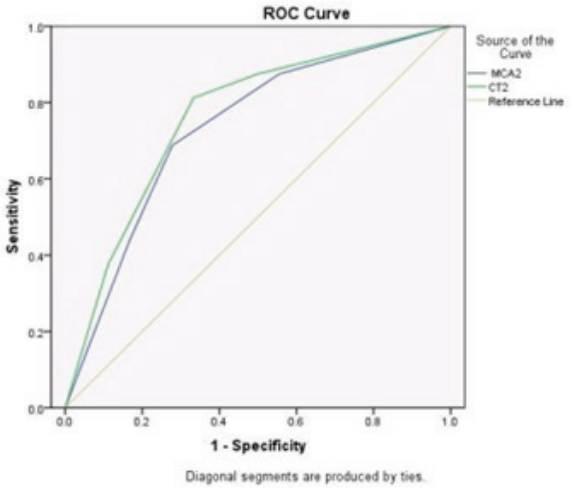


Figure 2. CT versus AR for MCA 2 (Binomal ROC Curves)



ROC analysis was used to predict specificity and sensitivity values change in CT versus AR findings for MCA1 and MCA2 subsequently. From ROC analysis, we were able to conclude that CT scans and AR readings compared reasonably well with the clinical diagnosis for each MCA. We used only postdecongestant values at each MCA when comparing the AR readings and CT scans in both ROC analyses.

The Spearman's correlation test between CT scan readings and percentage difference values between the two sides for MCA1 was r = 0.856 and the r value of MCA2 was 0.741 ($P < 0.01$). The overall sensitivity and specificity of AR readings in detection of anterior septal deviations according to CT findings were found to be 67% and 79%, respectively.

DISCUSSION

Although functional and anatomical analysis of the nasal cavity has been extensively studied, a standard objective measure of nasal obstruction has not yet been established. Deviation of the nasal septum is the most frequent structural deformity. Nasal septal deviation (NSD) is a common diagnosis made by otolaryngologists but is one that is not usually based on objective measurements. Septal deviation can be the cause of the various symptoms specifically, the internal nasal valve, the site of maximum resistance along the entire respiratory tract from the nasal vestibule to the alveoli, and it has been the target of much research. Small changes in nasal valve size result in large changes in airflow resistance, which in turn affects nasal function (9). The internal nasal valve is an extremely important area for surgeons to accurately assess before reconstruction or repair of the nose. Existing tools, including rhinomanometry and acoustic rhinometry, can be used to assess nasal resistance and the internal nasal area. To fill this void, computed tomography (CT) has been proposed as an objective tool to measure internal nasal valve anatomy preoperatively and postoperatively (10)

Cakmak and Poetker in their studies demonstrated that CT may be a valuable tool in objective assessing outcomes of functional nasal operations; however, neither study correlated the objective data to clinical findings (11).

The reasons for nasal obstruction are complex and varied and the causes can be simplified as reversible factors, such as mucosal edema and congestion, and nonreversible factors, such as anatomic deformities. An ideal nasal function test would give objective information on both types of factors.

In a number of studies the reliability and reproducibility of AR readings has been demonstrated, and a good correlation with both CT and MRI findings has been demonstrated (12, 13). The accuracy of AR decreases as the distance into the nose increases; consequently, measurements beyond 6 cm are not often advised. In a previous study, the AR was noted to be more accurate in detecting deviations located more anteriorly in the nose (9).

In this study, the correlation of AR readings was very highly significant at the MCA1 level (about 2.5 cm from the nostril). This correlation gradually decreased but remained significant at MCA2 (at about 4 cm, respectively). Comparison with normative values may be an indicator of DNS. Both DNS and non-DNS patients fell

within the normative-value range at the same rates for all MCA for the left and for the right side. The normative values are useful as references for average area but are not completely reliable to be used alone in determining deviations.

According to Corey et al. the area may not be the best way to look for septal abnormalities in the nose. It may be wrong to assume that one side should be larger than the other simply because of a deviation. A minimal MCA at any particular level may be due to septal deflection alone or to nonreversible turbinate hypertrophy. Other physiologic factors, such as the shape of the lateral nasal wall, as well as physical differences resulting from surgery and physical damage, may cause the side that we assume should be smaller, because the septum is caving in toward it, actually to be larger. In other words, we may have been wrong in assuming that the nose is divided perfectly enough so that each side normally has roughly an equal area under all conditions. A slight septal deviation in the nasal valve region can cause clear symptoms, whereas much larger deviation in the back of the nasal cavity may result in the far fewer symptoms (14).

Percentage differences are valuable in the determination of DNS. The percentage difference in area before and after decongestion of the two sides in DNS patients for MCA1 and 2 was much larger than that for non-DNS patients. Little difference in MCA1 would be expected because of the amount of erectile tissue in that area. The degree of congestion, perhaps resulting from turbinate hypertrophy, may be a better guide to DNS. It may be that greater congestion with or without turbinate hypertrophy occurs on the side that is deviated, regardless of the overall area of that nostril. Clinically, it is often related that there can be a compensatory turbinate hypertrophy leaving the larger side functionally smaller (15).

These findings agree with that clinical observation. In general, percentage differences can be used as better guidelines for inferring possible DNS (or turbinate hypertrophy).

From ROC analysis, we were able to conclude that CT scans and AR readings compared reasonably well with the clinical diagnosis for each MCA. Although the CT scans outperformed the AR readings slightly, one is about as reliable as the other. We used only postdecongestant values at each MCA when comparing the AR readings and CT scans in both ROC analysis and the Spearman test, to decrease the contribution of erectile tissue on the AR graphs. The anatomy of the nose becomes increasingly complex deeper inside the nasal cavity. At MCA1 (at the 2.5 cm mark inside the nose), the floor of the nose, the septum, and the anterior part of the inferior turbinate contribute to the structure and area as displayed on the AR graphs. However, farther inside the nose, the middle turbinate and lateral nasal wall, made up of the agger nasi cell, uncinate, medial wall of the maxillary sinus, and ethmoid bulla, contribute to the structure and area of the MCA on the AR graphs as well.

In this study, the correlation of AR readings and CT results was significant for MCA1. This correlation gradually decreased for MCA2.

Szücs and Clement found that AR was sufficiently sensitive to reveal severe deviations in the anterior nasal cavity. On the other hand, this study confirms that AR can detect even minimal anterior deviations with reasonable sensitivity and specificity (16).

Gilain et al. found reasonable agreement between AR and CT assessment of the nose. The findings of AR and CT volumes were statistically significant within the anterior part of the nose. This study differed regarding which CT scan frames representing the minimal cross-sectional areas (MCA) were selected. Gilain et al. stated that MCA 1, 2, and 3 were represented by the piriform aperture, by a site lying between the head of the inferior and middle turbinates, and by the choana, respectively (12).

Our study suggests that AR is a reasonable approach to an objective demonstration of anterior nasal deviation. However, although refinements in technology and/or interpretation may be necessary for improvement of the sensitivity and specificity of AR, it can be used as a routine clinical tool. In the current state of AR, this means that if the results are abnormal, AR can objectively document DNS as well as CT scans; a clinical diagnosis of DNS is not ruled out by a normal AR or CT.

Acoustic rhinometry may be particularly well suited to the evaluation of anterior nasal geometry during clinical studies. At the posterior part of the nose, acoustic measurements may be of limited clinical relevance. Nevertheless, CT scan has some limitations. It is not cost effective and leads to radiation exposure.

Further suggestion from Lee and Most (2015) in the article Evidence-Based Medicine Rhinoplasty, is that use of validated measures ensures reliability and consistency in outcomes reporting, and further recommends obtaining measurements both before and after applying topical

decongestant to determine to what degree mucosal hypertrophy is contributing to the patient's nasal obstruction, or to distinguish it from a true functional deformity (17).

CONCLUSION

Acoustic rhinometry is a particularly well suited method for evaluation of anterior and middle parts of nasal geometry during clinical studies and in assessing nasal septal deviations. Percentage differences between sides at each MCA are better indicators of deviation than are absolute area or normative values. As well as septal deviations and turbinate hypertrophy, irregularities of the nasal cavity often result in an obstruction of nasal breathing. In such cases, CT imaging does not provide complete description of this region. Thus, it may lead to misdiagnoses and failures in surgical treatments of impaired nasal breathing. This study also showed that CT imaging is a reliable method to obtain necessary anatomical information of nasal cavum. AR is better to be used because it is quicker and does not involve radiation. AR and CT are correlated to each other, but their accuracy is limited compared with that of the clinical diagnosis.

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Profesional paper

EPIDEMIC KERATOCUNJUNCTIVITIS, DIAGNOSIS, TREATMENT AND MENAGEMENT

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ABSTRACT

Epidemic keratoconjunctivitis (EKC) is a viral conjunctival and corneal inflammation with high contagiosity, which if it is not adequately treated, may cause blurred vision for several years. The purpose of this study was to describe the clinical and epidemiological characteristics of adenoviral keratoconjunctivitis, as well as to present the latest findings regarding diagnosis, treatment and prophylaxis.

There are known two well-defined clinical syndromes of adenoviral keratoconjunctivitis: epidemic keratoconjunctivitis and faringococcal fever, which are caused by various serotypes of adenoviruses. The exact incidence of adenoviral keratoconjunctivitis is not known.. However, it mainly occurs during the winter season. The infection can occur during direct contact or through equipments, devices in ophthalmologic ambulances, etc. The virus is extremely resistant to various chemical and physical agents. Symptomatology is similar to other types of conjunctivitis, which are with high incidence of conjunctival pseudomembrane formation. In the cornea, the changes vary from epithelial punctate keratitis to subepithelial infiltrates and the creation of nummular keratitis that leads to visual impairment. Diagnosis is mainly clinically decided, and etiology can be confirmed based on cell culture analysis.

CONCLUSION. Until now there is no approved therapy against epidemic adenoviral keratoconjunctivitis. The uncontrolled use of antibiotics, particularly the use of corticosteroids, which reduces tissue resistance, is responsible for the deterioration of such conditions. Priority in prevention EKC is the rigorous application of hygienic disinfectant measures in hospital areas, respectively medical devices in ophthalmologic ambulatory services.

Key words: epidemic keratoconjunctivitis, adenoviruses, epithelial punctate keratitis, nummular keratitis.

INTRODUCTION

Epidemic keratoconjunctivitis (EKC) is a viral conjunctival and corneal inflammation with high contagiosity that affects the eye surface, which if it is not adequately treated, may cause blurred vision for several years. It is called 'epidemic' because of epidemic spread of infection. Almost every kind of microorganism can cause inflammation of the eye, but about 92% of them are thought to be caused by viruses, mainly adenovirus.(1) This adenovirus family contains various serotypes which cause epidemic adenoviral keratoconjunctivitis (EKC), pharyngoconjunctival fever and non-specific follicular conjunctivitis. About 50% of patients with adenoviral keratoconjunctivitis are accompanied with upper respiratory tract infections that often precede EKC. At some of these patients the disease can be generalized with fever or gastrointestinal disorders with diarrhoea and vomiting.(2)

EPIDEMIOLOGY

Acute epibulbare human infections are one of the most commonly diagnosed eye diseases, and represent 2.3-10%

of all ophthalmologic diagnoses, with a prevalence of 0.6 - 3.5 per 1000 patients.(3)

Adenovirus keratoconjunctivitis generally includs adults between age of 20-40 years and are more common in males than in females (2: 1). The incubation of the virus is 2 to 12 days. The disease is very contagious, perhaps before the symptoms of the infection appear, and of course remains as long as the virus can be isolated in body fluids; for tears this period usually lasts two to three weeks from the day the virus is transmitted.(4) Human Adenovirus (HAdV) belongs to the Adenoviridae family, in the genus of Mastadenovirus that causes a variety of diseases including respiratory infections, gastroenteritis, and eye infections.(5)

There are 51 types of adenoviruses classified in 6 groups, from A to G, determined on the basis of oncogenicity, hemaglutination model of erythrocytes, and DNA homology.(5)

Table 1. Ophthalmological significance of adenovirus species in Europe.(6)

Follicular conjunctivitis	Ad3, 4, 7
Epidemic keratoconjunctivitis	KKE Ad8, 19, 37
Acute respiratory disease	ARD Ad1–3, 4, 6, 7, 14, 21
Pharyngoconjunctival fever	Ad3, 7, 1

They are highly resistant to external influences and can survive even after contact with ordinary disinfectants. They remain contagious for weeks at room temperature and have high ability to cause nosocomial infections. This demonstrates the need for proper selection and application of germicides for the disinfection of medical devices and instruments, especially tonometers, in order to prevent epidemic keratoconjunctivitis.

Human Type 19 Adenovirus (HAdC-19) is the leading etiologic agent of EKC while subgroups B and C are isolated from the respiratory tract.(5)

The infection can be spread in places where people are in groups such as: schools, kindergartens, health institutions, including ophthalmologic ambulances. EKC can touch any age group at any time of the year. Adenoviruses are transmitted from human to human through contact with infected hands, face and secretions, mainly through tears. The virus can also be spread by ophthalmologic contaminated instruments, dropper bottles, tonometers, and contaminated hands of medical personnel, which is the main risk factor for a nosocomial infection.

CLINICAL PRESENTATION

Infection usually begins with unilateral sensation of the foreign body and in most cases the other eye is infected a few days later. Patients usually tell that they had contact with someone who has had an eye infection or upper respiratory tract infection. Besides the feeling of foreign body in the eye, patients may have also photophobia, watery discharge, blurred vision if there is corneal involvement, ocular pain and redness of the eye.(6)

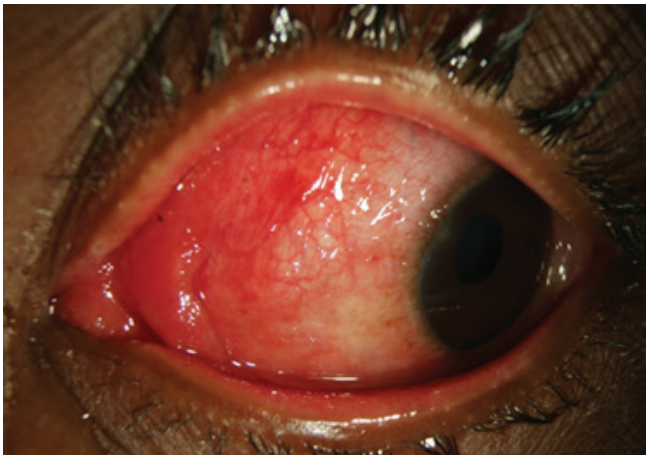

Figure 1. Epidemic keratoconjunctivitis, a patient with the appearance of conjunctival hyperemia

During clinical examination, we can notice swelling of eyelids, conjunctival hyperemia and chemosis, follicular conjunctivitis of lower eyelid, and subconjunctival hemorrhage (Figures 1 and 2).

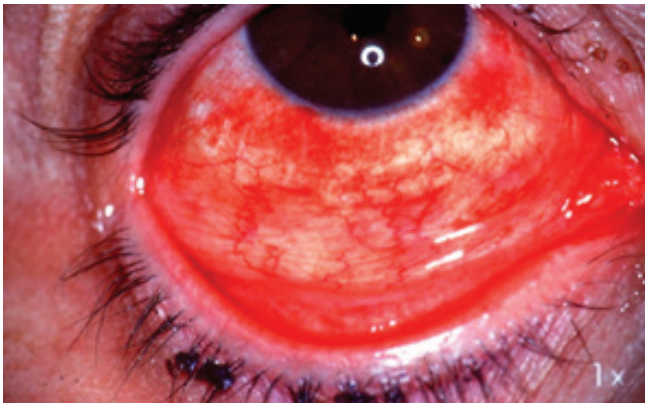

Figure 2. Epidemic keratoconjunctivitis, redness and ubconjunctival hemorrhage, chemosis of conjunctiva, caruncula and plica lacrimalis.

Follicular hypertrophy is more emphasized in the lower palpebral conjunctiva and may be present for 2 to 4 weeks (Fig. 3). Occasionally the follicular reaction may continue for several months.(7)

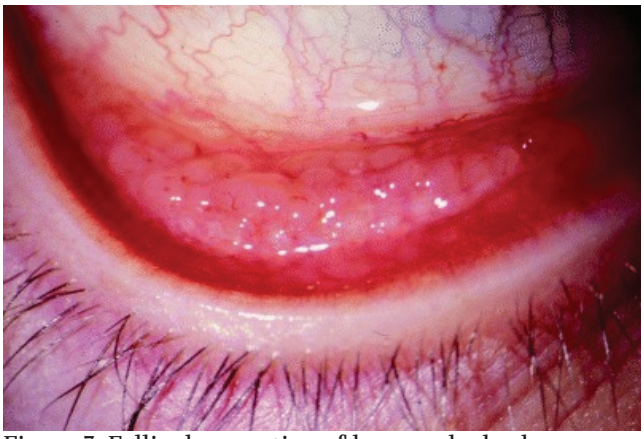

Figure 3. Follicular reaction of lower palpebral conjunctiva

In healthy eyes, most of these infections are limited and do not leave seizures, but pseudomembranes can be created in cases with compromised eyepieces (Fig. 4).(7)

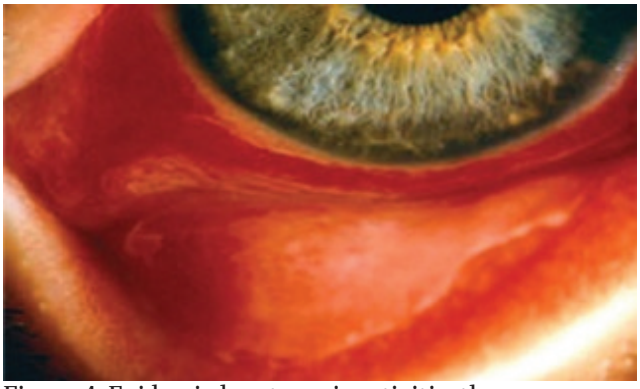

Figure 4. Epidemic keratoconjunctivitis, the appearance of subcutaneous hemorrhage and the creation of pseudomembranes.

Keratitis is common in adenoviral infections, usually it appears around the fourth day. Epithelial punctate keratitis (KEP) (which is characterized by the appearance of small infiltrates in the form of points in the cornea) may be created at the early stage of infection by all types of adenoviruses. The KEP infection lasts less than 3 weeks, except with type 8 and 19 adenovirus where it may last longer. While the subepithelial punctate keratitis (SEPK) is characterized by large and dense subepithelial opacities in the cornea. After several days in 95% of the cases, It may appear nummular, multifocal, avascular corneal infiltrates with central localization. These consist of immune complexes deposited under epithelium of the cornea.(8, 9) When Nummular infiltrates are enlarged, it may reduce the visual acuity. SEPK can disappear spontaneously within three months.(8)

Stromal diffuse infiltrates and corneal edema may be present in severe keratitis. In addition, an anterior uveitis can be manifested at the cases with adenovirus type 8 and 19.

Similarly, but usually less pronounced, the symptoms appear in the other eye, two to seven days later. The severity of the disease varies from subclinical conjunctivitis to a very severe disease with bacterial superinfection, keratitis and with systemic symptoms such as fatigue, artralgia along with signs of an upper respiratory tract infection.(10)

The acute phase can last about three to six weeks. Nummuli may persist even after this stage, continuing to reduce the visual acuity (but only in the first affected eye in most cases). Nummuli that damage the visioncan can be resolved within a few weeks, but in rare cases, can persist for years.(10)

More rarely, in patients who have undergone fulminant disease with the formation of pseudomembranes, it comes to the persistence of corneal irritation and the feeling of ocularpain. Also, as one of the most seriousequelas at the patient with dry eye syndrome with persistent infection and inflammation, pseudomembranous conjunctivitis, is formation of symblepharones (adhesion between the palpebral and bulbar conjunctiva).

In all cases with adenoviral infection, there is an preauricular, submandibular and cervical lymphadenopathy 48 hours after the appearance of the first symptoms. Any cytopathogenic agent that infects the ocular surface, including adenoviruses, results with dry eye due to loss of goblet cells.(9, 10)

DIAGNOSIS

The disease is usually diagnosed on the basis of a clinical signs, careful ophthalmological examination (biomicroscopy, fluorescence test, corneal sensitivity test) and supplemented by laboratory tests such as conjunctival cytology with Giemsa stain to look for intranuclear inclusions and lymphocytesto identify the cause of the corneal and conjunctival sample.

Adequate agents for detecting the infective agent are also antigen detection, nucleic acid detection, polymerase-chain reaction and cell culture.(11) To confirm the diagnosis, viral culture is the criterion standard.

Other diagnosis also includes other types of conjunctivitis as well as all cases of “red eye” such as uveitis, (epi-) scleritis, trauma, glaucoma, and so on.

CONTAGIOSITY

Adenoviruses are particularly resistant to various physical and chemical agents, and even in unfavorable pH environments are able to survive for a long time outside of the human body. Therefore, the high rate of spread of these infections comes by ophthalmologic ambulances. For example, HAdV19 resists 8 days on paper, 9 days on the tonometer, 10 days on textile and metal materials, and up to 35 days on plastic materials.(12) These findings increase the need for adequate and rigorous application of germicides to disinfect space and medical devices.(13) Studies have shown greater efficacy of disinfectant agents such as hydrogen peroxide and isopropyl alcohol for the elimination of adenoviruses.

TREATMENT

Epidemic keratoconjunctivitis has not an effective treatment. Antiviral medications have not been shown to be effective against viral conjunctivitis, especially to adenoviruses that are responsible for epidemic keratoconjunctivitis.(14)

The management of epidemic keratoconjunctivitis includes: the use of artificial tears, cold compresses, cycloplegic in severe cases of photophobia, topical corticosteroids (for short periods of time), topical anti-inflammatory and anti-viral agents. Depending on the severity of cinicalsigns and symptoms, patients should be followed up a few days or some weeks later. Patients on topical corticosteroid therapy should be observed regularly to monitor side effects, including increased intraocular pressure and cataract formation. In rare cases with cikatricialconjunctivitis and symblepharon, surgery is recommended for fornix reconstruction and repairs the entropion.(14)

The local use of steroids as eye drops almost always shows success during short-term use because it reduces corneal and conjunctive inflammatory signs, but does not have any significant effect at the time of recovery.(12) Topical corticosteroids can relieve subjective symptoms and may delay or prevent the formation of corneal infiltrates. However, in 30% of cases, recurrence of disease after discontinuation of corticosteroids has been observed due to increased adenovirus replication from corticosteroids. (15) The use of corticosteroids is only allowed in fulminant infections when loss of vision is at risk, in order to prevent symblepharonformation and pseudomembranes, subepithelial corneal infiltrates and iridocyclitis.(15)

Consensus on the use or dosage of corticosteroids does not exist. Only in one study, the use of cyclosporin A has been reported to be effective in relieving or eliminating corneal infiltrates. (4) While resistant cases are treated surgically with excimer laser, to improve visual acuity.

Scientific researchers are directed at the treatment of adenoviral keratoconjunctivitis with antiviral agents. In clinical studies for ribavirin, it is founded that ribavirin has a limited vitroactivity and low efficacity on three dominant serotypes of adenoviruses related with EKC (Ad8, Ad19 and Ad37).(16, 17)

During the topical administration of 0.15% ganciclovir in the form of ophthalmic gel, is reached the therapeutic level in humor aquosus and cornea, and is known as effective treatment for epithelial herpetic keratitis. Ganciclovir is recommended against the EKC because it has shown efficacity in vitro to specific adenovirus serotypes.(17)

Promising results have been noted in the treatment of adenoviral conjunctivitis with povidone iodine. Povidon-iodine has a broad spectrum in vitro, and is effective in eradication of bacteria, fungi, viruses and protozoa. A study by Pelletier et al. have reviewed the topical combination of povidone-iodine 0.4% as an antiviral agent and 0.1% dexamethasone as a potent steroid. (18) The results have shown that all eyes had rapid improvement of conjunctival injection with lowering of antiviral titers at the same time, thus guaranteeing the need for further studies of application of this combination. (19)

PREVENTION

Medical staff should be rigorously adviced for hand disinfection with 80% ethanol or 1% or 2%tosychloramide salt. It is also recommended that eye drops and eye ointmentto be used one time for each patient. Disinfection of ophthalmologic instruments is also needed mainly with chlorhexidine which is more preferable than 70% isopropyl alcohol.(20)

Close co-operation with infection control specialists can prevent the potential spread of infection in the healthy population as well as limiting laboratory costs for the diagnosis of the infection.(21)

CONCLUSION

Corneal and conjunctival viral diseases present an increasing problem due to frequent occurrence,

recurrence and resistance to medication. Uncontrolled use of antibiotics, particularly corticosteroids, which reduce tissue resistance, is responsible for the deterioration of such conditions.

Based on the fact that epidemy should be eradicated as soon as possible by taking adequate treatment, it is recommended first to report the epidemic desease and to apply recommendations from relevant referent institutions. Priority in treatment of patients with EKC is the rigorous application of disinfectant hygiene measures in hospitals, respectively ophthalmology departments, because there is still no adequate treatment for this disease. Until there is an effective antiviral therapy for EKC treatment, clinicians should be very careful in the use of corticosteroids considering the risk of infection duration.

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KERATOKONJUKTIVITI EPIDEMIK, DIAGNOSTIKIMI, TRAJTIMI DHE MENAXHIMI

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ABSTRAKTI

Keratokonjunktiviti epidemik (KKE) është inflamacion viral i konjunktivës dhe kornesë me kontagjiozitet të lartë, i cili nësë nuk trajtohet në mënyrë adekuate mund të shkakton shikim të mjegulluar për disa vite. Qëllimi i këtij punimi revial është që të përshkruajmë karakteristikat klinike dhe epidemiologjike të keratokonjuktivitit adenoviral, si edhe të paraqesim të rejat e fundit për sa i përket diagnostikimit, trajtimit dhe profilaksës.

Janë të njohura dy sindrome klinike mirë të definuara të keratokonjuktivitit adenoviral: keratokonjuktiviti epidemik dhe ethet faringokonjuktivale, të cilat janë të shkaktuara prej serotipeve të ndryshme të adenoviruseve. Incidenca e saktë e keratokonjuktiviteve adenovirale nuk është e njohur. Sidoqoftë, më së shpeshti paraqitet gjatë muajve të dimrit. Infektimi mund të ndodh gjatë kontaktit direkt ose përmes objekteve, aparateve në ambulantat oftalmologjike. Virusi është ekstremisht rezistent ndaj agjentëve të ndryshëm kimik dhe fizik. Simptomatologjia është e ngjajshme me llojet tjera të konjuktiviteve, me incidencë të lartë të pseudomembranave. Në korne, ndryshimet sillen prej keratitit epitelial punktiform deri te infiltratet subepiteliale dhe krijimi i keratitit numular që sjell deri te dëmtimi i shikimit. Diagnoza kryesisht vendoset kliniksht, ndërsa etiologjia mund të konfirmohet në bazë të analizave të kulturave qelizore.

Përfundim. Deri tani nuk ka terapi të aprovuar kundër keratokonjunktivitit adenoviral. Deri më sot nuk ka terapi të miratuar kundër keratokonjuktivitit epidemik adenviral. Përdorimi i pakontrolluar i antibiotikëve, përdorimi i kortikosteroideve, të cilat reduktojnë rezistencën indore, është përgegjës për keqësimin e gjendjeve të tilla. Prioritet në prevenimin e KKE është aplikimi rigoroz i masave dezinfektuese higjienike në hapësirat spitalore, respektivisht paisjet mjekësore në ambulantat oftalmologjike

Fjalë kyçe: keratokonjuktiviti epidemik, adenoviruset, keratiti epitalial punktiform, keratitis nummularis

Profesional paper

ПОВРЗАНОСТА НА ВОСПИТНИТЕ СТИЛОВИ НА МАЈКАТА СО НАВИКИТЕ ЗА ПИЕЊЕ АЛКОХОЛ КАЈ АДОЛЕСЦЕНТИТЕ

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АБСТРАКТ

Вовед: Семејството е првата социјална средина во која детето го започнува своето социјално живеење. Како последица на моралната криза на модерната цивилизација, следи отфрлањето на традиционалните вредности и институцијата брак, се повеќе семејства стануваат извор на ризик фактори и се одговорни за развој на ризичното однесување на адолесентите.

Цел на трудот: Да се утврди поврзаноста на воспитните стилови на мајката со навиките за пиење алкохол кај адолесцентите.

Материјал и методи: Спроведена е студија на пресек на примерок од 600 испитаници, ученици од основните и средни училишта на територијата на Полошкиот регион. Применета е скалата наменета за проценување на воспитните стилови на родителите-“Egna Minnen Batraffande Uppfostran” (EMBU), како и анкетниот прашалник на СЗО од “Глобалното истражување за здравјето на адолесцентите”. Статистичката анализа на податоците добиени од истражувањето беше направена во статистичкиот програм SPSS 17,0.

Резултати и дискусија: Структурата на испитаниците ја сочинуваа 264 (44%) машки и 336 (56%) женски ученици. Етничката структура на учениците ја сочинуваа 300 ученици Македонци и 300 Албанци, пришто 172 (28.67%) беа ученици од IX-то одделение, 203 (33.83%) од I-ва година средно училиште, и 225 (37.5%) беа ученици од II-ра година средно училиште. Во оваа група на ученици, 230 (38.33%) ученици пијат алкохол, односно преваленцијата на консумирање алкохол беше 38.3%.

Воспитниот стил на мајката во кој доминира недоследност има сигнификантно влијание на зачестеноста на пијанчење кај децата ($p<0.0001$). Кај децата кои никогаш не биле пијани беше регистриран значајно понизок скор за субскалата “недоследност“ во однос на децата кои до сега се опиле 3 до 9 пати (10.35 ± 2.4 vs 13.67 ± 3.3; $p=0.0005$).

Фреквенцијата на пијанчење кај децата сигнификантно зависеше и од воситниот стил на мајката во кој доминира отфрлање ($p=0.011$). Оваа сигнификантност се должеше на сигнификантно понизок скор на субскалата “отфрлање“ во групата деца кои негираат дека некогаш во животот не биле пијани во однос на децата на кои ова им се случило 10 и повеќе пати (31.41 ± 5.9 vs 35.77 ± 8.1; $p=0.0056$).

Воспитните стилови со доминирање на “емоционална топлина“, “презаштитеност“ и “фаворизирање“ не беа сигнификантно поврзани со честотата на пијанчење ($p=0.34$, $p=0.35$, $p=0.32$ консеквентно).

Заклучок: Резултатите од истражувањата покажаа дека воспитните стилови на мајката имаат значајно влијание на ризичното однесување на адолесцентите од аспект на пиење алкохол.

Клучни зборови: воспитни стилови, мајка, адолесценти, пиење алкохол

ВОВЕД

Здравиот и континуираниот однос меѓу мајката и детето, во првите пет години го одредува понатамошниот животен тек (1). Постојат многу причини, мотиви, потреби и ситуации при кои децата на училишна возраст (адолесценти, тинејџери) може да почнат, а подоцна и да продолжат со ризичното однесување во смисла на рано започнување со употреба на тутун и пушење, консумација на алкохол до степен на опивање, како и употреба и злоупотреба на марихуана и друг вид психоактивни субстанци. Меѓу причините за рано отпочнување со пиењето се и семејните фактори, модели на родителите кои пијат, но и нарушените односи во семејството (2).

Функционално семејство е она во кое родителите имаат способност (вештини) да го прилагодат пристапот во воспитувањето на однесувањето на детето, и нивното влијание позитивно да придонесе за обликување и структурирање на квалитетна личност. Од најрана возраст треба да се воспоставуваат односи во кои има чувство на поврзаност, безусловна љубов, и почит, пријатна атмосфера во која децата треба да се чувствуваат сигурни и среќни. Родителите на децата треба да им овозможат доволно сигурност, разбирање, но и надзор, во нивно целосно осамостојување и донесување на одлуки кои се важни за нивниот иден живот. Родителите треба да им овозможат на децата да развиваат систем на здрави вредности, да ги учат на социјални и други вештини како што е самодокажувањето, дружелубивоста, изборот на пријатели, постојано да им укажуваат на штетните последици кои ги носи на пример пиењето или некој друг вид на зависност, да се спротивставуваат на притисоци однадвор, со еден збор да формираат позитивна слика за себе (3). Родителите треба да го имаат во предвид фактот дека кај секое дете, а тоа значи и кај нивното дете, има ризик од неправилно однесување, како резултат на мноштво фактори, како од поширокатa околина, исто така и од семејството. Децата кои се најдуваат во период пред адолесценција мора да се навикнуваат на процес на донесување на самостални одлуки, на самосвесно насочување на сопствените одлуки и да се соочуваат со можните последици на тие одлуки, да го разликуваат ,,доброто“ од ,,злото“ и да се спротивставуваат на надворешни влијанија особено оние кои се негативни (4). Во истражувањата за склоноста на однесување на младите кое ги доведува во ситуација на зависност, често се поставува прашањето дали и до кое ниво основните социјализаторски заедници (семејство, образование, група на врсници за дружба и средствата за масовни информации) имаат капацитет да се насочат во реализација на своите примарни цели.

Постојат две клучни димензии на родителство. Првата димензија се однесува на родителското разбирање и родителската топлина, наспроти непријателското осудување и одбегнување. Втората димензија се однесува на родителскиот надзор. Комбинацијата на овие две димензии претставува она што заеднички се нарекува- родителски стилови (5)

Воспитните стилови се операционализирани преку содржината на универзалниот и интернационален прашалник “Egna Minnen Batraffande Uppfostran”- (EMBU) кој дава податоци за: емоционална топлина и прифаќање, претерано заштитување, отфрлање, недоследност и фаворизирање.
Воспитниот стил емоционална топлина и прифаќање, е карактеристичен за родители кои се емоцинално топли кон своите деца, полни со одобрување, разбирање, заинересираност за детето, кои даваат објаснување за дисциплината која ја бараат и кои ретко користат физички казни.Воспитниот стил на претерано заштитување, се одликува со емоционална приврзаност и доминација на родителите, со претерано поправање на однесувањето на детето и претерани барања, со присила и без почитување на неговите развојни можности.Отфрлање, претставува воспитен стил во кој најчесто родителите отворено покажуваат негативни чувства, постојан критички однос кон детето, поставуваат голем број барања, не ги разбираат мотивите за неговото однесување, не ги почитуваат детските потреби, строго ги казнуваат децата, ги заплашуваат, омаловажуваат и не им посветуваат доволно внимание.Недоследноста во воспитувањето е присутна доколку родителите се однесуваат различно од ситуација во ситуација, односно еднаш наградуваат еден вид однесување, а друг пат не реагираат на тоа однесување или пак, го казнуваат. Ваквото однесување на родителите речиси секогаш предизвикува невротски пореметувања кај децата.Фаворизирање е воспитен стил со кој родителите манифестираат фаворизираан однос кон едно од децата во однос на другите деца во семејството. (5)

Цел на трудот е да се утврди поврзаноста на воспитните стилови на мајката со навиките за пиење алкохол кај децата.

МАТЕРИЈАЛ И МЕТОДИ

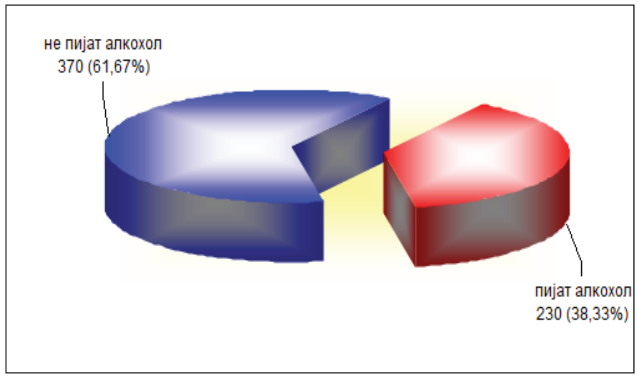
За целите на ова истражување се применија два анкетни прашалници. Скалата наменета за проценување на воспитните стилови на родителите- “Egna Minnen Batraffande Uppfostran” (EMBU) од Ликертов тип е сочинета од 64 прашања формулирани во облик на тврдења со четиричлена скала на избор. Конструирана е од шведскиот истражувач Перис (Perris), а адаптирана од Ариндел (Arrindell). Адаптираната верзија, која е користена во ова истражување, содржи 5 субскали: емоционална топлина, отфрлање, презаштитување, фаворизирање на детето и недоследност. Вториот прашалник е всушност анкетниот прашалник од Глобалното истражување за здравјето на адолесцентите. Станува збор за стандарден прашалник на СЗО и CDC кој содржи 24 прашања каде беше опфатено и пиењето алкохол. Прашалникот беше дизајниран така да одговара на возраста и полот на испитаниците. Статистичката анализа на податоците добиени од истражувањето беше направена во статистичкиот програм SPSS 17,0. Категориските (атрибутивни) варијабли се прикажани со апсолутни и релативни броеви. Нумеричките (квантитативни) варијабли се прикажани со просек, минимални вредности, максимални вредности, и стандардна девијација. За компарирање на скоровите меѓу децата што консумират и што не консумират алкохол беше користен Student-ов t-test. Логистичка Регресиона анализа беше користена за детерминирање на воспитните стилови сигнификантно поврзани со развивање навика за консумирање алкохол. Статистичката сигнификантност беше дефинирана на ниво на $p<0.05$.

РЕЗУЛТАТИ И ДИСКУСИЈА

Во истражувањето беа вклучени 600 испитаници, ученици од основните и средни училишта на територијата на Полошкиот регион.Половата структура на испитаниците ја сочинуваа 264 (44%) машки ученици, 336 (56%) ученици од женски пол. Етничката структура на учениците ја сочинуваа 300 ученици Македонци, 300 ученици Албанци, додека во однос на застапеноста по одделенија, 172 (28.67%) беа ученици од IX-то одделение , 203 (33.83%) од I-ва година средно училиште, и 225 (37.5%) беа ученици од II-ра година средно училиште.

Во оваа група на ученици, 230 (38.33%) ученици пијат алкохол, односно преваленцијата на консумирање алкохол беше 38.3%.

График 1.



На прашањето „ Колку години имаше кога го испи првиот алкохолен пијалок (не само неколку голтки)?”, повеќе од половина ученици одговориле дека првиот цел алкохолен пијалак го испиле на 14 или 15 години - 134 (58.26%). На 7-годишна возраст или помлади првиот алкохолен пијалок го испиле 18 (7.8%) од децата.

Табела 1.

Колку години имаше кога го испи првиот алкохолен пијалок (не само неколку голтки?)	Број и %
7 години или помалку	18 (7.83)
8 или 9 години	5 (2.17)
10 или 11 години	11 (4.78)
12 или 13 гоодини	37 (16.09)
14 или 15 години	134 (58.26)
16 години или повеќе	25 (10.87)
Вкупно	230

Овие резултати се слични со претходни истражувања, како што е Студијата на Националниот институт за злоупотреба на алкохол издадена во декември 2015 год. во Америка, која покажува дека децата уште во раната возраст почнуваат со употреба на алкохол (7).

Резултатите од истражувањето покажаа дека воспитните стилови на мајката во кои доминираат “недоследност“ и “отфрлање“ имаат значајно влијание на ризичното однесување на децата од аспект на консумирање на алкохол ($p<0.0001$; $p=0.023$ консеквентно). Останатите воспитни стилови со доминирање на “емоционална топлина и прифаќање“, “презаштитеност“ и “фаворизирање“ немаа сигнификантно влијание на ваквото ризично однесување на децата..

Во групата испитаници кои консумираат алкохол регистриравме сигнификантно повисок скор за

субскалата „недоследност" споредено со групата деца кои не пијат алкохол (11.32 ± 2.8 vs 10.18 ± 2.4). Овој статистички резултат сугерира заклучок дека воспитниот стил на мајката во кој доминира недоследност значајно е поврзан со ризично однесување анализирано преку консумирање алкохол. Мајките на децата кои пијат алкохол покажуваат во воспитувањето сигнификантно повисок степен на недоследност.

Просечниот скор за субскалата „ отфрлање" изнесува 32.4 ± 7.0 во групата деца кои пијат алкохол, а 31.22 ± 5.8 во групата кои не пијат. Тестираната разлика се потврди како сигнификантна за p=0.023, што пак иницира заклучок дека отфрленоста на детето од страна на мајката значајно го зголемува ризичното однесување анализирано преку пиење на алкохол. Мајките на децата кои пијат алкохол покажуваат во воспитувањето сигнификантно повисок степен на отфрлање.

Табела 2.

Дали пиеш алкохол?	Descriptive Statistics			p value
	N	mean ± SD	min – max	
недоследност (мајка)				
не пие алкохол	351	10.18 ± 2.4	7 – 18	p<0.0001
пие алкохол	216	11.32 ± 2.8	7 – 21	
емоционална топлина и прифаќање				
не пие алкохол	366	50.99 ± 8.9	17 – 65	p=0.184
пие алкохол	227	51.97 ± 8.3	27 – 66	
Отфрлање				
не пие алкохол	367	31.22 ± 5.8	–	p=0.023*
пие алкохол	227	32.4 ± 7.0	–	
Презаштитеност				
не пие алкохол	366	31.19 ± 6.9	15 – 52	p=0.663
пие алкохол	225	31.44 ± 6.5	16 – 62	
Фаворизирање				
не пие алкохол	358	8.03 ± 2.8	5 – 18	p=0.064
пие алкохол	221	7.58 ± 2.9	5 – 20	

(Student t- test) *p<0.05

Добиените резултати се идентични со резултатите од бројни истражувања кои покажуваат дека децата кои се изјасниле дека мајките поминуваат повеќе време со нив и комуницираат со нив почесто, во најголем процент не употребуваат алкохол (8).

Логистичка Регресиона анализа беше користена да се детерминираат воспитните стилови од страна на мајката, кои се сигификантни предиктори за развивање навика кај децата за консумирање алкохол.

Мултиваријантната Логистичка Регресиона анализа како воспитни стилови од страна на мајката сигнификантно поврзани со развивање навика за пиење алкохол кај децата, ги потврди: недоследноста (p<0.0001), и отфрлањето (p=0.029).

Со зголемување на вредноста на субскалата „недоследност" за единица скор, ризикот за развивање ризично однесување кај децата од аспект на консумирање алкохол се зголемува за 21.7% (OR: 1.217, 95% CI 1.121 – 1.321);

Со зголемување на вредноста на субскалата „отфрлање" за единица скор, ризикот за развивање ризично однесување кај децата од аспект на консумирање алкохол се зголемува за 2.1% (OR: 1.021, 95% CI 1.018 – 1.060);

Воспитниот стил на мајката во кој доминира недоследност има сигнификантно влијание на зачестеноста на пијанчење кај децата (p<0.0001). Кај децата кои никогаш не биле пијани беше регистриран значајно понизок скор за субскалата "недоследност" во однос на децата кои до сега се опиле 3 до 9 пати (10.35±2.4 vs 13.67±3.3; p=0.0005).

Фреквенцијата на пијанчење кај децата сигнификантно зависеше и од воситниот стил на мајката во кој доминира отфрлање (p=0.011). Оваа сигнификантност се должеше на сигнификантно понизок скор на субскалата "отфрлање" во групата деца кои негираат дека некогаш во животот не биле пијани во однос на децата на кои ова им се случило 10 и повеќе пати (31.41±5.9 vs 35.77±8.1; p=0.0056).

Воспитните стилови со доминирање на "емоционална топлина", "презаштитеност" и "фаворизирање" не беа сигнификантно поврзани со честотата на пијанчење (p=0.34, p=0.35, p=0.32 консеквентно)

Табела 3.

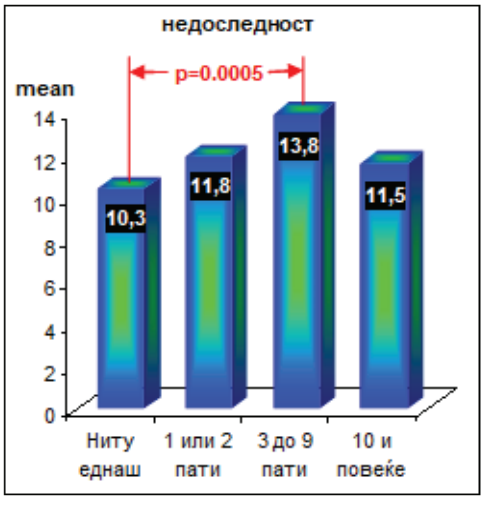
Мултиваријантна Логистичка Регресиона анализа за предикција на ризично однесување консумирање алкохол			
Варијабла	Unadjusted OR	CI 95%	p-value
недоследност	1.217	1.121 – 1.321	<0.0001**
емоционална топлина	0.927	0.903 – 1.051	0.228
отфрлање	1.021	1.018 – 1.060	0.029*
презаштитеност	0.974	0.943 – 1.007	0.121
фаворизирање	0.927	0.866 – 0.992	0.229

(Student t- test) *p<0.05

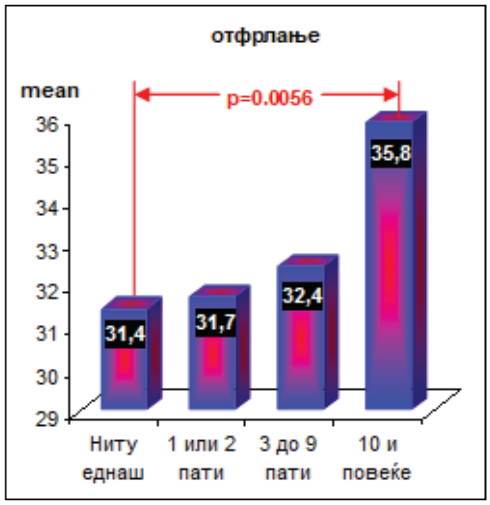
Табела 4.

Прашање 17	ЕМБУ скала									
	недоследност		емоционална топлина		отфрлање		презаштитеност		Фаворизирање	
	N	mean ± SD	N	mean ± SD	N	mean ± SD	N	mean ± SD	N	mean ± SD
Ниту еднаш	480	10.35±2.4	499	55.55±8.7	499	31.41±5.9	496	31.36±6.7	488	7.89±2.8
1 или 2 пати	51	11.80±2.8	52	50.61±8.97	52	31.71±6.3	52	30.59±6.1	51	7.20±2.4
3 до 9 пати	15	13.67±3.3	18	53.33±8.6	18	32.44±7.9	18	29.89±6.1	17	8.23±3.2
10 и повеќе	19	11.47±3.5	22	48.86±7.4	22	35.77±8.1	22	33.27±8.5	20	8.20±3.5
p-value	<0.0001		0.34 ns		0.011*		0.35 ns		0.32 ns	
Прашање 17:Во текот на твојот живот, колку пати си испил толку многу алкохол така што си бил навистина пијан?										

Слика 1



Слика 2



Зачестеноста на имање мамурлук и проблеми дома и на училиште заради пиење алкохол, сигнификантно зависеше од воспитните стилови на мајката во кои доминира "недоследноста" (p=0.00001), "отфрлањето" (p=0.0018), и "фаворизирањето" (p=0.037), а несигниификантно зависеше од воспитните стилови во кои доминира "емоционалната топлина" (p=0.54) и "презаштитеноста" (p=0.11).

Кај децата кои никогаш немале мамурлук и немале проблеми заради алкохолот беше регистриран значајно

понизок скор за субскалата “недоследност“ во однос на децата кои до сега имале вакви епизоди 10 пати и повеќе (10.42±2.5 vs 12.86±3.6; p=0.00013).

Кај децата кои никогаш немале мамурлук и немале проблеми заради алкохолот беше регистриран значајно понизок скор за субскалата “отфрлање“ во однос на децата кои до сега имале вакви епизоди 10 пати и повеќе (31.36±5.8 vs 40.0±11.1; p=0.0003).

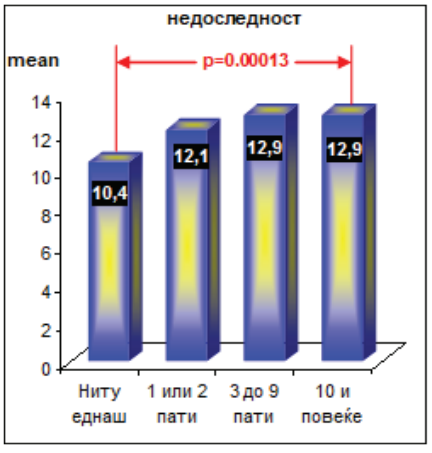
Кај децата кои никогаш немале мамурлук и немале проблеми заради алкохолот беше регистриран значајно понизок скор за субскалата “фаворизирање“ во однос на децата кои до сега имале вакви епизоди 3 до 9 пати (7.7±2.6 vs 11±4.3; p=0.0087).

Табела 5.

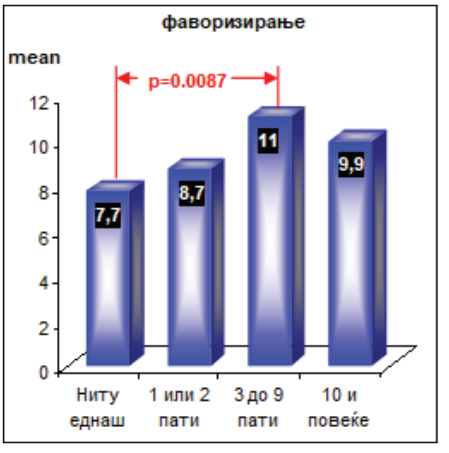
Прашање 19	ЕМБУ скала									
	недоследност		емоционална топлина		отфрлање		презаштитеност		фаворизирање	
	N	mean ± SD	N	mean ± SD	N	mean ± SD	N	mean ± SD	N	mean ± SD
Ниту еднаш	515	10.42±2.5	534	51.59±8.7	534	31.36±5.8	531	31.21±6.6	520	7.7±2.6
1 или 2 пати	33	12.14±2.9	37	49.73±8.6	38	32.60±6.3	38	31.39±7.6	37	8.7±3.1
3 до 9 пати	7	12.86±3.8	7	53.28±5.8	7	35.29±9.8	7	36.86±9.1	7	11± 4.3
10 и повеќе	7	12.86±3.6	8	50.0±8.5	8	40.0±11.1	8	33.87±.9	8	9.87±5.3
p-value	0.00001**		0.54		0.0018**		0.11		0.037*	

Прашање 19.Во текот на твојот живот колку пати си имал мамурлук и си се чувствувал болно, си имал проблеми со домашните или со пријателите, си отсуствувал од училиште или си учествувал во тепачки како резултат на пиење алкохол?

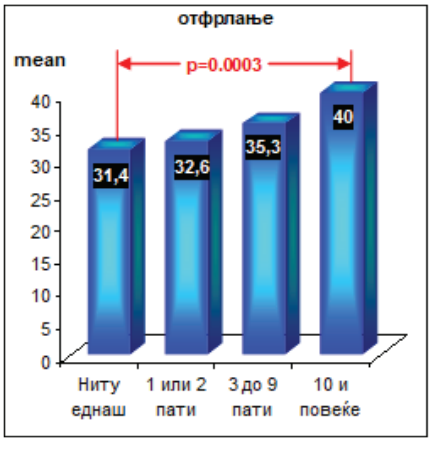
Слика 3



Слика 5



Слика 4



Ставовите на младите во однос на семејството говорат дека семејствата во најголем број се функционални. Младите во најголем процент добиваат доволно грижа и внимание од родителите; родителите најчесто знаат кај се нивните деца и со кого се. Но, студијата покажа дека постојат и родители кои не се грижат доволно за своите деца, па тие се повеќе препуштени во поглед на воспитанието на своите другари, на социјалните мрежи и интернетот.

Табела 6.

CD4	Spearman R	t-test	p-level
недоследност МАЈКА	0.204	t=4.94	p=0.000001
емоц. топлина и прифаќање МАЈКА	-0.044	t=1.06	p=0.289
отфрлање МАЈКА	0.077	t=1.87	p=0.062
презаштитеност МАЈКА	-0.0044	t=0.11	p=0.9148
фаворизирање МАЈКА	-0.041	t=0.99	p=0.3203

Да се биде родител не е едноставна улога. Желбата на секој родител е да создаде емоционално зрел и стабилен поединец, среќен поединец кој успешно ќе се интегрира во социјалната средина. Воспитните стилови на родителите се идентификувани како еден од најважните ризични, но од друга страна и заштитни фактори во врска со употреба на субстанции кај адолесцентите(4). Истражувањата на Ронер зборуваат за појава на тешки душевни пореметувања кај лицата изложени на негативни последици од воспитниот стил отфрлање (Rohner, според Kuburic, 1996) (4).

Резултатите добиени од истражувањето дадоа одговор на поставената цел. Униваријантната Логистичка Регресиона анализа покажа дека воспитниот стил во кои доминира недоследност и отфрлање имаат значајно влијание на ризичното однесување на децата од аспект на консумирање на алкохол. Научните докази покажуваат дека влијанието на родителските стилови на консумирање на алкохол кај адолесценти варира во различни земји. Алкохолот е всушност најстарата дрога. Речиси 50% од луѓето на возраст од 12 и повеќе години консумирале алкохол во САД. Повеќето луѓе не се во можност да консумираат алкохол одговорно. Сепак, заради една или друга причина, некои луѓе го злоупотребуваат алкохолот и развиваат зависност(5). Во информациите од Американскиот совет за едукација за дроги (ACDE) се наведува дека околу 10 до 15 милиони луѓе во САД може да се класифицираат како алкохоличари. Околу 4,5 милиони од овие луѓе се адолесценти. Проценка е дека зависноста од алкохол ќе влијае на 17% од мажите и 8% од жените во одреден момент во нивниот живот(6) Студијата на Националниот институт за злоупотреба на алкохол издадена во декември 2015 год. во Америка, покажува дека со возраста се зголемува преваленцата на употреба на алкохол кај учениците. Меѓутоа, во споредба со 2010 година, употребата на алкохол во последните месеци во 2015г. е намалена и изнесува 9,7%, 21,5%, а 35,3% за учениците од 8-мо, 10-то и 12-то одделение (13,8%, 28,9% и 41,2% во 2010 година(7)

На територијата на Р.Македонија, во учебната 2007/2008 година испитувани се состојбите со зависностите кај адолесцентите, пришто кај вкупно 2116 ученици на возраст од 11-17 год.,утврдено е дека само 48,9% од испитаниците никогаш не испиле цел алкохолен пијалок, многу ученици започнуваат со алкохол на рана возраст на 12-13 год, така што 16,3% прв пијалок испиле на таа возраст, додека голем дел од учениците на возраст од 13-15 години пијат алкохол еднаш или повеќе пати во месецот. Во деновите кога пијат алкохол 14.4% пијат по еден пијалок, додека 3.1% пијат по 5 и повеќе пијалоци во денот(8).

Истражувањето од 2009/2010 година покажа дека постои и значајна поврзаност помеѓу високата преваленца на пиење алкохол кај момчињата од македонските паралелки и имотноста на нивното семејство. Неделната употреба на алкохолот, раното и често опивање се во значаен пораст со возраста во речиси сите 39 земји од меѓународната (HBSC) студија, како кај момчињата, така и кај девојчињата(8). Во поглед на социјалните релации и поддршка, со возраста, младите во Македонија, полесно разговараат со родителите за темите што ги загрижуваат, за разлика од појавата на отежната комуникација со родителите кај возрасните деца од Европа. Веројатно однесувањата поврзани со здравјето варираат меѓу децата од различни земји укажувајќи на силното влијание на социјалните, културните и економските факторли врз нивното здравје, но исто така и воспитните стилови на родителите (9,10,11).

Резултатите во врска со дозволувањето на адолесцентите да пијат алкохол дома, зависат од структурата на семејството: адолесценти од целосни семејства на кои им било дозволено да пијат дома, се покажало дека имаат најниско ниво на употреба на алкохол и проблеми со текот на времето, додека оние кои не се од целосни семејства и на кои не им било дозволено да пијат дома, покажале највисоко ниво на зависност од алкохол(12,13). Родителите треба да бидат обучени со многубројни информации и знаења, во идните програми за превенција од употреба на алкохол, пред нивните деца да станат адолесценти (14,15). Младите сметаат дека е поголема пермисивноста кај мајките во однос на пијанството во споредба со користењето марихуана или екстази. Сепак, околу 2% од учениците сметаат дека на нивните мајки воопшто

не би им било грижа доколку користат ПАС или се во пијана состојба од консумирање алкохол.(16)

Во ЕСПАД истражувањето реализирано на територијата на град Скопје во 2012 година, 59,8% од лицата користеле алкохол во животот. Огромни разлики се забележуваат во однос на етничката структура на лицата кои воопшто не пиеле алкохол. Најголем е процентот на ученици Албанци кои изјавиле дека никогаш не пиеле алкохол во животот (86,3%), додека најмал е процентот кај Македонците (18,8%). Ова води кон заклучокот дека влијанието на семејните, супкултурните и религиозни аспекти имаат значајно влијание во однос на пиењето алкохол.(16)

Во споредба со претходните истражувања (од 2008 и 2012 година), во 2015 година се бележи надолен тренд - се намалува бројот на деца кои биле прекумерно пијани. Возраста на првото консумирање алкохол прогресивно расте со возраста на учениците, со најчеста застапеност на 14 и 15 години. Дел од учениците на возраст под 9 години за прв пат пиеле пиво (9%), вино (6%) и жесток пијалак (3%).Ставовите на младите во однос на семејството говорат дека семејствата во најголем број се функционални. Младите во најголем процент добиваат доволно грижа и внимание од родителите; родителите најчесто знаат кај се нивните деца и со кого се.Но, студијата покажа дека постојат и родители кои не се грижат доволно за своите деца, па тие се повеќе препуштени во поглед на воспитанието на своите другари, на социјалните мрежи и интернетот, имајќи го предвид податокот дека 1/5 од учесниците изјавиле дека користат интернет повеќе од 6 часа дневно, но и податокот дека 10,5% од учениците се изјасниле дека нивните родители делумно или воопшто не знаат каде одат тие во вечерните саботни часови.(16)

ЗАКЛУЧОК

Од добиените резултати се потврди дека воспитните стилови на мајката во кои доминира недоследност и отфрлање имаат значајно влијание на ризичното однесување на децата од аспект на консумирање на алкохол, додека воспитните стилови на мајката со доминирање на емоционална топлина; презаштитеност и фаворизирање не беа сигнификантно поврзани со честота на пијанчење.

Потребно е поттикнување на родителите да ги следат активностите и пријателствата на адолесцентите преку воспоставување на правила за тоа што е дозволено, а истите се ефикасни во спречување на децата, проблематично да се однесуваат.

Се препорачуваат мерки и активности за зголемување на свесноста кај децата и младината за штетните последици од неконтролирана употреба на алкохол преку поголема информираност од родителите, особено мајките и едукација во училиштата, на спортски и друг вид забавни настани, како и преку средствата за информирање.

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THE CONNECTION OF THE MOTHER'S UPBRINGING STYLES WITH THE DRINKING HABBITS AMONG THE ADOLESCENTS

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ABSTRACT

Introduction: Family is the first social surrounding in which the child starts its social life. As a consequence of the modern civilization moral crisis, it is followed by a rejection of the traditional values and the institution of marriage, so more and more families become a source of risk factors and are responsible for developing risky behavior of the adolescents.

Aim of the work: To detect the connection of the mother's upbringing styles with the drinking habits of the adolescents.

Materials and methods: A sample study has been conducted over 600 respondents, students from primary and secondary schools from the Polog region. The scale used for assessment of upbringing styles was applied- "Egna Minnen Batraffande Uppfostran" (EMBU), as well as the questionnaire by the WHO form "The global research of the adolescents' health". The statistical analysis of the data gained from the research was made with the statistical program SPSS 17,0.

Results and discussion: The structure of the respondents was composed of 264 (44%) male and 336 (56%) female students. The ethnic structure of the students was composed of 300 Macedonian students and 300 Albanian students, where 172 (28.67%) were students from 9th grade, 203 (33.83%) from 1st grade and 225 (37.5%) students from 2nd grade in high school. In this group of students, 230 (38.33%) of the students drink alcohol that is the prevalence of consumption was 38.3%.

The upbringing style of the mother dominated by inconsistency there is a significant influence over the frequency of drunkenness among the children ($p<0.0001$). Among the children who have never been drunk a significant lower score was registered for the subscale of "inconsistence" in comparison to the children who have been drunk 3-9 times so far (10.35+2.4 vs 13.67+3.3; $p=0.0005$).

The frequency of drunkenness among the children depended on the upbringing style of the mother dominated by rejection ($p=0.011$). This was due to the significantly lower score of the subscale "rejection" in the group of children who deny to have been drunk in comparison to the children who state that this happened to them 10 or more times (31.41+5.9 vs 35.77+8.1; $p=0.0056$).

The upbringing styles dominated by "emotional warmth", "overprotection" and "favoritism" were not significantly related with the frequency of drunkenness ($p=0.34$, $p=0.35$, $p=0.32$ consequently).

Conclusion: The results of the research have shown that the upbringing styles of the mother have significant influence towards the risky behavior of the adolescents in the aspect of drinking alcohol.

Key words: upbringing styles, mother, adolescents, drinking alcohol.

Profesional paper

MJEKIMI I KATARAKTËS ME PHAKO METODËN NË SPITALIN KLINIK TË TETOVËS

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REZYME

Hyrje: Katarakta njihet në popull edhe si perde e syrit, është një ndër shkaqet më të shpeshta të humbjes së rikthyeshme të pamjes. Më e shpesht është katarakta e pleqërisë (senile) e cila shfaqet në moshën mbi 60 vjet.

Qëllimi i temës: Qëllimi i punimit është përcaktimi i llojeve të kataraktave dhe përcaktimi i shfaqjes së kataraktës sipas gjinisë dhe moshës.

Materiali dhe metodat: Janë shfrytëzuar të dhënat nga reparti i Oftalmologjisë pranë Spitalit Klinik të Tetovës gjatë periudhës Janar 2016 Shtator 2017. Gjithsej janë 2174 pacientë prej moshës 51 deri 90 vjec.

Rezultatet: Në bazë të rezultateve të diskutuara kemi ardhur në këto përfundime: Lloji më i shpeshtë i kataraktave është katarakta matura me 1226 raste. Gjinia më e prekur është gjinia mashkullore me 127 raste. Grupmosha e të operuarave ma e prekur është nga 71-80 vjeç me 100 raste.

Mjekimi: Gjithë kataraktet trajtohen në menyrë kirurgjike.

HYRJE

Katarakta, llojet e kataraktës

Sytë në rrugët dhe qendrën e të pamurit përbëjnë shqisën më të rëndësishme të njeriut.

Lentja e njeriut ose kristalina ndodhet prapa irisit, është një trup i tejdukshëm me formën e mystë (bikonvekse) me diametra 9-10 mm dhe trashësi 4-5 mm, me peshë 0.3 gr. Në 70% ajo përmban ujë.

Lentja ka një sipërfaqe të përparshme e një të pasme, që kalojnë në njëra tjetra në ekuatorin e kristalinës. Kristalina mbështillet nga kapsula e saj. Ajo është një top i mbyllur në vetvete, që prodhon qeliza të cilat me vendosjen e tyre japin shtresave të kristalinës forma dalluese. Vendosja e tyre bëhet në formë rrezore, duke dhënë në prerje paraqitjen thelave të portokallit dhe koncetrike, që lejon të krahasohet me vendojen e fletëve të qepës [1.3].

Me rritjene moshës, fibrat vendosen njëra mbi tjetrën. Qelizat që i formonin e humbasin bërthamën dhe kufirin midis tyre. Ato shtyhen nga përpara prapa dhe formojnë bërthamën e kristalinës. Kjo humbet ujin dhe me kalimin e moshës bëhet e fortë [4,5,6].

Kështu, me kohë kristalina e humb elasticitetin e saj, duke u ulur me këtë rast dhe mundësia e syrit për tu përshtatur. Duke krahasuar lenten me lëmshin tokësor, dallojmë: një pol të përparshëm e një pol të pasëm të kristalinës. Ajo nuk ka enë gjaku, enë limfatike dhe as nerva. Kështu ushqimi i saj sigurohet vetëm me anën e difusionit ndërmjet lëngut ujor. Kristalina e ruan formën e vëllimin e vet, duke ndryshuar gjatë jetës peshën specifikale [1,2,5,6,7].

Pas moshës 25 vjeç vërejmë të formohet bërthama e kristalinës. Prapa kristalinës ndodhet trupi qelizor, ai i mbush pjesën e pasme të syrit. Kjo masë xhelatinoze e tejdukshme ka formën e një sfere të shtypur nga përpara, ku formon një gropës, që është vendi mbi të cilin qëndron lentja e syrit.

Çdo humbje e tejduekshmërisë së lentës së syrit, pavarsisht nga madhësia e saj, apo dendësi e turbullimit, qoftë edhe formimi i vakuolave në kristalinë, cilësohet si cataracta.

Një lentë plotësisht e tejdukshme është vështirë të gjindet. Turbullime në formë pllakash në periferi vështgohen dhe në fëmijërinë e hershme. Opacifikime të tilla nuk ndikojnë në pamjen dhe nga ana jonë nuk u kushtohet vëmendje. Ndryshe ndodhën me turbullimet e dendura e të tilla që përparojnë dhe bëjnë të domosdoshëm mjekimin, i cili deri më sot është kirurgjikal. Ekzistojnë disa lloje të cataractave [1,4,7,8].

MJEKIMI

Ekstraksioni ekstra kapsular i lens kristalina (ECCE). implantim të lentes intraokulare (IOL). Dallimi nga metoda e mëparshme qëndron në atë që në këto raste bëhet grisja e kapsulës së përparme të lensit me ç'rast pastrohen masa lentale bëhet ekspulzioni i nukleusit të lensit ndërsa kapsula e pasme e lensit nuk preket dhe shërben si shtrat për të implantuar IOL.

Ekzistojnë dy lloje të IOL të përparme dhe të pasme. Të pasmet implantohen pas irisit në dhomën e pasme të syrit, ndërsa të përparmet në dhomën e përparme të syrit.

Kjo metodë është shumë më e sigurt se metoda paraprake korrigjimi i pamjes është shumë më i sigurt se metoda paraprake korrigjimi i pamjes është më i mirë ndërsa rehabilitimi post operativ i pacientëve është më i shpejt. Me përparimin e teknologjis mjekësore kohëve të fundit metoda ECCE zëvendësohet me një metodë më të sofistikuar e quajtur FAKO emulsifikimit. (foto nr. 1)

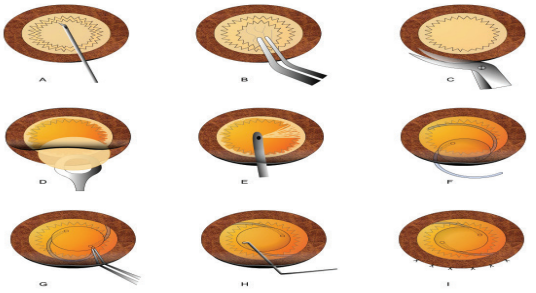


Foto 1.Ekstrakcioni ekstrakapsular i kataraktës

FAKO emulsifikim – zgjatja e operacionit është shumë e shkurtër.

Hapja e kornes me këtë metodë është shumë e vogël, coptimi dhe thithja e masave të nukleusit lental bëhet nëpërmes të sondës që punon në princip të ultrazërit me frekuencë shumë të lartë. Teknologjia e prodhimit të lentave ka mundësuar përdorimini e lenteve të buta që nëpërmjet instrumentit special futen në dhomën e pasme të syrit nëpërmes hapjes së limbit korneal me madhësi prej 1-2.8mm. Kjo metodë ka përparsitë e veta sepse mundëson rehabilitim të shpejtë të pacientit i cili pas intervenimit dërgohet në mjekim shtëpiak. Pamja e tij është shumë e pastër eliminohet edhe astigmatizmi post operativ i cili paraqitet pas metodës ECCE. (foto nr. 2)

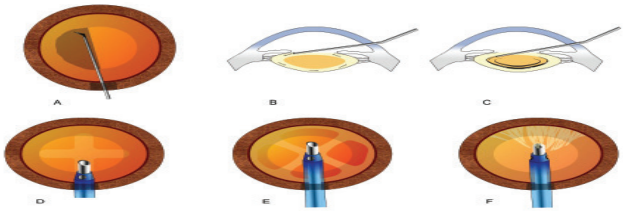


Foto 2. Fakoemulsifikimi

QËLLIMI I TEMËS

1. Të përcaktoj numrin e pacientëve me katarakte.
2. Të përcaktoj moshën më të prekur të pacientëve nga katarakta.
3. Tëpërcaktoj gjininë më të prekur nga katarakta.

MATERIALI DHE METODAT

Në punim janë përfshirë 2174 pacientë prej moshës 51 deri 90 vjeç. Studimi bazohet në materialin e repartit të syve, në librin e shënimeve të operacioneve të kryera dhe dokumentacioneve tjera ekzistuese në repartin e Syve pranë Spitalit Klinik të Tetovës, gjatë vitit kalendarik Janar 2016 Shtator 2017.

Për rregjistrim të pacientëve është përdorur metoda komjuterike, prej nga i kemi grumbulluar dhe përpunuar të dhënat për çdo pacient. Me përpunumin e të dhënave në programin kompjuterik EXEL janë fituar tabelat në të cilat janë dhënë përshkrimet numerike të parametrave të hulumtuar. Analizën e veçorive numerike të të dhënave të fituara e kemi bërë me metoda statistikore.

REZULTATET E PUNËS

Në sallën operative të repartit të Syve pranë Spitalit Klinikë të Tetovës janë operuar gjithsej 246 pacientë me kataraktë.

Llojet e kataraktave të operuara

Nga numri i përgjithshëm i operacioneve:

135 kanë qenë Katarakta mature

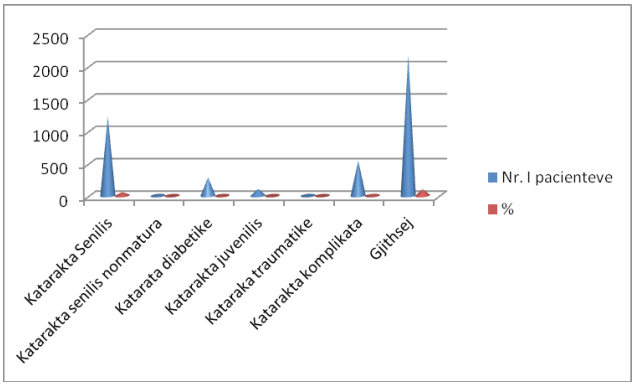
53 kanë qenë Katarakta diabetike

12 kanë qenë Katarakta të shoqëruara me glaukomë

46 kanë qenë Katarakta kortikale (Tabela 1)

Tab. 1 Llojet e kataraktave të operuara

Lloji I kataraktave	Nr. I pacienteve	%
Katarakta Senilis	1226	56.3
Katarakta senilis nonmatura	14	0.87
Katarata diabetike	280	12.8
Katarakta juvenilis	104	4.8
Kataraka traumatike	7	0.33
Katarakta komplikata	543	24.9
Gjithsej	2174	100



Diagrami 1.Struktura e llojeve të kataraktava të operuara

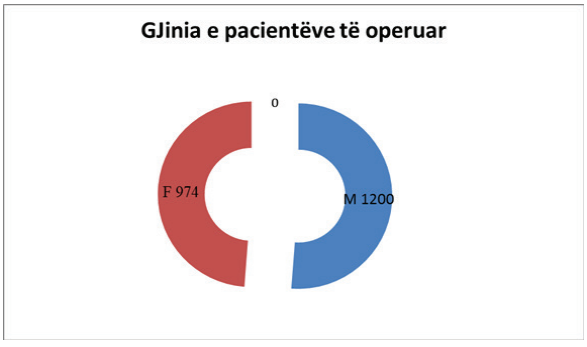
Gjinia e pacientëve të operuar

Nga numri i përgjithshëm i pacientëve të operuar:

- 1200 kanë qenë të gjinisë mashkullore
- 974 kanë qenë të gjinisë femrore (Tabela 2)

Tab.2 Gjinia e pacientëve të operuar

Meshkuj	Femra	Gjithsej
1200 (55.19 %)	974 (44.9 %)	2174 (100%)



Diagrami 2.Struktura e pacientëve sipas gjinisë

Grupmosha e pacientëve të operuar

Grupmosha 51-60 vjet

Gjithësej të operuar kanë qenë 20 nga të cilët 10 të gjinisë mashkullore dhe 10 të gjinisë femrore.

Grupmosha 61-70 vjet

Gjithësej të operuar kanë qenë 90 nga të cilët 43 të gjinisë mashkullore dhe 47 të gjinisë femërore.

Grupmosha 71-80 vjet

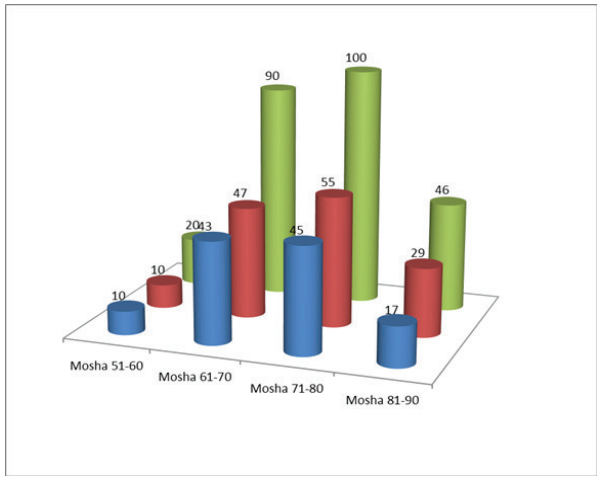
Gjithësej të operuar kanë qenë 100 nga të cilët 45 të gjinisë mashkullore dhe 55 të gjinisë femërore.

Grupmosha 81-90 vjet

Gjithësej të operuar kanë qenë 46 nga të cilët 17 të gjinisë mashkullore dhe 29 të gjinisë femërore. (Tabela 3)

Tab. 3 Grupmoshat dhe gjinia e pacientëve të operuar

Mosha 51-60		Mosha 61-70		Mosha 71-80		Mosha 81-90	
M	F	M	F	M	F	M	F
10	10	43	47	45	47	17	29
20 (8 %)		90 (37 %)		100 (41 %)		46 (19 %)	



Diagrami 3.Struktura e grupmoshës dhe gjinisë së pacientëve të operuar

PËRFUNDIMI

Katarakta është sëmundje që zvoglon mprehtësinë e pamjes dhe mund të shkaktojë verbim reverzibil.

Çdo humbje e tejduekshmërie se lentës së syrit, pavarsisht nga madhësia e saj, apo dendësia e turbullimit, qoftë edhe formimi i vakuolave në kristalinë, cilësohet si cataracta.

Sipas raportit të OBSH në vitin 1997 katarakta ka qenë si shkak i verbimit në mbi 50% të rasteve në tërë botën, ndërsa vlerësimet janë që në vitin 2020 numri i

kataraktave do të rritet në mbi 50 milion të popullatës botërore.

Në bazë të rezultateve të diskutuara kemi ardhur në këto përfundime:

- Lloji më i shpeshtë i kataraktave është katarakta senilis me 1226 raste ose 56.3%.
- Gjinia më e prekur është gjinia mashkullore me 1200 raste ose 55.19%
- Grupmosha e të operuarave ma e prekur është nga 71-81 vjeç me 100 raste ose 41%.
- Çdo humbje tejduekshmërie e lentës së syrit, pavarsisht nga madhësia e saj, apo dendësi e turbullimit, qoftë edhe formimi i vakuolave në kristalinë, cilësohet si katarakta.
- Mënyra e vetme e mjekimit është trajtimi kirurgjik i kataraktës.

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Profesional paper

GENERIC DRUGS - EFFECTIVE AND SAFE SUBSTITUTION

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ABSTRACT

According to EU Directive 2001/83/EC, generic medicinal product is a product which has the same qualitative and quantitative composition of active substance as the original (reference) medicinal product and is used at the same route of administration, with same dose(s) and strength to treat the same disease(s) as the original/reference medicine.

Bioequivalence studies are clinical studies for determining bioavailability of investigated medicinal product and are conducted in accordance with EU Directive 2001/20/EC and European bioequivalence guideline 2010.

With these studies rate and extent of absorption of the medicinal products and therefore the bioavailability of the active substance(s) are determined, thus providing data to demonstrate bioequivalence between a test product, i.e. the generic medicinal product, and a reference product, i.e. the originator.

Bioequivalence can be demonstrated by evaluation of primary and secondary pharmacokinetic parameters:

AUC Area under the curve (AUC): that is the area under the plasma concentration time curve, which represents the extent of exposure. (Usually the AUC0-t is evaluated, which means that a measurement from the time (0) of the drug administration until the last (t) blood sample was drawn, AUC0-inf, which means the AUC extrapolated to infinity and AUC0-72 for drugs with very long half-life, where measurement until a maximum of 72 hours after drug administration is performed.

Cmax- Maximum plasma concentration of the active substance after drug administration.

Tmax- time to reach the maximum plasma concentration after drug administration.

Two drugs are considered bioequivalent when demonstrates that their boiaviability (percentage of drug that reaches the blood unchanged) is similar, within certain limits. The data collected during the bioequivalence study undergo exacting statistical analyses, for which a 90% confidence interval is used.

For AUC and Cmax of the generic and reference drug, the 90% confidence interval has to be contained within the acceptance interval of 80-120% (0.80–1.25), known as "rule-20%/+25%". The agreed acceptance limits are valid throughout the EU and USA and accepted by EMA (European Medicines Agency) and FDA (Food and Drug Administration).

Objective: The objective of this study is evaluation and comparison of relative bioavailability, and therefore the bioequivalence of tablets RISPERIDONE 2 mg (test formulation) with RISPERDAL® (reference formulation) as well as safety evaluation by using monocentric, randomized, two way crossover study after single oral dose of 2 mg risperidone in 24 healthy male volunteers.

Material and methods: Clinical study includes twenty-four male healthy volunteers with fullfiled inclusion criteria and signed Informed consent in accordance with the Clinical Study Protocol approved by the Ethical Committee of Medical Faculty.

Clinical procedure: Each volunteer received in fasting condition under the randomization scheme single dose of

2 mg RISPERIDONE (as test or reference preparation) in two periods of treatment with 14 days wash out period between them.

Blood samples for determination of RISPERIDONE and its metabolite, 9-OH-Risperidone in plasma were withdraw at 0 (pre-drug), 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0, 12.0, 16.0, 24.0, 36.0, 48.0, 72.0 and 96.0 hours (20 blood samples) post-drug medication.

Validated HPLC-MS/MS method for RISPERIDONE and its 9-OH RISPERIDONE form plasma determination was used, and with pharmacokinetic analysis, pharmacokinetics parameters were determined: primary parameters: AUC (0- ¥), AUC (0-t), Cmax and secondary parameter: Tmax.

The correspondent 90% confidence intervals for AUC (0- ¥), AUC (0-t) and Cmax of the tested preparation as a difference to the correspondent values of the referent preparation using parametric and nonparametric methods with log-transformation of data were calculated. The differences in Tmax of test and reference preparations were analyzed by non-parametric Wilcoxon-test.

Results: Pharmacokinetic parameters

1. Primary (AUC(0-¥), AUC(0-t), Cmax) and secondary pharmacokinetic parameters (Tmax), for RISPERIDONE (mean value ± standard deviation) are:

   1a. For Test preparation: AUC(0-¥)-66.875 ± 86.516 h.mg/l; AUC(0-t)-65.235 ± 83.870 h.mg/l; Cmax-11.613 ± 5.201mg/l and for Tmax: 0.903 ± 0.249h

   1b. For reference preparation: AUC(0-¥)-69.286 ± 88.783 h.mg/l; AUC(0-t)-67.304 ± 85.634 h.mg/l; Cmax-12.119 ± 5.391 mg/l and for Tmax: 0.863 ± 0.308 h

2. Primary (AUC(0-¥), AUC(0-t), Cmax) and secondary pharmacokinetic parameters (Tmax), for 9-OH-RISPERIDONE (mean value ± standard deviation) are:

   2a. For Test preparation: AUC(0-¥)-199.394 ± 62.105 h.mg/l; AUC(0-t)-188.755 ± 61.988 h.mg/l; Cmax- 8.047 ± 3.425 mg/l and for Tmax:3.938 ± 4.941 h

   2b. For reference preparation: AUC(0-¥)-204.007 ±63.198 h.mg/l; AUC(0-t)-193.195 ±61.649 h.mg/l; Cmax-8.413 ±3.698 mg/l and for Tmax: 3.653 ±4.794 h

Statistical analysis

1 Statistical analysis using parametric and nonparametric methods with log-transformation of data, evaluated correspondent 90% confidence intervals for AUC(0-¥), AUC(0-t) and Cmax of the tested preparation as a difference to the correspondent values of the referent preparation, as follows:

   1a. Bioequivalence values for RISPERIDONE: AUC (0- ¥): 0.9141-1.0241, for AUC (0-t): 0.9121-1.0274 and for Cmax: 08886-1.0151.

   1b. Bioequivalence values for 9-OH-RISPERIDONE: AUC (0- ¥): 0.9448-1.0082, for AUC (0-t): 0.9417-1.0072 and for Cmax: 0.9206-0.9998.

2. Statistical analysis using non-parametric Wilcoxon-test, evaluated differences in Tmax of test and reference preparations as follows:

   2a. For RISPERIDONE, "p" or observed value is 0.552498 (>0.05)

   2b. For 9-OH-RISPERIDONE, "p" or observed value is 0.325877 (>0.05)

Conclusion:

From the results of the ratio analysis for AUC and Cmax for RISPERIDONE and 9-OH RISPERIDONE obtained under defined conditions, equivalence of the RISPERIDONE - Test and RISPERDAL® - Reference formulations can be concluded with respect to the rate and extent of absorption. Both medications are well tolerated with mild to moderate adverse events. Thus, in view of the clinical use, both formulations are exchangeable without restrictions.

Key words: generic drugs, brand-generic substitution, bioequivalence study

INTRODUCTION

RISPERIDONE is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin Type 2 (5HT2), dopamine Type 2 (D2), alpha 1 and alpha 2 adrenergic, and H1 histaminergic receptors. Risperidone as an antagonist at other receptors, but with lower potency. It has low to moderate affinity (Ki of 47 to 253 nM) for the serotonin 5HT1C, 5HT1D, and 5HT1A receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations >10-5 M) for cholinergic, muscarinic or ß1 and ß2 adrenergic receptors. [1]

The mechanism of action of risperidone, as with other drugs used to treat schizophrenia, is unknown. However, it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 (D2) and serotonin Type 2 (5HT2) receptor antagonism. Antagonism at receptors other than D2 and 5HT2 may explain some of the other effects of risperidone.

Risperidone is well absorbed. The absolute oral bioavailability of risperidone is 70% (CV=25%). The relative oral bioavailability of risperidone from a tablet is 94% (CV=10%) when compared to a solution. Plasma concentrations of risperidone, its major metabolite, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg BID). Following oral administration of solution or tablet, mean peak plasma concentrations of risperidone occurred at about 1 hour. Peak concentrations of 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers).

Food does not affect either the rate or extent of absorption of risperidone. Thus, it can be given with or without meals.

Risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. In plasma, risperidone is bound to albumin and alpha 1-acid glycoprotein. The plasma protein binding of risperidone is 90%, and that of its major metabolite, 9-hydroxyrisperidone is 77%. Neither risperidone nor 9-hydroxyrisperidone displaces each other from plasma binding sites. High therapeutic concentrations of sulfamethazine (100mcg/mL), warfarin (10 mcg/mL), and carbamazepine (10mcg/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and 9-hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance.

Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxy-risperidone by the enzyme, CYP 2D6. A minor metabolic pathway is through N-dealkylation. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity as risperidone. Consequently, the clinical effect of the drug (i.e., the active moiety) results from the combined concentrations of risperidone plus 9-hydroxyrisperidone.

Extensive CYP 2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP 2D6 metabolizers convert it much more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of the active moiety, after single and multiple doses, are similar in extensive and poor metabolizers. Co-administration of known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause a decrease in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone. It would also be possible for risperidone to interfere with metabolism other drugs metabolized by CYP 2D6. Relatively weak binding of risperidone to the enzyme suggests this is unlikely. Excretion of risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the feces. The apparent half-life of risperidone was 3 hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. The pharmacokinetics of the active moiety, after single and multiple doses were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours.

In patients with moderate to severe renal disease, clearance of the sum of risperidone and its active metabolite decreased by 60% compared to young healthy subjects. risperidone doses should be reduced in patients with renal disease.

While the pharmacokinetics of risperidone in subjects

with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidoen in plasma was increased by about 35% because of the diminished concentration of both albumin and doses should be reduced in patients with liver disease. In healthy elderly subjects renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients.

STUDY OBJECTIVE

The objective of this study was to evaluate and compare the relative bioavailability, and therefore the bioequivalence of tablets RISPERIDONE 2 mg (REPLEKFARM, test formulation) with RISPERDAL® (JANSSEN-CILAG, reference formulation) as well as safety evaluation by using a randomized two way crossover study in 24 healthy male volunteers after single oral dose under fasting conditions. [2][3][4]

MATERIAL AND METHODS

Twenty-four male healthy volunteers (aged 19-49 years, with Ideal Body Weight according to the Body Mass Index 18-28, non-smokers) consisting of university students and members of the community at large, recruited from the Department of Pharmacology database of suitable clinical trial volunteers, were included in the study. All volunteers were medically checked–up with health condition established on the base of history, physical examination, ECG, biochemical and hematological tests performed at the Institute of Preclinical and Clinical Pharmacology and Toxicology,

Prior to entering the study, all volunteers signed the "Informed consent".

The following treatments were administered in the fasting state:

- Treatment T (Test): RISPERIDONEâ 1x 2 mg film-coated tablets (with a 240 ml of water) after a 10 hour fast.
- Treatment R (Reference): RISPERDAL® (JANSSEN-CILAG) 1x 2 mg film-coated tablets (with a 240 ml of water) after a 10 hour fast

The study was a single center, open, randomized, two - way crossover study in 24 healthy male volunteers after oral administration of single dose of investigated drug with a wash - out period of two weeks between administration of Test and Reference drug.

The volunteers received Test formulation according the randomization scheme. After washout period of 14 days, Reference formulation was administered.

Criteria for pharmacokinetic assessments

During the study periods, 20 blood samples were drawn at the following times for each period:

At Day 1 and Day 14: 0* (*before dosing), 0.33h, 0.67h, 1.0h, 1.33h, 1.67h, 2.0h, 2.5h, 3.0h, 3.5h, 4.0h, 6.0h, 8.0h, 12.0h, 16.0, 24.0h, 36.0h, 48.0h, 72.0h and 96.0h (total of blood samples per subject in two periods = 40).

Samples were collected using direct venepuncture or an intravenous cannula in a forearm vein.

Blood samples were collected into heparinized polypropylene tubes and centrifuged within 10 minutes. Obtained plasma was divided into polypropylene tubes. The tubes were labeled with a code number that corresponds to subject, study period and sampling time, but does not reveal formulation identity. The plasma samples were caped and stored frozen at χ18 ± 4ºC until assayed. All frozen samples were delivered on sufficient dry ice to keep the samples frozen using data logger in two separate shipments to the analytical facility in TDM & Clinical Pharmacology, Alexander Univ. Hospital, Faculty of Medicine, Medical University of Sofia, Bulgaria. The second shipment was sent after receipt in good condition of the first shipment.

Determination of Risperidone and 9-OH-Risperidone in plasma was performed in internal standardization mode after liquid / liquid extraction with 1-Chlorobutane. Detection was carried out on a tandem mass spectrometer with positive electro spray ionization and SRM - MS/MS monitoring of the protonated molecular ions of drug, metabolite and internal standard, decomposing under controlled conditions to the most dominant respective fragments.

The lower limit of quantification (LLOQ) was established at 0.105 µg/l for RISPERIDONE and 0.101 mg/l for 9-OH-RISPERIDONE with an upper limit of quantification (ULOQ) of 33.6 µg/l for RISPERIDONE and 32.32 mg/l for 9-OH-RISPERIDONE. Analysis of calibration standards confirmed that the assay was linear over this range. The calibration curve and standards and the quality control standards met the acceptance criteria demonstrating acceptable performance of the method.

All analyses were stable when exposed to three freeze/thaw cycles and when left in refrigerator at 2-8° C (no light exposure) for 48 hours. The analytes were shown to be stable in plasma at room temperature (6 h in dark cabinet and 3 h exposed to light). All stock solutions were shown to be stable when stored for 43 days. There were no significant interfering peaks at the retention times of the analytes or internal standard in chromatograms from six different plasma samples.

Pharmacokinetic variables calculations

According to the obtained plasma concentrations/time data of RISPERIDONE and 9-OH- RISPERIDONE the following pharmacokinetic parameters were calculated using software KINETICA™ 2000 (Innaphase corporation, USA) (see Pharmacokinetic and statistical report):

- Primary parameters: AUC (0-t) and AUC (0-¥) (area under the curve of the plasma concentrations until the last sampling time and infinity), Cmax (maximum plasma concentration).
- Secondary parameters: Tmax (time of reaching the maximum plasma concentrations).

RESULTS

Twenty six (26) male Caucasian subjects were recruited for participation in the trial. Among the 26 subjects recruited for the trial, twenty four (24) were included and finished the study

There were no drop outs, withdrawals from the trial and treatment discontinuations.

Mean values (minimum-maximum) of anthropometric data of the 24 volunteers are: age (31.83 ± 10.19) years, height (176.42 ± 5.53) cm and weight (79.67 ± 9.92) kg.

Analysis of pharmacokinetic parameters

Figures 1a and 1b illustrate the mean plasma concentration time-course of RISPERIDONE obtained after the administration of 2 mg RISPERIDONE as RISPERIDONE formulation (treatment T = test) and as the reference formulation RISPERDAL® (treatment R = reference) in the twenty four healthy male volunteers, in linear (a) and semi-logarithmic (b) scale.

Figure 1a.

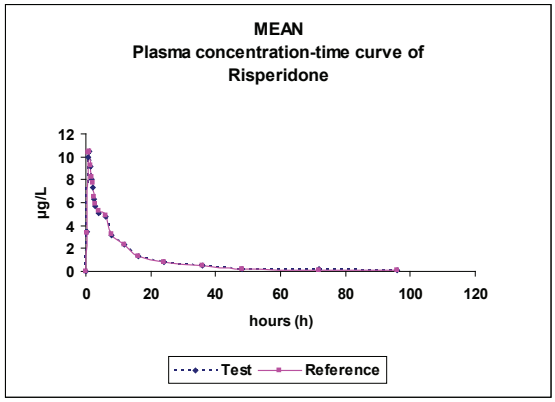


Figure 1b.

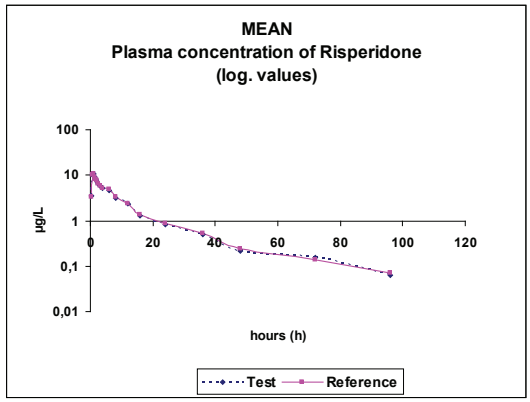


Figure 2a.

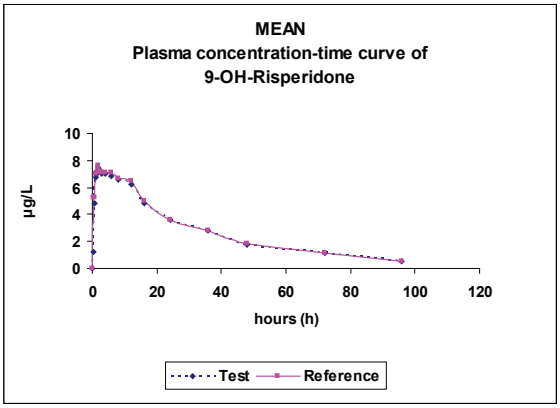
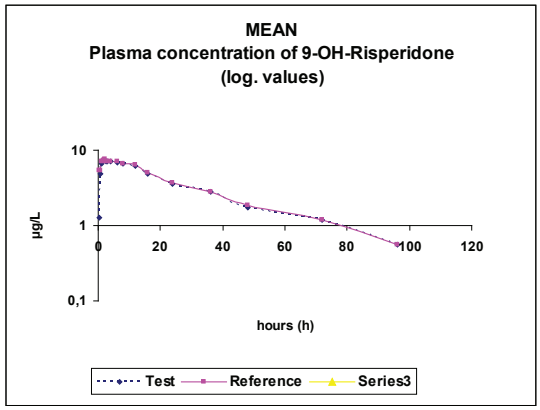


Figure 2b.



Figures 2a and 2b illustrate the mean plasma concentration time-course of 9-OH-RISPERIDONE obtained after the administration of 2 mg RISPERIDONE as RISPERIDONE formulation (treatment T = test) and as the reference formulation RISPERDAL® (treatment R = reference) in the twenty four healthy male volunteers, in linear (a) and semi-logarithmic (b) scale.

Mean pharmacokinetic parameters of RISPERIDONE are presented in the tables 1 and 2:

Table 1.

Preparation	RISPERDALÒ (REFERENCE)					
Parameter	n	Mean	Median	Min	Max	SD
AUC0-¥ (mg/l.h)	24	69.286	36.801	11.656	402.461	88.783
AUC0-t (mg/l.h	24	67.304	36.172	11.217	388.316	85.634
Cmax (mg/l)	24	12.119	10.909	5.287	28.682	5.391
tmax (h)	24	0.863	0.670	0.670	2.000	0.308
Kel (1/h)	24	0.225	0.265	0.018	0.421	0.118
T ½ (h)	24	7.211	2.616	1.645	38.151	9.948
MRT (h)	24	6.979	3.913	2.576	25.720	6.509

Table 2

Preparation	RISPERIDONE® (TEST)					
Parameter	n	Mean	Median	Min	Max	SD
AUC0-¥ (mg/l.h)	24	66.875	35.298	9.757	394.714	86.516
AUC0-t (mg/l.h	24	65.234	34.708	9.256	381.864	83.870
Cmax (mg/l)	24	11.613	10.497	5.014	22.734	5.201
tmax (h)	24	0.903	1.000	0.330	1.330	0.249
Kel (1/h)	24	0.229	0.250	0.027	0.369	0.104
T ½ (h)	24	5.421	2.782	1.878	25.280	6.614
MRT (h)	24	6.625	4.107	2.654	25.761	6.209

Mean pharmacokinetic parameters of 9-OH-RISPERIDONE are presented in the tables 3 and 4:

Table 3

Preparation	RISPERDALÒ (REFERENCE)					
Parameter	n	Mean	Median	Min	Max	SD
AUC0-¥ (mg/l.h)	24	204.007	216.471	64.774	364.500	63.198
AUC0-t (mg/l.h)	24	193.195	208.074	57.050	345.817	61.649
Cmax (mg/l)	24	8.413	8.574	1.026	16.886	3.698
tmax (h)	24	3.653	2.000	1.000	24.000	4.794
Kel (1/h)	24	0.030	0.030	0.022	0.039	0.005
T ½ (h)	24	23.043	23.421	3.085	31.500	5.929
MRT (h)	24	31.658	28.912	22.062	49.492	7.444

Table 4

Preparation	RISPERIDONE (TEST)					
Parameter	n	Mean	Median	Min	Max	SD
AUC0-¥ (mg/l.h)	24	199.394	204.072	63.175	333.608	62.105
AUC0-t (mg/l.h)	24	188.755	192.122	54.922	322.407	61.988
Cmax (mg/l)	24	8.047	8.221	0.939	13.657	3.425
tmax (h)	24	3.938	2.000	0.670	24.000	4.941
Kel (1/h)	24	0.030	0.029	0.019	0.043	0.006
T ½ (h)	24	22.943	23.667	2.893	36.236	6.296
MRT (h)	24	31.930	29.134	22.778	50.991	8.110

Statistical analysis and bioequivalence trial of tested treatment versus treatment of reference for RISPERIDONE and 9-OH-RISPERIDONE.

The results of the statistical analysis of the pharmacokinetic parameters of RISPERIDONE between the RISPERIDONE test formulation and the reference formulation RISPERDAL® are resumed in the table 5 and results of the statistical analysis of the pharmacokinetic parameters of 9-OH- RISPERIDONE between the test RISPERIDONE formulation and the reference formulation RISPERDAL® are resumed in the table 6:

Table 5

Used test for the statistical comparison	Tmax	AUC(0-∞)	AUC(0-t)	Cmax
Wilcoxon test	N.S.	-	-	-
ANOVA				
Treatment	-	N.S.	N.S.	N.S.
Subject		N.S.	N.S.	N.S.
Period		N.S.	N.S.	N.S.
Bioequivalence test	-			
90% standard confidence interval		0.9142–1.0242	0.912 –1.0274	0.888–1.0152
Two one-sided T-tests (Schuirmann)		can conclude Equivalence	can conclude Equivalence	can conclude Equivalence

Table 6

Used test for the statistical comparison	Tmax	AUC(0-∞)	AUC(0-t)	Cmax
Wilcoxon test	N.S.	-	-	-
ANOVA				
Treatment	-	N.S.	N.S.	N.S.
Subject		N.S.	N.S.	N.S.
Period		N.S.	N.S.	N.S.
Bioequivalence test	-			
90% standard confidence interval		0.9449–1.0082	0.9418–1.0072	0.921–0.9998
Two one-sided T-tests (Schuirmann)		can conclude Equivalence	can conclude equivalence	can conclude Equivalence

The results showed bioequivalence for the Tmax, Cmax, AUC (0-t) and AUC (0-∞) parameters for RISPERIDONE and 9-OH-RISPERIDONE.

Safety evaluation

The medication had acceptable tolerance in all volunteers. Adverse events were reported in 23 volunteers in both parts. Only volunteer No 10 had no adverse events. Analysis of adverse events for intensity and relationship to study drug is resumed in the tables 7 and 8:

Table 7. Intensity of adverse events

Adverse effect	Test formulation		Reference formulation	
	Mild	Moderate	Mild	Moderate
Somnolence	6	17	6	17
Vertigo	1	1	/	/

Table 8. Relationship Correlation between adverse events and study drug

Adverse effect	Test formulation		Reference formulation	
	Probable	Possible	Probable	Possible
Somnolence	2	21	2	21
Vertigo	1	1	/	/

There is no difference between two treatments in respect to intensity and correlation between adverse events and study drug.

DISCUSSION

Discussion of the methodology:

The objective was to evaluate and compare the relative bioavailability, and therefore the bioequivalence of RISPERIDONE 2 mg formulation versus a reference formulation RISPERDAL® 2 mg, following a single 2 mg administration under fasting conditions. The study was carried out according to the protocol and all the pharmacokinetic and safety assessments were performed as planned in the protocol.

From the 24 subjects included in this study, 24 were analyzed and included in the pharmacokinetic and statistical analysis for the RISPERIDONE and 9-OH-RISPERIDONE.

After the administration of 2 mg RISPERIDONE as RISPERIDONE formulation and as the reference formulation RISPERDAL®, the mean plasma concentration time-courses of RISPERIDONE and 9-OH-RISPERIDONE present the same pharmacokinetic profiles with minor differences between the two formulations.

The peak plasma concentration of RISPERIDONE is bioequivalent between the RISPERIDONE test formulation and the reference formulation (11.613 ± 5.201 mg/l and 12.119 ± 5.391 mg/l, respectively). The peak plasma concentration of RISPERIDONE is attained at about 54 minutes (0.903 hours) for the test and 52 minutes (0.863 hours) for the reference formulations. The AUC parameters showed that the AUC0-t of RISPERIDONE (65.234 ± 83870 mg.h/l and 67.304 ± 85.634 mg.h/l for the RISPERIDONE formulation and the reference formulation respectively) and the AUC0-¥ of RISPERIDONE (66.875 ± 86.516 mg.h/l and 69.286 ± 88.783 mg.h/l for the RISPERIDONE formulation and the reference formulation respectively) are bioequivalent after the administration of the RISPERIDONE test formulation and after the administration of the reference formulation RISPERDAL®.

The peak plasma concentration of 9-OH-RISPERIDONE is bioequivalent between the RISPERIDONE test formulation and the reference formulation (8.047 ± 3.425 mg/l and 8.413 ± 3.698 mg/l respectively). The peak plasma concentration of 9-OH-RISPERIDONE is attained at about 236 minutes (3.938 hours) for the test and 219 minutes (3.653 hours) for the reference formulations. The AUC parameters showed that the AUC0-t of 9-OH-RISPERIDONE were 188.755 ± 61.988 mg.h/l and 193.195 ± 61.649 mg.h/l for the RISPERIDONE test formulation and the reference formulation respectively, and the AUC0-¥ of 9-OH-RISPERIDONE were 199.394 ± 62.105 mg.h/l and 204.007 ± 63.198 mg.h/l for the RISPERIDONE test formulation and the reference formulation respectively, are bioequivalent after the administration of the RISPERIDONE test formulation and after the administration of the reference formulation RISPERDAL®.

The statistical analysis of the half life of elimination, rate of elimination and mean residence time showed no significant difference between the values of RISPERIDONE after the administration of the RISPERIDONE test formulation and after the administration of the reference formulation RISPERDAL®.

As conclusion, the RISPERIDONE test 2 mg is

bioequivalent for RISPERIDONE and 9-OH-RISPERIDONE (Cmax, Tmax, AUC0-t and AUC0-¥ parameters) to the reference formulation RISPERDAL® 2 mg, after single oral administration of 2 mg RISPERIDONE. The peak plasma concentration, the time of peak plasma concentration of RISPERIDONE and 9-OH-RISPERIDONE (Cmax and Tmax) and the AUC parameters didn't showed statistical significant differences between the two formulations and can conclude that the test formulation is bioequivalent to the reference formulation in respect to these parameters.

Discussion of safety:

All the subjects included in this study (24 subjects) were considered for safety analysis.

No death and no serious adverse event did occur during the study. Mild to moderate adverse events were registered in 23 volunteers.

The safety analysis shows that there is no difference between two treatments.

From cardiovascular safety point of view, the cardiovascular data, blood pressures, heart rates and electrocardiogram parameters, didn't show clinically significant changes from the baseline for all the subjects.

From the laboratory safety, the biological assessments showed no clinically significant abnormalities at the end of study.

CONCLUSION

The objective of the present study was to evaluate and compare the relative bioavailability, and therefore the bioequivalence of RISPERIDONE 2 mg test formulation (REPLEKFARM, Macedonia) versus a reference formulation RISPERDAL® 2 mg reference formulation (JANSSEN-CILAG Ltd, UK), following a single 2 mg administration under fasting conditions. The results presented herein showed that the criteria used to estimate the bioavailability and the bioequivalence of the REPLEKFARM formulation (RISPERIDONE) and the reference formulation were fulfilled. In fact, the 90% confidence interval of the relative mean Cmax and AUC parameters for RISPERIDONE and its metabolite 9-OH-RISPERIDONE as well as the ratio of the geometric means were strictly within the acceptance range for bioequivalence.

Therefore, it can be concluded that the RISPERIDONE 2 mg test formulation is bioequivalent for the drug RISPERIDONE and main metabolite, 9-OH-RISPERIDONE to the reference RISPERDAL® following a single 2mg administration under fasting conditions.

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Review

THE ROLE OF THE CIRCULATING PLACENTAL ANGIOGENIC FACTORS SFLT-1/PLGF RATIO IN PATIENTS WITH PREECLAMPSIA – A REVIEW

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ABSTRACT

Preeclampsia (PE), a progressive, multisystem disease of pregnant women, is the leading cause of maternal and fetal / neonatal morbidity and mortality with an incidence of 3-8% at a global level. PE is defined as de novo occurrence of hypertension and proteinuria after the 20th gestation week of pregnancy. The diagnosis of PE has long been based on the measurement of those two non-specific signs the diagnostic value of which is often insufficient given the clinical diversity of the disease as well as the different impact on the mother and the fetus. In the absence of specific preeclampsia therapy, clinical management consists of symptomatic / substitution therapy and monitoring for the detection of worsening of the maternal or fetal state and delivery as the ultimate remedy. The fact that only the delivery, or more precisely, the removal of the placenta leads to a definitive stop of PE, puts the placenta at a central place in the pathogenesis of the disease. More and more studies have suggested the connection of placental angiogenic factors with preeclampsia. These factors include circulating angiogenic proteins such as soluble fms-like tyrosine kinase-1 (sFlt-1), the anti-angiogene responsible for vasoconstriction, and the placental growth factor (PLGF) pro-angiogene responsible for placental pseudo-vasculogenesis and vasodilatation. In preeclampsia patients, the anti-angiogene sFlt-1 predominates due to increased production in the placenta, which reduces the effect of pro-angiogene PLGF whose concentrations in the serum are significantly reduced. All this leads to the clinical expression of PE with hypertension due to vasoconstriction and multisystemic involvement due to systemic endotheliosis, i.e. microvasculopathy. The determination of the serum sFlt-1 / PLGF rate is recommended as a possible useful test for diagnosis of PE and the determination of the severity of the clinical picture, and as a useful tool in its management.

Keywords: preeclampsia, angiogenic, sFlt-1, PLGF.

INTRODUCTION

Pre-eclampsia (PE) is a serious, life-threatening condition that occurs with an incidence of 3-8% of pregnant women at the global level (1,2). It is the cause of death of about 50,000 mothers in the world per year and is one of the most common causes of perinatal mortality due to prematurty, causing 15% of premature births. Preeclampsia is defined as de novo occurrence of hypertension (> 140/90 mmHg) and proteinuria (> 300 mg / 24h) after the 20th gestational week (g.w.) of pregnancy. It may appear early, before 34th gestational week, or late, after 34th g.w. and with a clinical expression in a moderate and in a severe form (3). Severe PE occurs in about 20% of patients and is defined with hypertension above 160/110mmHg, proteinuria of 5g or more in 24 hours, or the occurrence of involvement of one or more organs (liver, lungs, kidneys), onset of haematological (thrombocytopenia, haemolysis, HELLP) or neurological symptoms (eclampsia) as the final stage of PE with tonic-clonic seizures and coma due to edema and brain damage (4,5,6,7). The severe form of PE, especially when it occurs early in pregnancy, is associated with high maternal and perinatal morbidity and mortality. It is beyond doubt that the optimal management of patients with PE depends

on timely detection and reliable diagnosis, intensive monitoring in specialized perinatal centers, in order to reduce maternal, fetal and neonatal morbidity and mortality (8,9,11). Table 1 denotes the criteria that indicate the suspicion of a clinical diagnosis of preeclampsia (12).

Table 1. Criteria for a possible clinical diagnosis of preeclampsia(PE)

Clinical signs and symptoms
Deterioration of pre-existing hypertension
Proteinuria > 300 mg / 24h in pregnancy
Deterioration of the pre-existing proteinuria
Increase in body weight (> 1 kg/week in 3 trimesters)
Excessive swelling/edema (legs, hands, face)
Headache
Visual disturbance
Epigastric pain
Thrombocytopenia
Elevated liver enzymes (AST, ALT, GGT)
Intrauterine growth restriction (IUGR)
Pathological Doppler of the uterine artery

Ethiopathogenesis of PE is complex; numerous genetic, immunological and various external factors are in mutual correlation. There are more and more findings showing that PE is a two-stage disease. The first phase is asymptomatic, characterized by the release of a large amount of placental material in the maternal circulation in the first trimester of pregnancy, due to abnormal placentation and consecutive placental insufficiency. This leads to the second phase, the symptomatic one, when a pregnant woman develops distinctive symptoms described above with a different clinical severity and impact on the mother and the fetus (10,13).

PLACENTAL ANGIOGENS

Given that the definitive cure of PE is achieved by the removal of the placenta, and that in the case of a molar pregnancy when the placenta develops without a fetus and the occurrence of PE is common, a logical conclusion is drawn that the placenta plays the central role in the etiopathogenesis of the disease. Numerous recent published research results on the effects impact of some placental angiogenic markers and their possible use in diagnostics and further prognosis of preeclampsia are carried out in that direction. Namely, it has been unambiguously confirmed that the excessive production of one placental anti-angiogenic protein, sFlT-1 (soluble fms-like tyrosine kinase receptor-1), antagonist of a vascular endothelial growth factor (VEGF) and the placental growth factor (PLGF), a member of the VEGF family, plays an important role in the pathogenesis of preeclampsia. Anti-angiogenic factor sFlt-1 is a shortened form of the VEGF receptor Flt-1, freely circulating in the blood where it binds with high affinity to VEGF and PLGF and thus neutralizes their effect. The proangiogenic factor PIGF is responsible for normal placentation with trophoblastic invasion and transformation (pseudo-vasculogenesis) and survival of the endothelium, vasodilatation, and vascular permeability necessary for optimal placental function. In normal pregnancy, the level of sFlT-1 in the plasma is stable up to 20-24 weeks of gestation, from which it constantly grows until delivery. Conversely, the level of PLGF progressively increases in the first and second trimesters, and then decreases approaching the term of delivery. In pregnant women with PE, the level of sFlT-1 is significantly elevated, while the concentration of the circulating free PLGF is significantly reduced. An increased level of sFlT-1 and a decreased level of PIGF in the serum, which results in an increased ratio of sFlt-1 / PlGF, is more pronounced in the second half of pregnancy when the symptomatic phase of the PE disease occurs (14,16,17,27).

Pathophysiologically, the predominance of the antiangiogene sFlt-1 (sVEGF-r1) inhibits and reverses the pro-angiogenic effect of PlGF which results in inhibition (disturbance) of the placental neo-vasculogenesis, inhibition of vasodilatation subsequently inducing hypertension with multisystemic dysfunction of the vascular endothelium, ultimately causing the syndrome (21).

SFLT-1 AND PIGF (SFLT-1/PLGF RATIO) IN PREECLAMPSIA

The elevated serum level of sFlT-1 and the decreased level of PIGF, consecutively result in an increased sFlt-1 / PlGF ratio in preeclampsia. Recent studies confirm that determining the sFlt-1 / PlGF ratio in the patient's serum has multiple benefits in PE management. Namely, the sFlt-1 / PlGF ratio is higher in the earlier occurrence of PE than in the later occurrence and in severe form of the disease. The imbalance of angiogenic factors can be noticed even before the onset of clinical symptoms, which contributes to a better prognostic triage of patients with a high risk of PE occurrence. Secondly, sFlt-1 / PlGF can be used as a biomarker for the distinction between patients with PE and patients with some other hypertensive condition in pregnancy who do not need

hospital treatment (gestational hypertension, chronic hypertension). And thirdly, taking into account the fact that with the current definition of PE it is not possible to predict the clinical course in terms of a prediction of the undesirable outcome, sFlt-1 / PlGF could be used for a more objective determination of the clinical state and the urgency in treatment due to high risk of additional complications (22,23).

SFLT-1/PLGF IN CLINICAL PRACTICE

More controlled as well as prospective studies have emphasized the role of determining sFlt-1/PlGF in the peripheral blood of pregnant women as a diagnostic test for preeclampsia and as a predictor of the course of the disease (24,25,26). It has been unequivocally demonstrated that patients with severe PE forms have a significantly higher sFlt-1/PlGF ratio, compared with others, and that the sFlt-1 / PlGF ratio correlates with a high risk, which indicates that there is a need for immediate termination of pregnancy. In addition, other studies report on the use value of sFlt-1 / PlGF in the differential diagnosis of PE. Namely, patients with gestational or chronic hypertension do not have sFlt-1 / PlGF significantly different from healthy patients. The measuring of sFlt-1 / PlGF with the fully automated method (Elecsys system) as an additional bio-marker for PE evaluation has recently been incorporated in the manual for the treatment of hypertensive conditions in pregnant women in some European countries (15,18). The formal recommendation for sFlt-1 / PlGF ratio has not yet been included into the official protocol, but international experts on the use of angiogenic markers are close to a consensus on the clinical use of sFlt-1 / PlGF in PE patients. The serum factor sFlt-1 / PlGF does not exclude other techniques for monitoring and treatment of patients with PE, but is used in the context of these in accordance with clinical signs and symptoms (19,20).

SFLT-1/PLGF VALUES IN WOMEN WITH SIGNS AND SYMPTOMS OF PE

1. sFlt-1/PlGF < 38 excludes PE independent of the gestational age (treatment at the discretion of the physician)
2. sFlt-1/PlGF ratio 38 – 85 anticipate the risk of PE occurrence in the next 4 weeks (treatment - more frequent check-up in 1-2 weeks depending on gestation, planning delivery with the approaching of the term of delivery).
3. sFlt-1/PlGF > 85 from 20th g.w. to 34th g.w. and >110 after 34th gestational week confirmation of PE with a sensitivity of 95% and specificity of 84%. (treatment according to established clinical pathways)
4. sFlt-1/PlGF > 650 – severe PE in any gestational week (treatment in a specialized clinical unit with intensive maternal and neonatal monitoring due to the need for delivery in the next 24-48 hours)

An analysis of sFlt-1 / PlGF ratio can provide valuable information on the clinical course of PE and the rate of progression of the disease, as well as serve to differentiate the various forms of hypertension in pregnancy. At the same time, the rapid and realistic individualization of the risk based on sFlt-1 / PlGF allows to adjust the clinical management of patients with PE, thereby reducing the overall morbidity and mortality (28).

CONCLUSION

Even though the mosaic of pre-eclampsia is still not complete, the study of placental angiogens is a major step towards a better understanding of its aetiology and clinical course. For now, circulating placental angiogens sFlt-1 / PlGF have not been included in the official clinical protocols but are intended to be part of the management algorithm for patients with preeclampsia, in accordance with the postulates of good clinical practice. Of course, further research is needed, especially prospective, to clarify the association of circulating placental angiogen ratio (sFlt-1 / PlGF) and the preeclampsia syndrome.

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Review

COMPARATIVE ANALYSIS OF THE MICROBIAL QUANTIFICATION DURING USING OF PERIOCHIP CHLORHEXIDINE GLUCONATE IN CHRONIC PERIODONTAL DISEASE

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ABSTRACT

Aim. To complete a comparative microbial analyze and quantification of the microbiological findings in patients in whom was applied the conventional therapy (scaling + rinsing with Chlorxedine Gluconate) and the standard method in which was used (PerioChip Chlorxedine Gluconate).

Materials and methods. For the realization of the targeted set in this study were involved 60 patients from both sexes at the age between 40—65 years in which were diagnosed chronic periodontal disease in the second stadium with clinic and radiographic confirmation. The patients were divided in 2 groups – the first group in which was used only the conventional method (standard method) and the second group – where was applied the combined method – conventional standard with added PerioChip Chlorxedine Gluconate.

In all patients were conducted clinical examination and was taken material for microbilogical analyses. The microbilogial determination was conducted on each patient. The material was collected directly from the dental plaque or from periodontal pockets before and after the dental therapy in the both groups.

Results: The results show reduction of the perio-pathogens after in the group in which where was used the combined method (conventional method following with an application of PerioChip Chlorxedine Gluconate) in comparison with the group where was used only the conventional method. The results stated in the table show that does not exist significant difference in the quantitative and qualitative values of the perio-pathogens in the group in which was used only the conventional method in comparison with the values of the group in which was used the combined method (with PerioChip Chlorxedine Gluconate).

Conclusion:. Using of the combined method / conventional - standard method with PerioChip Chlorxedine Gluconate, posses significantly efficient antimicrobial effects against perio-pathogenic in patients with chronic periodontal.

Keywords: chronic periodontal disease, microbiological findings, conventional therapy, PerioChip Chlorxedine Gluconate.

INTRODUCTION

Dental biofilm, as unavoidable etiologic factor in its content and structure, contains bacterial conglomerate with toxins, enzymes and other associated factors which cause progressive destruction of connective tissue attachment and alveolar bone (1).

Control of dental plaque through daily oral hygiene, removal of newly supragingival and subgingingival deposits in clinical conditions are one of the ways to act preventively and to preserve the achieved treatment success (2). Certainly improper and unprofessional mechanical instrumentation can be the cause of damage the hard tissues and the occurrence of gingival recession (3.4).

Besides the mechanically removal of plaque microorganisms, in clinical practice are used local or systemic antimicrobial chemotherapy.

CIST- protocol or otherwise called, modification of conventional (basal) periodontal method as therapeutic procedure includes antimicrobial agents or modern antiseptic agents in form of a chip, in which the primacy belongs to chlorhexidine.

In dentistry, chlorhexidine is used as a disinfectant before the surgery, but later is being used as an anti-plaque agent (5). After its presentation to the American market in 1986, started the first attempts of its use as an adjuvant agent in non-surgical treatment of chronic periodontitis (6).

Soskolne (7) found that subgingivally controlled and prolonged release of antibacterial agents (gels) in the treatment and control of periodontitis is superior compared with the use of antimicrobials in the form of rinse solution or spray.

Greenstein (8) using several systems for local therapy, has verified the effectiveness of the mono therapy combined with conventional method. Application of chlorhexidine chips significantly improves clinical parameters of periodontal disease (9) due to their impact on microorganisms Porphyromonas gingivalis, Prevotella Intermedia, Fusobacterium nucleatum, Eikenella corrodens, Campylobacter rectus (10).

Considering literature data and modern scientific knowledge, and starting from the fact that the use of antiseptics in the form of solutions has an effect on microorganisms, was a challenge for us to set the goal of this research: to perform comparative microbiological analysis and quantification of microbiological finding in patients who received conventional therapy and in patients with standard therapy aided PerioChip Chlorxedine Gluconate)..

MATERIAL AND METHOD

For the realization of the targeted set in this study were involved 60 patients from both sexes at the age between 40–65 years in which were diagnosed chronic periodontal disease in the second stadium with clinic and radiographic confirmation. The patients were divided in 2 groups – the first group in which was used only the conventional method (standard method) and the second group – where was applied the combined method – conventional standard with added PerioChip Chlorxedine Gluconate.

In all patients were conducted clinical examination and was taken material for microbilogical analyses. The microbilogial determination was conducted on each patient. The material was collected directly from the dental plaque or from periodontal pockets before and after the dental therapy in the both groups.

Material was stored in sterile test tubes, and then in the shortest period of time, was taken for microbiological examination in the appropriate anaerobic conditions. The growth of microorganisms was conducted on blood agar under aerobic conditions and the other growth on Shedler neo-vanko under anaerobic conditions.

Laboratory tests were performed at the IPM department for microbiological analyzes at Military Hospital and Institute of Public Health - microbiological department.

The results are processed and displayed in percentages.

RESULTS

The data show the findings from swabs taken at admission and control after 30 days of therapy with conventional-standard method in respect of all tested bacteria. They are presented in Table 1.

The results in Table 1 showed a reduction in perio-patogenic bacteria after applying the conventional method with application of Chlorhexidine gluconate Chip.

The results in Table 2 indicate that perio-patogenic bacteria on admission and after the conventional method have not high percentage differences, unlike the findings after the use of conventional therapy with application of Chlorhexidine gluconate chip.

On table 3. Display distribution of dental plaque (examination control after 5, 10 and 30 days) to the patients treated with KM method and to the patients treated with KM-CH).

For F=1,47 and p>0,05 (p=0,23) in the shown distribution do not exist significant difference (table 3 and chart 2)

Table 4: Are displayed values of dental plaque – Post-hoc Test/Bonferroni test/ on the both groups compared with the day of receipt, 5, 10 and 30 day of the treatment.

There isn't any significant difference (p>0,05) for the dental plaque, between two groups from the first treatment.

Table 1. Representation of microorganisms in swabs taken after the standard method and after the method supported by application of (PerioChip Chlorxedine Gluconate) agent.

Bacteria	Conventional method		(standard)		Conventional method with (PerioChip Chlorxedine Gluconate) application		(standard)	
	negative after 30 days		possitive after 30 days		negative after 30 days		possitive after 30 days	
	n	%	n	%	n	%	n	%
Aggregatibacter actinomicetemcomitans	5	33,33	10	66,67	6	40,00	9	60,00
Bacteroides gingivalis	3	20,00	12	80,00	6	40,00	9	60,00
Bacteroides internedius	3	20,00	12	80,00	6	40,00	9	60,00
Peptostreptococcus micros	5	33,33	10	66,67	7	46,67	8	53,33
Fusobacterium nucleatum	4	26,67	11	73,33	6	40,00	9	60,00
Eikinela corrodens	6	40,00	9	60,00	6	40,00	9	60,00

Table 2. Representation of microorganisms on admission and swabs taken after the standard method and the method followed by application of chip agent

Bacteria	On admission		Conventional (standard) method				Conventional (standard) method with chip application			
	Positive findings		negative after 30 days		possitive after 30 days		negative after 30 days		possitive after 30 days	
	n	%	n	%	n	%	n	%	*n*	*%*
Aggregatibacter actinomicetemcomitans	11	73,33	5	3,33	10	66,67	6	60,00	*9*	*60,00*
Bacteroides gingivalis	11	73,33	3	20,00	12	80,0	6	40,00	*9*	*60,00*
Bacteroides internedius	12	80,00	3	20,00	12	80,00	6	40,00	*9*	*60,00*
Peptostreptococcus micros	11	73,33	5	33,33	10	66,67	7	46,67	*8*	*53,33*
Fusobacterium nucleatum	11	73,33	4	26,67	11	73,33	6	40,00	*9*	*60,00*
Eikinela corrodens	10	66,67	6	40,00	9	60,00	6	40,00	*9*	*60,00*

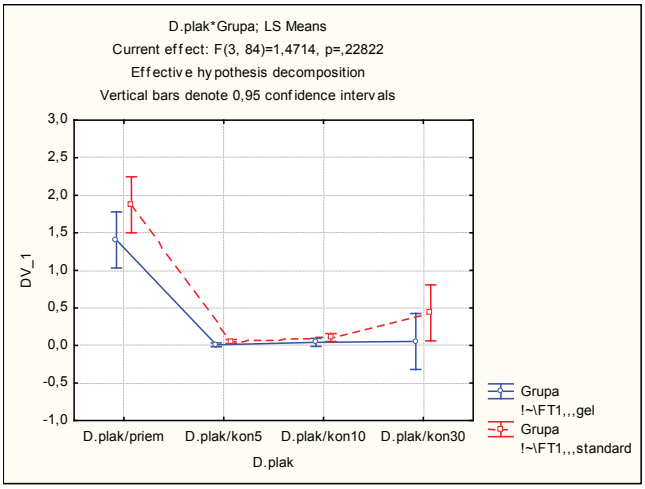
Table 3. Display of dental plaque on the examined groups in different time periods in patients treated with both methods.

D.plaque*group; LS Means; Current effect: F(3, 84)=1,47, p=,23 Effective hypothesis decomposition							
	Group	Dental plaque	DV_1 Mean	DV_1 Std.Err	DV_1 -95,00%	DV_1 +95,00%	N
1	KM-CH	Treatment	1,41	0,18	1,03	1,78	15
2	KM-CH	after 5 days	0,01	0,01	-0,02	0,03	15
3	KM-CH	after 10 days	0,04	0,03	-0,01	0,09	15
4	KM-CH	after 30 days	0,05	0,18	-0,32	0,43	15
5	KM	Treatment	1,42	0,18	1,50	2,23	15
6	KM	after 5 days	0,05	0,01	0,03	0,08	15
7	KM	after 10 days	0,11	0,03	0,05	0,16	15
8	KM	after 30 days	0,43	0,18	0,06	0,81	15

Table 4. Display of dental plaque – Post-hoc Test/Bonferroni test/ on the both groups compared with the day of receipt, 5, 10 and 30 day of the treatment.

	Group	Dental plaque	{1} 1,41	{2} 0,01	{3} 0,04	{4} 0,05	{5} 1,87	{6} 0,05	{7} 0,11	{8} 0,43
1	KM-CH	receipt		0,000	0,000	0,000		0,000	0,000	0,000
2	KM-CH	after 5 days	0,000				0,000			
3	KM-CH	after 10 days	0,000				0,000			
4	KM-CH	after 30 days	0,000				0,000			
5	KM	Receipt		0,000	0,000	0,000		0,000	0,000	0,000
6	KM	after 5 days	0,000				0,000			
7	KM	after 10 days	0,000				0,000			
8	KM	after 30 days	0,000				0,000			

Chart 1. The presence of dental plaque among respondents after application of different treatment modalities in both groups in different time periods



There isn't any significant difference (p>0,05) for the dental plaque, between two groups from the first treatment.

The patients who were treated with KM-CH after the 5th day for p<0,001 (p=0,000) they have significantly lower presence of the dental plaque (0,01) compared with the reception day (1,41). Identical results were observed on the patients treated with KM-CH after the 5th day of control, for p<0,001 (p=0,000) they have significantly lower presence of dental plaque (0,01), compared with the patients treated by KM, (0,04), as well as the control after the 10th day to the examinees who were at KM-CH for p<0,001 (p=0,000) they have much lower presence of dental plaque (0,04) compared with those who were treated with KM (0,11).

The patients treated with KM-CH after the 30th day for p<0,001 (p=0,000) they have significantly lower presence of dental plaque (0,05), compared with the group treated on KM (0,43).

DISCUSSION

In this study, microbiological analysis showed that there is a difference in the qualitative composition of bacteria in periodontal pockets in group with standard therapy and in group with standard therapy with application of chlorhexidine gluconate chip.

Combined method (conventional method and application of antiseptic chip vehicle) showed a moderate difference in the composition of perio-pathogenic bacteria in patients with chronic periodontitis , compared with patients under standard method and composition of bacteria before the combined treatment. Our findings are in agreement with other authors (1,11,12,13). Findings for perio-pathogenic bacteria in patients with chronic periodontitis after 30 days therapy with conventional-standard method, showed no major differences in the composition of bacteria in the pathological substrate of periodontal pocket for Aggregatibacter Actinomycetemcomitans (Aa), Bacteroides gingivalis (BG), Bacteroides intermedius (BI), Peptostreptococus micros (PM), Fusobacterium nucleatum (FN), and Eikenella Corrodens (EC). The obtained qualitative microbiological findings show that periodontal treatment without additional application of antimicrobial therapy does not alter the qualitative composition of bacteria significantly, not for the period during the course of the examination. In this examination was made only qualitative microbiological analysis, but not quantitative. Qualitative reduction of Aggregatibacter actinomycetemcominitans after local application of antiseptic was found in several studies (14,15), which coincides with our obtained results.

The results of microbiological analysis for perio-pathogenic bacteria in patients with chronic periodontitis

in relation admission / control after 30 days of combined therapy method (conventional method and application of antiseptic chip) showed that: Aggregatibacter actinomycetemcominitans (Aa) in relation, admission / control 30 days after treatment was negative at 93,33% of the patients examined after completion of therapy, and there was a significant difference; for Bacteroides gingivalis (BG) in relation, admission / control 30 days after treatment , the findings were negative at 86.67% and there was significant difference; identical results were found for Bacteroides intermedius (BI) in relation admission / control 30 days after treatment (86.67%) and the also existed significance of differences. Results for Peptostreptococus micros (PM) on day 30 after the therapy showed a 100% negative findings and there was significant difference; in terms of Fusobacterium nucleatum (FN) in relation admission / control 30 days after treatment noted 93,33% negative findings, and there also was a significant difference; findings of Eikenella Corrodens (EC) in relation admission / control 30 days after treatment were negative 100% and no significant difference;

Our results are consistent with the results of the study (11) in which subgingival application of (PerioChip Chlorxedine Gluconate), resulted in a significant reduction in the number of colonies versus group where periodontal therapy consisted only root planning. The test results showed that there are significant differences between the two methods applied, where the combined method showed significant difference ($p < 0.001$), compared to the standard method where were no significant difference ($p = 0.71$). These findings are in agreement with Senel et al. (12) who found satisfactory clinical effects after long stability of bio adhesive chips in the periodontal pocket and high therapeutic efficacy. Identical findings are obtained from other researchers (16,17,18).

CONCLUSION

Based on the obtained results, we can conclude that the use of combined method (conventional-standard method with addition of antiseptic chip, has a significant effect on perio-pathogenic bacteria in patients with chronic periodontitis. Because of the easy application, easy degradable power, nontoxic and we could definitely recommend it like an adjuvant of the conventional treatment on periodontal disease.

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БИЛАТЕРАЛЕН РЕТИНОБЛАСТОМ

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РЕЗИМЕ

Ретинобластом претставува најчест интраокуларен тумор во детска возраст. На него отпаѓаат 3% од сите детски малигноми. Инциденцата на ретинобластомот во светот е приближно 1 на 18 000 новородени. Овој тумор е многу малигден, метастазира по лимфен и крвен пат или низ lamina cribrosa.

Во трудот прикажуваме машко дете на 20 месечна возраст со билатерален ретинобластом. Ретинобластомот при дијагностицирањето е во напредната фаза, на десното око е класифициран во група Е, а на левото око - во група Ц. Кај детето е спроведен третман на интра-артеријална хемотерапија (ИАЦ) - 2 циклуси и туморот е во регресија.

Рана дијагноза, мултидисциплинарен пристап и третман, како и долготрајно следење, се приоритети во менаџирањето на овој интраокуларен тумор. Тоа ќе придонесе во зголемување на стапките на преживување, зачувување на очното јаболко и доколку е можно зачувување на видната функција.

Клучни зборови: ретинобластом, билатерален, интра-артеријална хемотерапија (ИАЦ)

ВОВЕД

Ретинобластом претставува најчест интраокуларен тумор во детската возраст. На него отпаѓаат 3% од сите детски малигноми. (1) Инциденцата на ретинобластомот во светот е приближно 1 на 18.000 новородени. (2-5) Овој тумор се јавува во првите години од животот и тоа во 2/3 од случаите до третата година. 5% од причините за слепило во детската возраст отпаѓаат на ретинобластомот. Ретинобластомот е многу малигден тумор, метастазира по лимфен и крвен пат или низ lamina cribrosa. Нетретираниот ретинобластом секогаш завршува летално, поради неговата интракранијална екстензија и дисеминација. Околу 1% од морталитетот од канцер кај деца помлади од 16 години отпаѓа на ретинобластомот.

Овој вид на интраокуларен тумор може да биде унилатерален или билатерален, а може да биде и хередитарен. (6) Околу 75% од случаите се унилатерални, а 35% - билатерални. (1)

Ретинобластомот потекнува од недиференцирани ембрионални клетки на ретината – ретинобласти. Овој тумор е високо целуларен и васкуларен и често подлегнува на дегенеративни промени со некроза и калцифицирани депозити.

Модалитетите на третманот на овој малигном зависат од позицијата, големината, односно во кој стадиум е дијагностициран истиот според Меѓународната класификација за ретинобластом (3), дали е унилатерален или билатерален или пак се работи за рецидив на ретинобластом. (1,2,4-6)

ПРИКАЗ НА СЛУЧАЈ

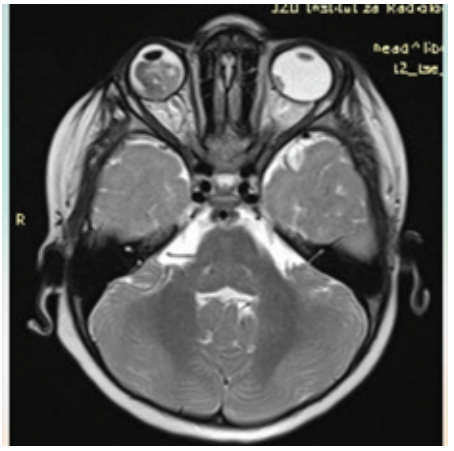
Пациентот е машко дете кое на 20 месечна возраст се јави на преглед на ЈЗУ Уклиника за очни болести во Скопје. Анамнестички родителите дадоа податок дека детето е родено со нормални очи и негираат појава на слични случаи во поблиското семејство. Родителите пред околу 3-4 месеци забележуваат беличаст рефлекс во десното око.

Покрај присутната леукокорија на десното око, направена е директна и индиректна офталмоскопија во медикаментозна мидријаза, ехографија, а за потврдување на дијагнозата на билатерален ретинобластом направена е и магнетна резонанца (МР) на глава.

На МР на глава е констатирано присуство на груби калцификати во проекција на обете очни јаболка, повеќе од десната страна. Од десната страна

евидентирана е ретинална промена со димензии од 13 x 14 мм. Идентична промена, со помали димензии е евидентирана и на задниот и долен аспект од левата страна. Нема екстраокуларна екстензија, оптичките нерви и ретробулбарниот простор билатерално, се без евиденти промени. (фиг. 1)

Фигура 1. МР на глава



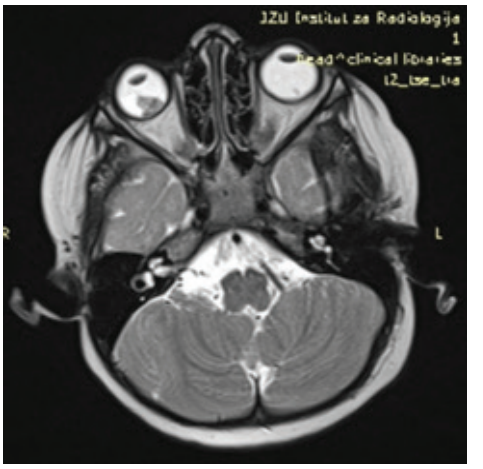
Според клиничките карактеристики ретинобластомот на десното око е класифициран во Е група, додека во левото око се присутни мултипли тумори, класифицирани во Ц група. По поставување на дијагнозата билатерален ретинобластом во напредната фаза, пациентот е испратен на понатамошно лекување во повисок референтен центар во Р. Турција за апликација на интра-артеријална хемотерапија (ИАЦ).

На родителите на детето им е кажано за каков тип на тумор се работи и дека примарна цел е да се сочува животот на детето, а во втор план се очите, односно зачувување на очите како орган и зачувување на видната функција, доколку е возможно.

До сега се направени 2 циклуси на интра-артеријална хемотерапија (ИАЦ). После секој циклус е направена контролна крвна слика и МР на глава, за да се следи регресијата на туморот. На направените контролни крвни слики не се евидентирани несакани ефекти од хемотерапијата.

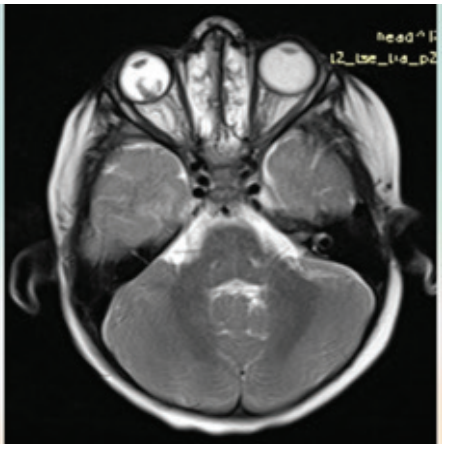
Уште после направениот прв циклус на ИАЦ на направената контролна МР на глава се констатирани резултати од ИАЦ. На истата е евидентно дека ретиналните промените во проекции на обете очни јаболка се со помали димензии. Десно туморозната промена е со димензии 10,4x7мм, а лево со промер од 3,8мм. Ретробулбарните простори се слободни, оптичките нерви без евидентни промени, а оптичката хијазма уредна. (фиг. 2)

Фигура 2. Контролна МР на глава после прв циклус на ИАЦ



После вториот циклус на интра-артеријална хемотерапија (ИАЦ) на направената контролна МР на глава се евидентира дека ретиналната промената во левото очно јаболко е скоро невоочлива во однос на претходните прегледи, односно истата е помала од 2мм. Туморозната промена во десното очно јаболко е со идентични димензии како и на претходниот преглед. Билатерално, поизразено десно е евидентирано присуство на калцификати. Ретробулбарниот простор, билатерално како и оптичката хијазма се со уреден наод. (фиг.3)

Фигура 3. Контролна МР на глава после втор циклус на ИАЦ



На последниот офталмолошки преглед во општа анестезија е констатирано дека двете очи покажаа добар одговор после извршените две сесии интра-артеријална хемотерапија (ИАЦ). Туморот на левото око е целосно во регресија. Туморот на десното око е калцифициран, но постои можност за негово рецидивирање, бидејќи ретинобластом на ова око беше класифициран во група Е. На родителите им е кажано

дека детето треба да доаѓа на редовни офталмолошки контроли и доколку дојде до рецидивирање на туморот на десното око, кое не може да се контролира со хемотерапија, ќе треба да се изврши енуклеација.

ДИСКУСИЈА

Ретинобластомот е најчеста окуларна малигност кај децата и е иницран со мутација на генот RB1. (6) Во Германија се дијагностицираат околу 40 нови случаи на ретинобластом годишно. (9)

Просечната годишна стапка на инциденца на ретинобластом во САД и Европа е 2 до 5 на милион деца. (1) За жал, сеуште повеќе од 3000 деца умираат од овој вид малигном секоја година, при што стапките на морталитет се значително повисоки во Азија и Африка. (3)

Во последните децении третманот на ретинобластомот е значително подобрен. Третманот на ретинобластомот е мултидисциплинарен и се базира првенствено на спасување на животот и зачувување на видот. (1) Зачувувањето на видот и зачувувањето на очното јаболко кај дете со ретинобластом претставува предизвик за секој офталмолог. (3) Додека енуклеацијата останува стандарден третман за напреднатите интраокуларни тумори, конзервативните модалитети кои можат да резултираат со зачувување на очното јаболко, како и зачувување на видната функција успешно се применуваат кај значителен број пациенти. (10) Постојат повеќе опции за конзервативен третман на ретинобластомот, вклучувајќи системска хеморедукција, ласерска фотокоагулација, термотерапија, криотерапија, брахитерапија и локална хемотерапија (субконјуктивална, субтенонска или интра-артериска). (3,9) Во зависност од туморските карактеристики, се одредува и протоколот за третман.

Севкупното преживување, зачувување на очното јаболко и зачувувањето на видот во голема мера зависи од стадиумот на болеста во моментот кога ќе се дијагостицира истиот. (6) Децата со билатерален ретинобластом се изложени на висок ризик за појава на рецидив и поради тоа треба внимателно да се следат.

Во текот на последните две децении, јапонските истражувачи ги објавија своите искуства со интервентната радиолошка техника на внесување на мелфалан во каротидна артерија во случаи со ретинобластом. (11,12) Мелфалан е моќен алкилирачки агенс, но неговите системски апликации биле ограничени, поради неговата токсичност на коскената срцевина.

Abramson и сор. го објавија своето првично искуство со директна хемотерапија, преку директна интра-артериска (a.ophthalmica) употреба на мелфалан кај 10 деца со ретинобластом во напредната фаза, кој кои била поставена индицикација за енуклеација. (13)

Abramson и сор. со интра-артериската апликација на мелфалан постигнале значајна регресија на туморите, како и регресија на неговото расејувањето во стаклестот тело и субретинално. (13,14) Во нивата студија не се појавиле сериозни системски несакани ефекти, како што се сепса, анемија, неутропенија или смртност. (13) Немало појава на токсичност на предниот очен сегмент, ниту испади во мотилитетот. Кај само еден пациент во студијата на Abramson и сор. е констатиран минимален системски несакан ефект (неутропенија од 3 степен).

Резултатите од извршени 248 процедури на интра-артериска (ИАЦ) суперселектива хемотерапија во студијата на Requejo и сор. (2018), укажуваат на појава на ниска стапка на компликации од интра-артеријална хемотерапија: хипотензија и брадикардија за време на постапката (5 случаи), транзиторна тромбоза на феморалната артерија (2 случаи), крварење на мрежницата (1 случај), алопеција (1 случај) и анафилактичен шок на карбоплатин (1 случај). (15)

Објавените студиите укажуваат дека не постојат сериозни екстра-окуларни компликации со примената на ИАЦ. (13,14)

ИАЦ е безбедна и ефикасна техника во третман на напреден интраокуларен ретинобластом, со ниска стапка на комликации. (13-17)

Кај пациентот кој го прикажуваме во овој труд со примената на интра-артериската хемотерапија (ИАЦ) превенирана е енуклеацијата. Оваа суперселективна хемотерапија, кај овој пациент доведе до значајна регресија на туморот на двете очи и истата не доведе до појава на окуларни и екстра-окуларни компликации.

ЗАКЛУЧОК

Рана дијагноза, мултидисциплинарен пристап и третман, како и долготрајно следење, се приоритети во менаџирањето на овој интраокуларен тумор. Повеќе опции за третман на ретинобластом се достапни

во окуларната онкологија, кои може да ја избегнат потребата од енуклеација. Целта на третманот на овој малигном е пред се да се зголемат стапките на преживување, да се зачува видната функција, а со тоа и да се овозможи поквалитетен животот на овие децата.

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BILATERAL RETINOBLASTOMA

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ABSTRACT

Retinoblastoma is the most common intraocular tumor in childhood. It occurs in 3% of all childhood malignancies. The incidence of retinoblastoma in the world is approximately 1 in 18 000 newborns. Retinoblastoma is very malignant, metastases through the lymphatic and bloodstream or through lamina cribrosa.

In the paper we present a male child of 20 months with a bilateral retinoblastoma. Retinoblastoma is diagnosed in an advanced phase, the right eye is classified in group E, and the left eye in group C. The child is treated with intra-arterial chemotherapy (IAC) - 2 cycles and the tumor is in regression.

Early diagnosis, multidisciplinary approach and treatment, as well as long-term follow-up, are priorities in managing this intraocular tumor. That will contribute for increase in survival rates, preservation of the eyeballs and, if possible, the preservation of the visible function.

Key words: retinoblastoma, bilateral, intra-arterial chemotherapy (IAC)

ILEAL DIFFUSE LARGE B CELL LYMPHOMA AS A LEAD POINT FOR AN ADULT ILEO-ILEO-COECCAL INTUSSUSCEPTION

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ABSTRACT

Intussusception is defined as an invagination of one segment of the gastrointestinal tract and its mesentery (intussusceptum) into the lumen of an adjacent distal segment of the gastrointestinal tract (intussuscipiens). Adult intussusception is a rare condition which can occur in any site of gastrointestinal tract from the stomach to the rectum. More than 80% of the cases of adult intussusception are reported to be caused by neoplasms. Primary malignant lesions (carcinoma and lymphoma) are the most common underlying malignant lesions. In adults, intussusception typically manifests as an acute or chronic obstruction and its presentation is similar to that of bowel obstruction. Diagnosis may be delayed because of its longstanding, intermittent, and non-specific symptoms.

A case of 40-year old male patient with abdominal discomfort, distension, pain, diarrhea and occasional constipation in the few weeks' period prior to admission on our department is presented. Gastrografin contrast-enhanced imaging bowel investigation was performed and it showed a narrowed segment of the terminal ileum with an enlarged segment proximally, 20-30cm in length. This finding was an indication for an abdominal CT scan and an ileo-colonic invagination was detected. The terminal ileal segment was invaginated to the coecum and ascending colon. The circulation of the invaginated segment was not compromised. As soon as the diagnosis was made, a laparotomy was performed. The intraoperative finding was an ileo-ileo-coeccal invagination with an ileal tumor lesion and local fibrinopurulent peritonitis in the site of the invagination, accompanied with uncomplicated Meckel's diverticulum. The ileo-coeccal invagination was spontaneously reduced and a resection of the terminal ileum including the Meckel's diverticulum with ileo-coeccal latero-lateral anastomosis was performed. The resected segment was subject to a pathohistological analysis. The patohistological finding was a diffuse large B cell lymphoma of the terminal ileum.

Keywords: ileo-ileo-coeccal intussusception, B cell lymphoma, Meckel's diverticulum

INTRODUCTION

Intussusception is defined as an invagination of one segment of the gastrointestinal tract and its mesentery (intussusceptum) into the lumen of an adjacent distal segment of the gastrointestinal tract (intussuscipiens).1 Adult intussusception is a rare condition which can occur in any site of gastrointestinal tract from stomach to rectum.1

Approximately 5% of all intussusceptions occur in adults, accounting for 1% of all bowel obstructions. Intussusceptions are classified according to their location (enteroenteric, ileocolic, ileocecal, or colocolic) and cause (benign, malignant, or idiopathic).2 Unlike children, where most cases are idiopathic, intussusception in adults has an identifiable etiology in 80- 90% of cases.1 More than 80% cases of adult intussusception are reported to be neoplasms.3,4 Primary malignant lesions

(carcinoma and lymphoma) are the most common underlying malignant lesions.3,5,6

The spectrum of clinical presentations depends on the site of the intussusception, the timing of the clinical presentation, and the predilection for spontaneous reduction.1 In adults, intussusception typically manifests as an acute or chronic obstruction and its presentation is similar to that of small and large bowel obstruction.1,7,8 Unlike intussusception in children, an acute abdomen is very often present in adults. The most common symptom in the acute presentation is abdominal pain (71-100%), intermittent abdominal pain and vomiting (40-60% of the cases) and bleeding per rectum (8-27% of the cases).1,5

Diagnosis can be delayed because of its longstanding, intermittent, and non-specific symptoms and most cases are diagnosed during an emergency laparotomy.9 Several procedures are used in diagnosing an intussusception.

Plain abdominal film report signs of acute intestinal obstruction (air-fluid levels) with average sensitivity about 25%.1

Barium enema signs of intussusception include a spiral, ''coil spring'' or ''stacked coin'' appearance with narrowed central canal. These signs result from the retrograde filling of the contrast between the walls of the invaginated bowel loop. The narrowed central canal is the edematous, obstructing intussusceptum. Barium enema remains limited to the ileocolic or colonic lesions.1

Ultrasonography is characterized with a "target and doughnut" sign (an even thickened hypoechoic outer and a central hyperechoic core on transverse view), a "crescent-in-doughnut" sign (an even outer hypoechoic rim with a central hyperechoic crescent) or a "multiple concentric rings" sign (a mass with multiple alternating hypoechoic and hyperechoic concentric rings).1

Color Doppler may be helpful in determining the degree of vascular compromise of the involved segments. 1,10

Abdominal CT is the most useful diagnostic tool, not only for detecting an intussusception, but it also helps in identifying the underlying cause. While the appearance of intussusception is characteristical on a CT scan, its etiology usually cannot be established. 5,8,12

After the bowel intussusception is diagnosed, it should be treated adequately. There is no universal agreement upon the correct treatment of adult intussusception, although surgical intervention is considered to be necessary.3,11 The type of intervention depends on the patient's medical history and intraoperative findings.5,11 All patients with enteric lesions who have not had a previous laparotomy should undergo a resection without reduction, because of the high incidence of associated malignancy and should be treated by oncological principles.1,13 Primary resection without reduction should also be performed due to theoretical risks of perforation and seeding of the bowel's microorganisms or tumor to the peritoneal cavity and/or venous embolization.10

CASE REPORT

Our patient was a 40-year old male complaining of abdominal discomfort, distension, pain, diarrhea and occasional constipation during the few weeks' period prior to admission to our department. The onset of medical condition started with epigastric pain. A gastroscopy was performed, which showed an inflamed gastric mucosa, and the H. pylori test was positive. Oral diet and treatment for H. pylori infection was recommended. The suggested therapy did not resolve the condition, on the contrary, a week before the admission, the patient had symptoms of bowel obstruction presented with vomiting, absence of gases and stool. The condition was partly resolved with an intravenous rehydration and bowel peristaltic stimulation. Two days prior the admission, a gastrografin contrast-enhanced imaging bowel investigation was performed, which showed a narrowed segment of the terminal ileum with an enlarged segment proximally, 20-30cm in length. Despite the narrowing, the contrast passed through the segment into the colon. (Fig.1)

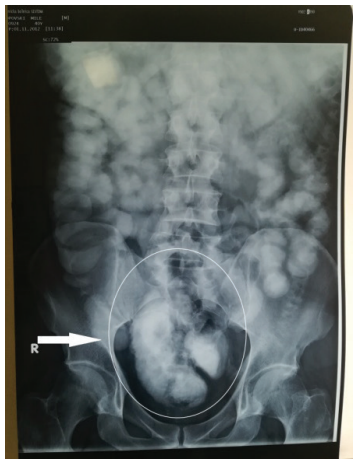

Fig.1: Gastrografin contrast-enhanced imaging bowel investigation

This finding was an indication for an abdominal CT scan. A day before the admission, a contrast-enhanced CT scan was performed and an ileo-colic invagination was detected. The terminal ileal segment was invaginated to the coeccum and ascending colon. The vascularization of the invaginated segment was not compromised. (Fig. 2-4)

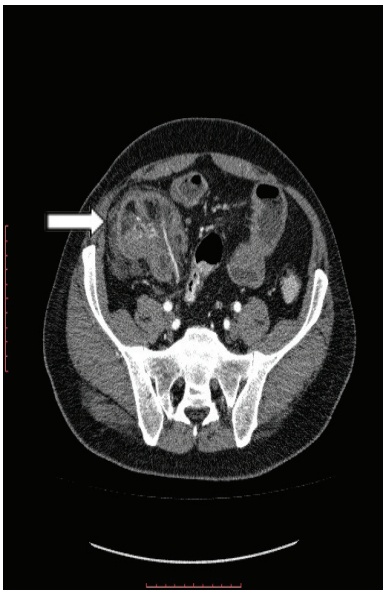

Fig.2: Transverse plane

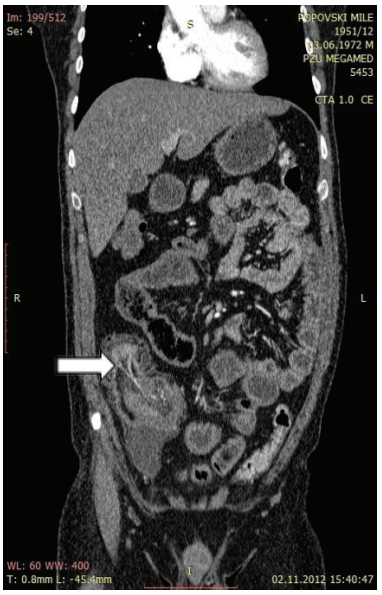

Fig.3: Coronal plane

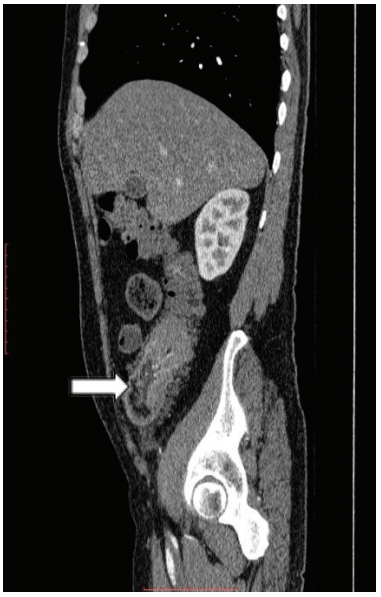

Fig.4: Sagittal plane

A laparotomy was performed and the intraoperative finding was an ileo-ileo-coeccal invagination with ileal tumor lesion and a local fibrinopurulent peritonitis of the site of the invagination. (Fig. 5, 6) A secondary finding was an uncomplicated Meckel's diverticulum. (Fig. 7)

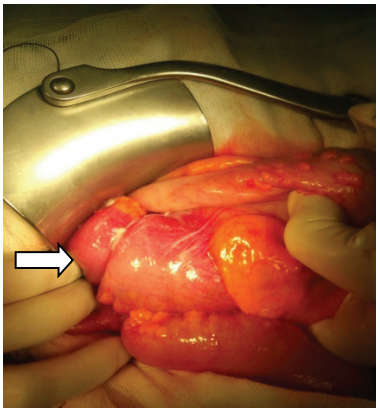

Fig.5: Ileo-ileo-coeccal invagination

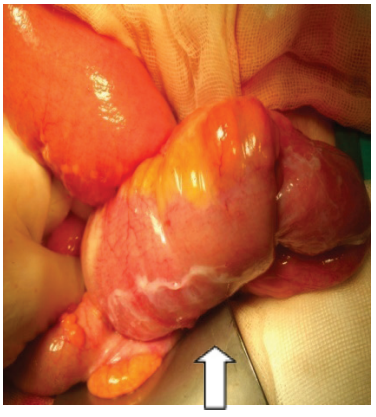

Fig.6: Local fibrinopurulent peritonitis

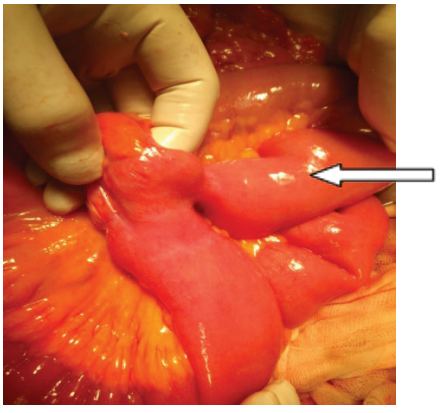

Fig.7: Meckel's diverticulum

The ileo-colic invagination reduced spontaneously and resection of the terminal ileum including the Meckel's diverticulum with ileo-coeccal latero-lateral anastomosis was performed. The resected segment was a subject to pathohistological analysis. (Fig. 8, 9) The patohistological finding was a diffuse large B cell lymphoma of the terminal ileum.

After the surgery, the patient was suggested to consult a hematologist for appropriate chemotherapy. Prior to the chemotherapy treatment, a whole-body PET scan was performed. There were no signs for metastases. (Fig. 10) The 5 years follow up period was uneventful

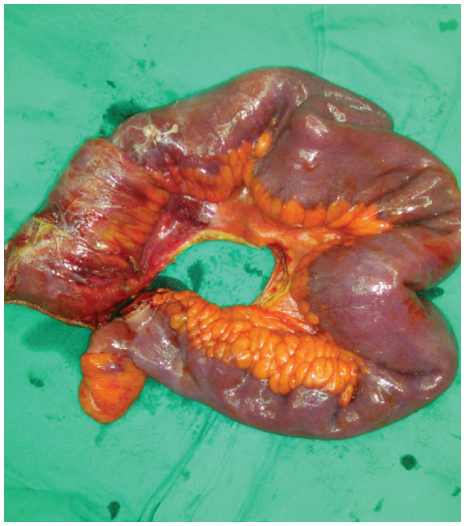

Fig.8: Resected bowel segment

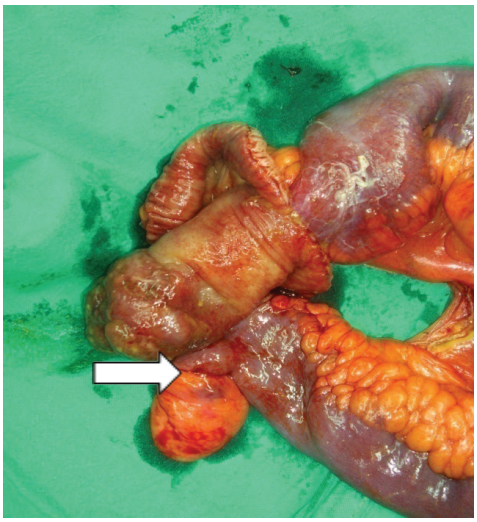

Fig.9: Ileal tumor lesiona

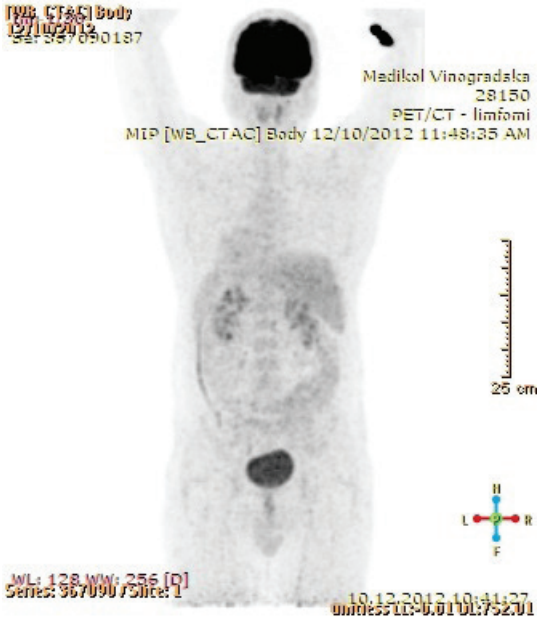

Fig. 10: PET scan

DISCUSSION

Adult intussusception is a rare condition which can occur in any site of gastrointestinal tract from stomach to rectum.1 Intussusception commonly occurs at the junctions between freely-moving segments and retroperitoneally or adhesionally fixed segments.10 More than 80% of the cases of adult intussusception are reported to be neoplasms. 3 Malignant causes of small bowel intussusception include primary leiomyosarcomas, malignant gastrointestinal stromal tumors, carcinoid tumors, neuroendocrine tumors and lymphomas.1 Non-Hodgkin lymphomas of the ileum can be the leading point for ileo-colic intussusceptions, such as in our presented case.7,14,15 Carcinoma of the appendix is a rare etiological factor for small bowel intussisception.

Diagnosis can be delayed because of its longstanding, intermittent, and non-specific symptoms and in most cases are diagnosed during an emergency laparotomy. Several procedures are used to set the diagnosis of intussusception. Abdominal CT is the most useful diagnostic tool, not only for detecting an intussusception, but it also helps in identifying the underlying cause.5,8

Intussusceptions seen on CT that had a neoplastic lead point are significantly longer and have a significantly larger diameter than non-neoplastic ones.5,8,12 Proximal dilatation of the small bowel is significantly more common in intussusceptions with a neoplastic lead point, which correlates with the finding during our gastrografin contrast investigation.

After setting the diagnosis of adult intussusceptions, primary resection without reduction should be the method of choice for treatment of these patients. Bowel resection with oncological principles should be followed in every case where a malignancy is suspected. The theoretical risks of preliminary manipulation and reduction of an intussuscepted bowel include: (1) intraluminal seeding and venous tumor dissemination, (2) perforation and seeding of microorganisms and tumor cells to the peritoneal cavity and (3) increased risk of anastomotic complications of the manipulated friable and edematous bowel tissue.7,16 Reduction of the intussuscepted bowel is considered safe for benign lesions in order to limit the extent of resection or to avoid the short bowel syndrome

in certain circumstances.7,17,18

In the presented case, the intraoperative finding was an ileo-ileo-coeccal invagination with ileal tumor lesion and local fibrinopurulent peritonitis in the site of the invagination. According to the basic principles, ileo-colonic invagination was spontaneously reduced and resection of the terminal ileum including the uncomplicated Meckel's diverticulum with ileo-coeccal latero-lateral anastomosis was performed. The patohistological finding was diffuse large B cell lymphoma of the terminal ileum, which belongs to the group of Non-Hodgkin's lymphomas of the ileum. They are reported as a most common malignant leading points for ileo-colic intussusceptions.3,5

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ILEAL DIFFUSE LARGE B CELL LYMPHOMA AS A LEAD POINT FOR AN ADULT ILEO-ILEO-COECCAL INTUSSUSCEPTION

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АПСТРАКТ

Интусусцепција се дефинира како инвагинирање на еден сегмент од гастоинтестиналниот тракт и неговиот мезентериум (интусусцептум) во луменот на дистален сегмент од гастроинтестиналниот тракт (интусусципиенс). Интусусцепцијата кај возрасни е ретка состојба која може да се случи на било кое ниво од гастроинтестианлниот тракт, од желудник до ректум. Повеќе од 80% од случаите на интусусцепција кај возрасни се смета дека се должат на неоплазми. Примарните неоплазми (карциноми и лимфоми) се најчести. Интусусцепцијата кај возрасни се манифестира со акутна или хронична опструкција, клиничка слика која одговара на цревна опструкција. Дијагнозата може да биде одложена поради долготрајните, повремени и неспецифични симптоми.

Презентиран е случај на 40 годишен маж со симптоми на абдоминален дискомфорт, дистензија, болка, дијареа и повремена опстипација во периодот од неколку недели пред хоспитализацијата. Реализирана е пасажа на цревата со гастрографин, со наод за стеснет сегмент од терминален илеум и проксимално дилатиран сегмент во должина од околу 20-30 cm. Овој наод беше причина за реализирање на компјутерска томографија на абдомен, на која се верифицираше илео-колична инвагинација. Терминалниот илеум беше инвагиниран во цекумот и асцендентниот колон. Васкуларизацијата на инвагинираниот сегмент не беше компромитирана. По поставување на дијагнозата, се реализираше лапаротомија. Интраоперативниот наод беше илео-илео-цекална инвагинација со туморска формација на илеум, локален фибринопурулентен перитонит на место на инвагинацијата, придружена со некомплициран Мекелов дивертикулум. Илео-цекалната инвагинација се редуцираше спонтано, се направи ресекција на терминалниот илеум вклучувајќи го и Мекеловиот дивертикулум и креирање на илео-цеко латеро-латерална анастомоза. Ресецираниот сегмент беше пратен на патохистолошко иследување и добиен е наод за diffuse large B cell lymphoma на терминален илеум.

клучни зборови: илео-илео-цекална интусусцепција, B cell lymphoma, Мекелов дивертикулум

ANGINA LUDWIG OR ANGINA OF THE ORAL CAVITY FLOOR AS A COMPLICATION OF THE SUBMANDIBULAR GLAND SIALOLITHIASIS

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ABSTRACT

Ludwig's angina is a severe infection on the floor of the oral cavity of the subcutaneous and connective tissue which most commonly occurs as a secondary tooth infection or other infection of the oral cavity and if not treated properly it can cause obstruction of the upper respiratory organs.

The condition that starts as limited quickly causes alarming local symptoms, which make it one of the most terrifying diseases. If the treatment is not fast, mortality is high in the early stage, approximately 50 percent given by different authors.

Case Report: A 49 year old male patient who presents with a painful, warm and hard swelling in the submandibular and submental region with pronounced dysphagia and difficulties in speech. Before, in several occasions he experienced a sudden swelling of the right submandibular gland which retreated quickly, but the patient did not do any investigations. Sublingually in the region of the ostia is present an almond shaped swelling from which thick pus is drained. The patient is admitted immediately to the otorhinolaryngology department, is being observed and treated with infusion therapy with three ampullar antibiotics in infusion solutions, intravenous corticosteroid therapy by scheme in high doses, symptomatic therapy, local treatment. Laboratory investigations, echosonography of salivary glands and X-ray of the floor of the oral cavity are made. After a short period of 24-48 hours an improvement occurred and in the first 12 hours the patient experienced spontaneous elimination of a large ovate concretion of 25 mm x 15 mm through a natural opening sublingually and in the next 24 hours an elimination of two smaller stones as well as sand.

A consultation with the maxillofacial clinic for the treatment of the submandibular gland was made. An extirpation of the right submandibular gland was performed one month after the occurrence of Angina Ludwig.

Keywords: Ludwig's angina, sialolithiasis, echosonography, upper respiratory obstruction.

INTRODUCTION

Ludwig's angina, also known as Angina Ludovici, is named after a german physician, Wilhelm Frederick von Ludwig, who first described this condition in 1836.

Ludwig's angina is a type of severe, diffuse cellulitis, involving the bilateral tissue spaces on the floor of the mouth, namely the submandibular, submental and sublingual spaces. Cellulitis is a spreading infection of connective tissue through tissue spaces, normally with virulent and invasive organisms being the causative agents. This condition has an acute onset and develops rapidly, over a short course of hours and majority of cases follow an inadequately managed or neglected odontogenic infection. Other causes include parapharyngeal abscesses, mandibular fracture, oral lacerations or piercing, or submandibular sialodentitis. The external signs of Ludwig's angina may include bilateral lower facial oedema around the mandible and upper neck. Intraoral signs

may include elevation of the floor of the mouth, due to sublingual space involvement and posterior displacement of the tongue, creating the potential for a compromised airway. Additional symptoms may include painful neck swelling, tooth pain, dysphagia, shortness of breath, fever and general malaise. Stridor, trismus and cyanosis may also be seen when an impending airway crisis is nearing.

The most prevalent cause of Ludwig's angina is odontogenic, accounting for approximately 75% to 90% of cases. However oral ulcerations, infections of oral malignancy, mandible fracture, bilateral sialolithiasis-related submandibular gland infection and penetrating injuries of the floor of the mouth have also been reported as potential causes of Ludwig's angina.

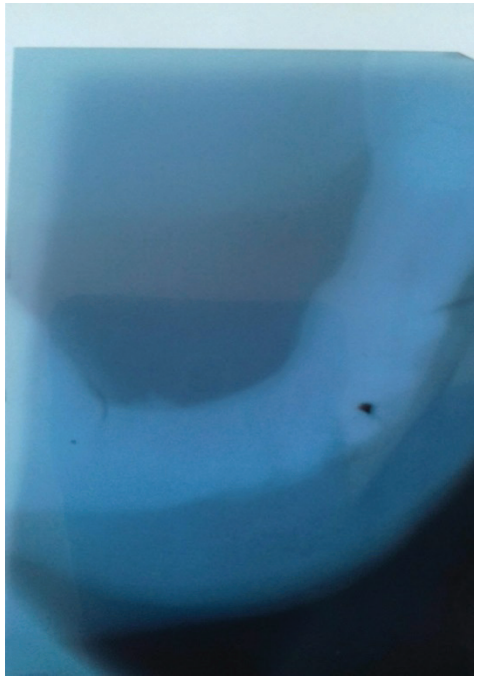
Sialolithiasis is more frequent in male patients. Incidence peaks between the age of 30 and 60 years and it is uncommon in children, only 3% of all sialolithiasis cases occur in the pediatric population. Sialolithiasis affects the submandibular gland in 80-90% of cases, mainly unilaterally but without a preferred side; this finding is partly explained by recent post-mortem morphometric studies which found a symmetry between the right and left gland. In our experience, the average size of submandibular stones is about 7.3 mm, although giant sialoliths measuring up to 7 cm have occasionally been described . The majority of calculi are located in the distal third of the duct or at the hilum of the gland; pure intraparenchymal stones are infrequent .

Salivary stones, also known as sialoliths, are calcified concrements in the salivary glands. Sialoliths are more frequently located in the submandibular gland (84%), than in the parotid gland (13%). The majority of the submandibular stones are located in Wharton's duct (90%), whereas parotid stones are more often located in the gland itself.

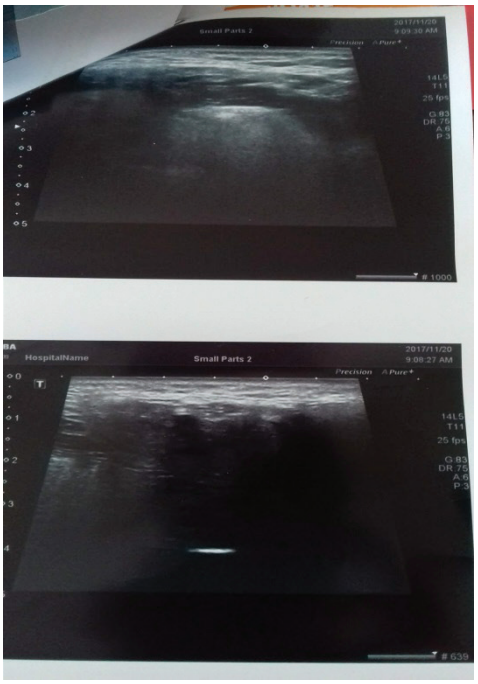
Ultrasonography currently represents an excellent first-level diagnostic technique insofar in experienced hands, it reveals ductal and highly mineralised stones with a diameter of at least 1.5 mm with an accuracy of 99%. X-ray, sialography, CT scan et MRI has more recently been introduced as a new diagnostic tool for visualising the duct system of salivary gland.

CASE REPORT

A 49 year old male patient who presents with a painful, warm and hard swelling in the submandibular and submental region with pronounced dysphagia and difficulties in speech. Before, in several occasions he experienced a sudden swelling of the right submandibular gland which retreated quickly, but the patient did not do any investigations. Sublingually in the region of the ostia is present an almond shaped swelling from which thick pus is drained. The patient is admitted immediately to the otorhinolaryngology department, is being observed and treated with infusion therapy with three ampullar antibiotics in infusion solutions, intravenous corticosteroid therapy by scheme in high doses, symptomatic therapy, local treatment. Laboratory investigations, echosonography of salivary glands and X-ray of the floor of the oral cavity are made. Laboratory follow-up showed high leukocytes, high sedimentation and high levels of CRP. Echosonography of the salivary glands and X-ray of the salivatory duct system, CT scan and MRI show any process in the spaces on the floor of the mouth, namely the submandibular, submental and sublingual space. After a short period of 24-48 hours an improvement occurred and in the first 12 hours the patient experienced spontaneous elimination of a large ovate concretion of 25 mm x 15 mm through a natural opening sublingually and in the next 24 hours an elimination of two smaller stones as well as sand. A consultation with the maxillofacial clinic for the treatment of the submandibular gland was made. An extirpation of the right submandibular gland was performed one month after the occurrence of Angina Ludwig.



X-ray (Radiography) of the floor of the oral cavity



Echosonography of the submandibular gland

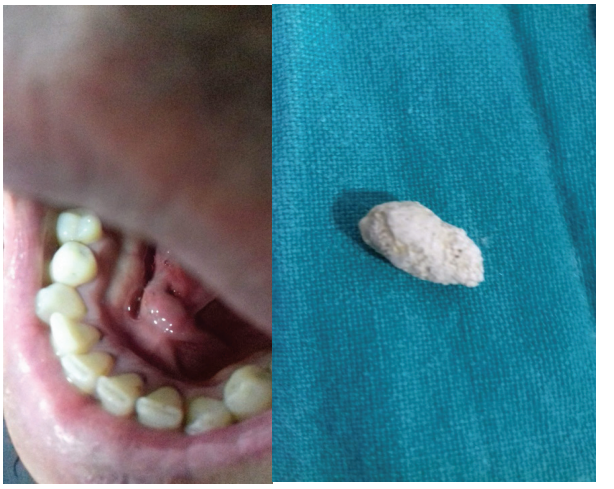
METHODS & MATERIALS

Initially we use clinical investigation, laboratory investigation, radiological investigation, echosonographic investigation. Additional investigations show us what cause led to the occurrence of Angina Ludwig. When sialolithiasis of the submandibular gland is the cause of Angina Ludwig the following investigations are made.

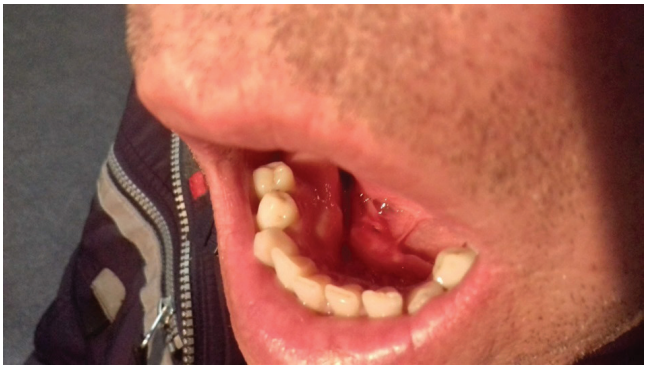
Ultrasonography is first-level diagnostic technique. The traditional diagnostic approach to duct stenosis includes sialography, which is still considered the diagnostic gold standard, and also plays a therapeutic role by stretching the duct walls as a result of contrast medium injection. Sialo-CT has also been proposed for the diagnosis of abnormalities in the duct system. However, these imaging modalities visualise the salivary duct system indirectly, expose patients to radiation and may be complicated by infections or iatrogenic lesions of the duct wall.

Magnetic resonance (MR) sialography has more recently been introduced as a new diagnostic tool for visualising the duct system up to the tertiary branches and the parenchymal tissue. It has the advantages that it does not require contrast medium, there is no radiation and no need for ductal cannulation, it can also be performed during acute gland infection and finally, the use of citric acid to stimulate salivary secretion (dynamic sialo-MR) allows a functional evaluation of the affected gland.

Salivary stone / Sialolith of the submandibular gland



Before treatment



After treatment

DISCUSSION

Surgical incision and drainage are the main methods in managing severe and complicated deep neck infections and treatment has multidisciplinary approach. Different imaging studies can be used in the evaluation. Ultrasound is useful as a quick evaluator, but clinical diagnosis is very important. For each patient, the treatment plan should be done with consideration of each of the individual patient's differing factors. They are namely the stage of the disease and co-morbid conditions at the time of presentation, physician experience, available resources and personnel are critical factors in formulation of a treatment plan. There are four principles that guide the treatment of Ludwig's Angina: sufficient airway management, early and aggressive antibiotic therapy, incision and drainage in case of a fail in medical management or forming localized abscesses, adequate nutrition and hydration support. Each will be explained in detail below.

Sufficient airway management

Airway management has been found to be the most

important factor in treating patients with Ludwig's Angina, i.e. it is the "primary therapeutic concern". Airway compromise is known to be the leading cause of death in Ludwig's Angina.

Early and aggressive antibiotic therapy

Antibiotic therapy is empirical, it is given until culture and sensitivity results are obtained. The empirical therapy should be effective against both aerobic and anaerobic bacteria species commonly involved in Ludwig's Angina. Only when culture and sensitivity results return should the therapy be tailored to the specific requirements of the patient. Empirical coverage should consist of either a penicillin with a B-lactamase inhibitor such as amoxicillin/ticarcillin with clavulanic acid or a Beta-lactamaseresistant antibiotic as cefoxitin, cefuroxime, imipenem or meropenem. This should be given in combination with a drug effective against anaerobes such as clindamycin or metronidazole. Parenteral antibiotics are suggested until the patient is no longer febrile for at least 48 hours. Oral therapy can then commence to last for 2 weeks, with amoxicillin with clavulanic acid, clindamycin, ciprofloxacin, trimethoprim-sulfamethoxazole, or metronidazole.

Incision and drainage in case of a fail in medical management or forming localized abscesses.

Respond to medical management within 48 hours.

Nutritional support

Adequate nutrition and hydration support is essential in deciding the outcomes in any patient following surgery.

CONCLUSION

Salivary gland diseases are relatively common. The most frequent non-neoplastic salivary disorder is obstructive sialadenitis, which may be due to calculi, fibromucinous plugs, duct stenosis, foreign bodies, anatomic variations, or malformations of the duct system leading to a mechanical obstruction associated with stasis.

Patients with obstructive sialadenitis present with a history of recurrent painful periprandial swelling of the involved gland, best known as the "meal-time syndrome", which is often complicated by recurrent bacterial infections, with fever and a purulent discharge at the papilla. Finally, early detection is imperative to preventing the complications and having good airway management to save life.

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АНГИНА ЛУДВИГ ИЛИ АНГИНА НА ПОДОТ НА УСНАТА ШУПЛИНА КАКО КОМПЛИКАЦИЈА НА СИЈАЛОЛИТИЈАЗА НА СУБМАНДИБУЛАРНАТА ЖЛЕЗДА

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АПСТРАКТ

Ангина Лудвиг е тешка инфекција на подот на усната шуплина и тоа на подкожно и сврзно ткиво која најчесто се јавува како секундарна инфекција на забите или друга инфекција на усната шуплина и која ако не почне да се третира соодветно може да предизвика опструкција на горно респираторни органи.

Состојбата која почнува ограничено, брзо предизвикува алармантни локални симптоми, што ја прави една од најстрашните болести. Ако третманот не е брз, во раната фаза морталитетот е висок, по различни автори е даден приближно околу 50 проценти.

Приказ на случај: Пациент на 49-годишна возраст кај кој е присутен болен, топол и тврд оток во субмандибуларна и субментална регија со изразена дисфагија и отежнат говор. Предходно во неколку наврати се случувало одеднаш да му отече десната субмандибуларна жлезда која бргу се повлекувала, но пациентот не направил никакви иследувања. Сублингвално во предел на остиумите присутен оток како бадем од кој се цеди густ гној. Пациентот веднаш примен на орл одделение опсервиран и поставен на инфузиона терапија со три ампуларни антибиотици во инфузиони раствори, интравенозна кортикостероидна терапија по шема во високи дози, симптоматска терапија, локален третман. Реализирани лабораториски иследувања, ехосонографско иследување на плунковните жлезди, ртг графија на под на усна шуплина. По краток временски период од 24-48 часа настапи подобрување при што пациентот во првите 12 часа следи спонтана елиминација преку природен отвор сублингвално на голем овален конкремент од 25 мм x 15 мм за да во наредите 24 часа исфрли уште 2 помали каменчиња, како и песок. Направена консултација со максилофацијална клиника за третман на субмандибуларна жлезда. Реализирана екстирпација на десна субмандибуларна жлезда по еден месец од настанување на Ангина Лудвиг.

Клучни зборови: ангина Лудвиг, сијалолитијаза, ехосонографија, горно респираторна опструкција.

TRE ANËTARË TË SHMSHM MARIN TITULLIN DOKTOR SHKENCE NË FUSHËN E SHKENCAVE MJEKËSORE

DR MERAL REXHEPI

Dr Meral Rexhepi, mjek specialist gjinekolog-obsteter, e punesuar ne Spitalin Klinik ne Tetove, me daten 05.02.2018 ne Fakultetin e Mjekesise, prane Universitetit "Shen Kirili dhe Metodi" ne Shkup, me sukses e e mbrojti tezen e doktoratures me titull "Heparina me peshe molekulare te vogel, me ose pa aspirin ne prevenim te komplikacioneve maternale dhe perinatale te shtatzanite e rrezikuara", perpara komisionit arsimor-shkencor ne perberje: Prof.Dr Borce Georgievski, Prof. Dr Slavejko Sapunov, Prof. Dr Milenka Blagoevska, Prof. Dr Vasil Iliev dhe Prof.Dr Nevzat Elezi.

Autori ne tezen e saj te doktoratures ben nje analize te ndikimit te tromboprofilakses antenatale ne prevenim te komplikacioneve maternale dhe perinatale te shtatzanite e rrezikuara. Motiv per kete studim ka qene ajo se shume studime epidemiologjike ne dy deceniet e fundit kane vertetuar lidhjen ne mes gjendjes hipertrombotike te nena dhe graviditetit me perfundim negativ. Komplikimet me te shpeshta per shkak te gjendjes hipertrombotike, e cila rezulton me alteracione vazo-okluzive ne perfuzionin placentar gjate shtatzanise, jane: aborted spontane perseritese, lindjet e parakohshme, SGA frytet, preeklamsioni, abrupcioni i placentes dhe vdekja intrauterine e frytit. Kjo teme eshte problematike qe nuk eshte e studjuar mjaftueshem ne praksen tone si dhe nuk kemi qendrim plotesisht te sqaruar per tromboprofilakse antenatale te shtatzanite e rrezikuara si pasoje e semundjes ishemike placentare.

Qellimi i studimit ka qene te analizohet se sa do te rritet numri i te posalindurve te gjalle te shtatzanite e rrezikuara dhe sa do te zvogelohet numri i shtatzanive me komplikime, si pasoje e semundjes ishemike placentare, me perdorim te terapise antenatale antitrombotike ne krahasim me shtatzanite pa tromboprofilakse antenatale. Rezultatet e ketij studimi kane treguar rritje te perqindjes te te posalindurve te gjalle te shtatzanite e rrezikuara duke e redukuar numrin e aborteve spontane. Nuk eshte verejtur redukim i rendesishem i komplikimeve te vonshme ne mes shtatzanive te trajtuara dhe jo te trajtuara me tromboprofilkse antenatale.

Per shkak se perqindja e morbiditetit dhe mortalitetit perinatal ne vendin tone eshte shume i madh ne krahasim me mesataren europiane, studimi eshte plotesisht i arsyeshem dhe besojme se do te jete i dobishem ne perdorimin e terapise antitrombotike per perfundim pozitiv te shtatzanite e rrezikuara. Punimi eshte studimi i pare klinik ne shtetin tone nga kjo fushe dhe besojme se do te kontribuoje ne prevenim te morbiditetit dhe mortalitetit perinatal dhe do te jete suport i mire dhe nxitje per studim te metutjeshem ne kete fushe.

DR BEKIM TATESHI

Dr.Bekim Tateshi, i lindur më 13 shtator 1969 në Strugë. Shkollën fillore e vijoi në vendlindje në SHF "Vëllezërit Milladinovci", ndërsa të mesmen në QAMO "Hajdar Dushi" në Gjakovë, drejtimi teknik I biologjisë. Fakultetin e mjekësisë e kreu ne Universitetin e Zagrebit në Kroaci. Pas mbarimit të stazhit dhe provimit shtetëror u angazhua në Entin për Nefrologji në Strugë, në repartin për hemodializë kronike. Në vitin 2002 filloi specializimin në fushën e oftalmologjisë në Klinikën Universitare të Syve në Shkup dhe me sukses e mbaroi në vitin 2007. Prej vitit 2003 është i angazhuar në Klinikën Universitare të Syve në Shkup – në repartin e oftalmologjisë pediatrike dhe strabizmit. Ne vitin 2008 është emerëruar me titullin asistent në katedrën e oftalmologjisë pranë fakultetit të mjekësisë në Shkup. Nga Ministria e Shëndetësisë është i caktuar si koordinator nacional për Retinopatinë Prematurike dhe qysh nga viti 2009 me sukses udhëheq skriningun e Retinopatisë Prematurike si dhe aplikon operacionet me lazerfotokoagulacion dhe aplikimin e anti-VEGF te foshnjet e rrezikuara. Poashtu është ekspert në fushën e kirurgjisë të strabizmit, fakokirurgjise dhe ehografise te syrit. Në vitin 2016 me sukses mbrojti disertacionin e doktoraturës me temë: "Retinopatia e prematurit – skriningu dhe terapia bashkëkohore" dhe fitoi titullin Doktor i Shkencave të Mjekësisë. Është pjesëmarrës në shumë kongrese, seminare, puntori me karakter nacional dhe ndërkombëtar.

DR ILIR HASANI

Dr. Ilir Hasani ka lindur më 23 maj 1977 në Kumanovë, ku edhe ka përfunduar arsimin fillor dhe të mesëm. Ai u regjistrua në Fakultetin e Mjekësisë në Univerzitetin "Shën Kirili dhe Metodi" në Shkup në vitin akademik shkollor 1994/95 dhe u diplomua në vitin 2001 me mesatare 8.8.

Pas përfundimit të praktikës obligative mjekësore , ai u punësua në Institucionin Mjekësor Privat "Zana" si mjek i përgjithshëm. Që nga viti 2003 ai punoi vullnetarisht në Klinikën e Traumatologjisë në Shkup, ku edhe ishte i përfshirë në mënyrë aktive në praktikën e përditshme. Ai u punësua në Klinikën e Traumatologjisë në vitin 2004. Titullin specialist në kirurgji të përgjithshme e arriti në qershor të vitit 2008. Në vitin 2006 ai u zgjodh si asistent i ri, në vitin 2011 si asistent, dhe në vitin 2015 u zgjodh asistent-doktorant në Fakultetin e Mjekësisë në lëndën e kirurgjisë. Nga viti 2009 deri në vitin 2010 ka mbajtur postin e drejtorit të Klinikës për Sëmundje Ortopedike në Qendrën Klinike-Shkup. Në vitin 2009, ai u zgjodh për përfaqësues kombëtar i Komitetit të shoqatës mjeksore të Forcave të NATO-s.

Në qershor të vitit 2010 u emërua zëvendës kordinator i klinikave kirurgjikale me Qendrën Emergjente, Klinikën për Anestezion, Rianimim dhe Kujdes Intensiv dhe Klinika e Sëmundjeve Ortopedike.

Nga viti 2011 deri në vitin 2017 ishte drejtues i Qendrës Emergjente Kirurgjikale, ku dha kontribut të madh në organizimin e shërbimeve emergjente,në dijagnostikën emergjente, në kujdesin emergjent të pacientëve me sëmundje akute kirurgjikale në kushte normale dhe në kushte të ndodhive masive.

Që nga gushti i vitit 2017, me vendimin e Qeverisë së Republikës së Maqedonisë, ai u emërua Drejtor i ISHP KU të Traumatologjisë, Sëmundjeve Ortopedike, Anestezisë,Reanimimit dhe Kujdesit Intenziv, Qendrës Emergjente në Shkup. Në vitin 2017 ai u emërua Këshilltar Nacional i Ministrit të Shëndetësisë.

Ai ka marrë pjesë në shumë kongrese, simpoziume dhe takime të tjera profesionale dhe shkencore të karakterit ndërkombëtar dhe kombëtar si ligjërues i ftuar dhe është autor dhe bashkëautor i shumë botimeve dhe punimeve shkencore që janë shqyrtuar në revista , në kongrese dhe simpoziume.

Flet rrjedhshëm gjuhën angleze, për të cilën ka certifikatë të pranuar ndërkombëtarisht nga Universiteti i Kembrixhit. Ai ka njohuri në gjuhën gjermane dhe posedon aftësi kompjuterike të jashtëzakonshme.

Është anëtar i Shoqatës Mjekësore të Maqedonisë, anëtar i Shoqatës Maqedonase të Ortopedëve dhe Traumatologëve, anëtar i Shoqatës Ao Alumni, anëtar i Shoqatës AO Spine dhe anëtar i Kryqit të Kuq të Republikës së Maqedonisë.

UDHËZIME PËR AUTORËT

Këto të dhëna janë në pajtim me "Kërkesat uniforme për Dorëshkrimet e Pranuara në Revistat Biomjekësore" Dokumentin komplet mund ta gjeni në www.icmje.org)

Medicus është revistë ndërkombëtare që boton punime origjinale shkencore, vështrime revyale, punime profesionale, prezentime rasti, kumtesa të shkurtra, recenzione librash, raporte nga tubime shkencore, letra dhe editoriale nga fusha e mjekësisë, stomatologjisë, farmakologjisë si dhe nga fusha tjera të përaferta bio-mjeksore.

Revista është organ i "Shoqatës së Mjekëve Shqiptarë në Maqedoni."

Gjuha e botimeve është në Gjuhë Shqipe dhe Angleze (këshilli redaktues mund të vendosë nëse botimet do të jenë edhe në gjuhë tjera). Autorëve u kërkohet të lektorojnë dhe të redaktojnë unimin e tyre vetë, në gjuhën përkatëse.

Ju lutemi përdoreni madhësinë standarde të punimit në format: *Word për Windows*, Times New Roman 12.

Dorëshkrimet dërgohen në format elektronik, qoftë me

CD ose përmes e-mailit tek Kryeredaktori,
Prof. Dr. Nevzat Elezi,
Zyra e Redaksisë, rr. Mehmed Pashë Deralla
nr.16, 1200 Tetovë, apo në
e-mail: shmshm@live.com

Revista për një numër pranon jo më shumë se një artikull nga një autor, dhe jo më shumë se dy si ko-autor.

Autorët duhet të deklarojnë se kontributi i tyre nuk është publikuar apo pranuar për publikim diku tjetër, përderisa nuk përfundon procedura vlerësuese ne Revistën tonë.

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Revista do të **njoftojë pranimin** e artikullit tuaj brenda shtatë ditësh dhe do t'ju bëjë me dije se kur do të informoheni për vendimin e këshillit redaktues.

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These guidelines are in accordance with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (The complete document appears at www.icmje.org)

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The language of publication is Albanian and English (the editorial board may decide whether other language will be used for publications). Authors are requested to have their paper proof-readed and edited for the respective language.

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Numri i faqeve (përfshirë tabelat dhe/ose figurat/ ilustrimet) varet nga lloji i artikullit:

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prezantim rasti apo kumtesë e shkurtër – deri 6 faqe dhe maksimum 3 tabela dhe/ose figura/imazhe.

Letër redaksisë - deri 2 faqe

Së bashku me dorëshkrimin, dorëzoni një faqe me **titullin** e artikullit; **emrin/at e autorit/ve**, duke përfshirë emrin me jo më shumë se dy tituj shkencor; emrin e departamentit dhe institucionit në të cilin është bërë punimi; institucioni ku punon (për secilin autor); si dhe emri dhe adresa e autorit të cilit do ti adresohen kërkesat nga ana e Redaksisë (shihni Informacionet plotësuese për autorët)

Abstrakti duhet te jete me jo më shumë se 250 fjalë. Duhet të konsistojë në katër paragrafë, i klasifikuar në Hyrje, Metodat, Rezultatet dhe Diskutimi (Përfundimet). Ato duhet të përshkruhen shkurt, respektivisht, problem qenësor i studimit, se si është kryer studimi, rezultatet e fituara, dhe perfundimi.

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Fjalët kyqe -Tri deri pesë flaje apo fraza te shkurtëra duhet t'i shtohen pjesës së fundme të faqes së abstraktit.

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Shkurtimet (**akronimet**) përdoren për njësitë matëse, kurse në raste tjera kur përmendet për herë të parë, ai duhet të jetë i sqaruar me fjalën bazë bashkangjitur.

Për të gjitha barnat duhet të përdoren **emrat gjenerik** ndërkombëtar. Nëse në hulumtim janë të përdorura brendet e patentuara, përfshini emrin e brendit në kllapa në paragrafin e Metodave.

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The number of pages (including tables and/or figures/ illustrations) is dependent upon the type of the article:

original research paper - up to 12 pages and no more than 6 tables and / or graphs / pictures;

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Provide an **abstract** of not more than 250 words. It should consist of four paragraphs, labeled Backround, Methods, Results and Conclusions. They should briefly describe, respectively, the problem being in the study, how the study was performed, the salient results, and what the authors conclude from the results.

Tables, figures and legends (see Additional Information for Authors)

Three to five **key words** or short phrases should be added to the bottom of the abstract page.

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The authors receive two copies of the relevant issue.

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I. Faqja e parë – *ballina*: Duhet të përmbajë: (a) titullin e punimit, të shkurtër, por informativ; (b) emri, inicialet e emrit të mesëm dhe mbiemrit të secilit autor; (c) institucioni; (d) emri i departamentit që i atribuohet punës shkencore; (e) emri dhe adresa e autorit për t'iu përgjigjur në lidhje me dorëshkrimin; (f) burimi/përkrahja në formë të granteve, paisjeve, barnave dhe në përgjithësi.

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III. Faqja e tretë dhe të tjerat – *teksti i plotë i artikullit*: Teksti i plotë I artikujve hulumtues ose vrojtues normalisht, por jo domosdoshmërisht, duhet të jetë i ndarë në paragraf me këta nëntituj: hyrja, metodat dhe materialet, rezultatet dhe diskutimi.

1. Hyrja: Krijoni një kontekst apo prapavijë(trualli) të studimit (që në fakt është natyra e problemit dhe rëndësia e tij). Për të bërë këtë duhet të bëni një hulumtim të literaturës – duke kërkuar, gjetur dhe lexuar punimet përkatëse, që duhet të jenë si referencë në dorëshkrimin tuaj. Sqaroni hipotezat tuaja dhe planifikoni t'i testoni ato, si dhe përshkruani qëllimet tuaja. Kini qëndrim të qartë se çka prisni të gjeni dhe arsyet që ju udhëhoqën tek hipotezat që keni krijuar. Objekti i hulumtimit më së shpeshti fokusohet kur parashtrohet si pyetje. Mos përfshini të dhëna apo rezultate nga puna që do të raportohet.

2. Metodat & Materialet: Ky paragraf duhet të përfshijë atë informacion që ishte në dispozicion në kohën që plani apo protokoli i studimit po shkruhej. Të gjitha informacionet e marra gjatë studimit i takojnë paragrafit të Rezultateve.

Përshkruani përzgjedhjen tuaj të pjesëmarrësve së vrojtimit ose eksperimentit (pacientët ose kafshët laboratorike, përfshirë kontrollat) qartë, duke përfshirë kriteret e përshtatshme (inkluzive) dhe përjashtuese (ekskluzive).

Parimi udhëheqës duhet të jetë i qartë se si dhe pse studimi është bërë në një mënyrë të caktuar. Jepni detaje të mjaftueshme për metodat, mjetet dhe materialet (jepni emrin dhe adresën e prodhuesit në kllapa), dhe procedurat për të lejuar të tjerët të kuptojnë dhe riprodhojnë rezultatet tuaja.

Nëse një metodë e caktuar që është përdorur është e njohur, atëherë nuk është e nevojshme të jepet përshkrim komplet i saj. Mund t'i referoheni punimit në të cilin së pari herë është përshkruar dhe të

Additional Information for Authors

I. First page - *front page*: It should contain: (a) title of paper, a short, but informative; (b) the first name, initials of middle name and last name of each author; (c) the institution; (d) the name of the department that is attributable to the scientific work; (e) the name and address of the author with whom to correspond about the manuscript (f) source/support in the form of grants, equipment, drugs, or all.

II. Second page - *abstract and keywords*: The abstract should be written with a maximum of 150 words for unstructured abstracts and 250 words for structured abstracts (containing parts: objective(s) of study or research, basic procedures, such as selection of subjects or laboratory animals, observational and analytical methods, then, the main findings/results (data and their statistical significance, if possible), and the main conclusions. Emphasize the new and important aspects of the study or observation.

Below the abstract identify and write the keywords: 35 words or short phrases that will assist in indexing the paper and publication of the abstract.

Use terms from the list of Index Medicus for Medical Sub-Headings (MeSH); if there is no appropriate MeSH term for some newly introduced terms, we can use the given terms.

III. Third and further pages – *full text of the article*: The full text of research or observational articles should normally be, but not necessarily, divided into sections with the following headings: introduction, material and methods, results and discussion.

1. Introduction: Provide a context or background for the study (that is, the nature of the problem and its significance). To do this you must complete a literature review – searching for, finding and reading relevant papers, which must be referenced in your manuscript. Explain your hypotheses and the plan to test them, and describe your aims. Clearly state what you expect to find and the reasoning that led you to the hypotheses that you have made. The research objective is often more sharply focused when stated as a question. Do not include data or conclusions from the work being reported.

2. Methods & Material: This section should include only information that was available at the time the plan or protocol for the study was being written. All information obtained during the study belongs in the Results section.

Describe your selection of the observational or experimental participants (patients or laboratory animals, including controls) clearly, including eligibility and exclusion criteria.The guiding principle should be clarity about how and why a study was done in a particular way.

Give sufficient details of the methods, apparatus and materials (give the manufacturer's name and address in parentheses), and procedures to allow others to understand and reproduce your results.

If a particular method used is well known then there is no need to give a complete description. You can reference the paper in

përmendni ndonjë modifikim/ndryshim që keni bërë. Jepni arsyet për përdorimin e tyre dhe vlerësoni kufizimet e tyre. Në fund, përshkruani se si i keni analizuar të dhënat tuaja, duke përfshirë metodat statistikore dhe pakon programore që keni përdorur.

Autorët e doreshkrimeve të rishqyrtuara duhet të përfshijnë një paragraf që përshkruajnë metodat që kanë përdorur për lokalizimin, përzgjedhjen, ekstrahimin dhe sintetizimin e të dhënave. Përdorni formën joveprore të foljes, në vetën e tretë, kur dokumentoni metodat, gjë që do të fokusonte vëmendjen e lexuesit tek puna që është bërë e jo tek hulumtuesi (P.sh. Janë marrë, janë realizuar, janë prezantuar etj.)

2. a) Statistikat: Përshkruani metodat statistikore me detaje të mjaftueshme për t'ia mundësuar një lexuesi me njohje në atë fushë t'i qaset të dhënave origjinale për të verifikuar rezultatet e raportuara. Kur është e mundur, përcaktoni sasinë e zbulimeve dhe prezantoni ato me indikatorë përkatës të gabimeve në matje apo pasiguri (siç janë inter-valet e besueshmërisë). Evitoni mbështetjen vetëm në testet statistikore të hipotezave, siç janë vlerat p, që dështojnë të transmetojnë informacion të rëndësishëm mbi madhësinë e efektit. Jepni detaje rreth përzgjedhjes së rasteve (randomizimi) dhe përshkruani metodat dhe sukseset e vro¬jtimit gjatë realizimit të studimeve të verbuara. Definoni termet statis¬tikore, shkurtesat dhe më së shumti simbolet. Specifikoni programin kompjuterik që është përdorur.

3. Rezultatet: Ky paragraf duhet t'i bëjë gjetjet tuaja të qarta. Prezantoni rezultatet tuaja në rend logjik në tekst, tabela dhe ilustrime, duke dhënë së pari rezultatet kryesore ose më të rëndësishme. Mos i përsërisni të gjitha të dhënat në tabela apo ilustrime, në tekst. Nënvizoni ose përm-bledhni shkurtimisht vetëm vrojtimet më të rëndësishme.

Kur të dhënat përmblidhen në paragrafin e Rezultateve, jepni rezultate numerike jo vetëm si derivate (për shembull, përqindja) por gjithashtu si numra absolut nga të cilët derivatet janë llogaritur, dhe specifikoni metodat statistikore që janë përdorur për t'i analizuar ato.

Kufizoni tabelat dhe figurat në aq sa janë të nevojshme për të sqaruar argumentin e punimit dhe për të vlerësuar të dhënat ndihmëse. Duke përdorur grafikonet për të reprezentuar të dhënat tuaja si alternativë e tabelave, do të rrisë kuptueshmërinë e lexuesit. Mos i dyfishoni të dhënat në grafikone dhe tabela. Duhet të jeni të qartë se cili lloj i grafikoneve është i përshtatshëm për informacionet tuaja. Për shembull, për të reprezentuar korelimin mes dy ndryshoreve, preferohet grafiku vijëzor, krahasuar me grafikun rrethor apo në formë shtyllash.

Sa i përket të gjitha paragrafeve, qartësia dhe të qënit i thuktë është kyçe. Mos prezantoni të njëjtat të dhëna më shumë se një herë. Kufizojeni veten në të dhënat që ndihmojnë në adresimin e hipotezave tuaja. Kjo është e rëndësishme edhe nëse të dhënat i aprovojnë ose nuk i pranojnë ato. Nëse keni bërë analiza statistikore, duhet të jepni vlerën e proba¬bilitetit (p) dhe të tregoni se është shprehës (sinjig në nivelin që ju po testoni. Varësisht nga analizat e përdorura, gjithashtu mund të jetë e rëndësishme të jepni intervalet e besueshmërisë së rezultateve (Confidence Interval –

which it was first described and mentioned any modifications you have made. Give the reasons for using them, and evaluate their limitations. Finally,, describe how you analysed your data, including the statistical methods and software package used.

Authors submitting review manuscripts should include a section describing the methods used for locating, selecting, extracting, and synthesizing data.

Use the third person passive voice when documenting methods which would focus the readers' attention on the work rather than the investigator.(e.g. Were taken, was performed, were presented itd.)

2. a) Statistics: Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as p values, which fail to convey important information about effect size. Give details about the randomization and describe the methods and success of observations while using blinded trials. Define statistical terms, abbreviations, and most symbols. Specify the computer software used.

3. Results: This section should make your findings clear. Present your results in logical sequence in the text, tables, and illustrations, giving the main or most important findings first. Do not repeat all the data in the tables or illustrations in the text. Emphasize or summarize only the most important observations.

When data are summarized in the Results section, give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical methods used to analyze them.

Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Using graphs to represent your data as an alternative to tables will improve the reader's understanding. Do not duplicate data in graphs and tables. You need to be clear what type of graphs is suitable for your information. For example, to represent the correlation between two variables, a line graph is preferred to a pie chart or a bar chart.

As with all sections, clarity and conciseness is vital. Don't present the same data more than once. Restrict yourself to the data that helps to address your hypotheses. This is important whether the data supports or disproves them. If you have carried out a statistical analysis, you should give the probability (P) value and state it is significant at the level you are testing. Depending on the analysis used, it may also be important to give the confidence intervals of the results, or the statistical parameters such as the odds ratios. Provide a caption for each figure making the gen¬eral meaning clear without reference to the main text, but don't discuss the results. Let the readers decide for themselves what they think of the data. Your chance to say what you think comes next, in the discussion.

3. Tables: Each table should be inserted at the point of the text where they have to be placed logically, typed by the same rules

CI), ose parametrat statistikorë si proporcionet e rastit (odds ratio). Bëni përshkrimin tek secila figurë duke bërë të qartë domethënien e përgjithshme pa referencë në tekstin kryesorë, por mos diskutoni rezultatet në të. Lëreni lexuesin të vendosë vetë se çfarë men-don për të dhënat. Mundësia juaj për të thënë se çfarë mendoni, është në vazhdim, tek diskutimi.

3. Tabelat: Secila tabelë duhet të vendoset në vendin e tekstit ku duhet të vihet logjikisht, e plotësuar me të njëjtat rregulla sikur teksti i plotë. Mos i dërgoni tabelat si fotografi. Secila tabelë duhet të citohet në tekst. Tabelat duhet të jenë me numra ashtu që të jenë në koordinim me refer-encat e cituara në tekst. Shkruani një përshkrim të shkurtë të tabelës nën titullin. Çdo sqarim shtesë, legjendë ose sqarim i shkurtesave jostan¬darde, duhet të vendoset menjëherë poshtë tabelës.

4. Diskutimi: Ky paragraf është pjesa ku ju mund të interpretoni të dhë-nat tuaja dhe të diskutoni duke ballafaquar dhe krahasuar gjetjet tuaja me ato të hulumtuesve të mëparshëm. Rishikoni referencat e literaturës dhe shihni nëse mund të përfundoni se si të dhënat tuaja përkojnë me atë që keni gjetur.

Ju gjithashtu duhet të llogarisni rezultatet, duke u fokusuar në mekaniz¬mat në prapavij të vrojtimit. Diskutoni nëse rezultatet tuaja mbështesin hipotezat tuaja origjinale. Gjetjet negative janë aq të rëndësishme në zhvillimin e ideve të ardhshme sikur gjetjet pozitive.

E rëndësishme është se, nuk ka rezultate të këqija. Shkenca nuk të bëjë me të drejtën dhe të gabuarën, por merret me zgjerimin e njohjeve të reja.

Diskutoni si janë paraqitur gabimet në studimin tuaj dhe çfarë hapa keni ndërmarrë për të minimizuar ato, kështu duke treguar se ju çmoni ku¬fizimet e punës tuaj dhe fuqinë e përfundimeve tuaja. Duhet gjithashtu të merrni në konsideratë ndërlikimet e gjetjeve për hulumtimet në të ardhmen dhe për praktikën klinike. Lidhni përfundimet me qëllimet e studimit, por evitoni qëndrimet dhe përfundimet e pakualifikuara, që nuk mbështeten në mënyrë adekuate nga të dhënat. Shmangni prioritetet deklarative apo të aludoni në punën që nuk është krahasuar.

5. Referencimi: Referencat janë baza mbi të cilën është ndërtuar raporti juaj. Shqyrtimi i literaturës dhe leximi i referencave gjithmonë duhet të jetë pikë fillestare e projektit tuaj. Ky paragraf duhet të jetë i saktë dhe të përfshijë të gjitha burimet e informacionit që keni përdorur.

Në formatin " Vancouver" , referencat numërohen një nga një, sikur që shfaqen në tekst dhe identifikohen me numra në bibliografi..

Shënoni të gjithë autorët kur janë gjashtë e më pak; kur janë shtatë ose më tepër, shënoni tre të parët, pastaj shtoni "et.al." Pas emrave të autorëve shkruhet titulli i artikullit; emri i revistës i shkurtuar sipas mënyrës së Index Medicus; viti i botimit; numri i vëllimit; dhe numri i faqes së parë dhe të fundit.

Referencat e librave duhet të jepen sipas emrit të autorit, titulli i librit (mund të citohet edhe titulli i kapitullit para titullit), vendi i botimit, botuesi dhe viti.

as for the full text. Do not send tables as photographs. Each table should be cited in the text.Tables should be numbered so that they will be in sequence with references cited in the text. Provide a brief explanation of the table below the title. Any additional explanations, legends or explanations of non¬standard abbreviations, should be placed immediately below the table.

4. Discussion: This section is where you interpret your data and discuss how your findings compare with those of previous researchers. Go over the references of your literature review and see if you can determine how your data fits with what you have found.

You also need to account for the results, focusing on the mechanisms be¬hind the observation. Discuss whether or not your results support your original hypotheses. Negative findings are just as important to the de¬velopment of future ideas as the positive ones.

Importantly, there are not bad results. Science is not about right or wrong but about the continuing development of knowledge.

Discuss how errors may have been introduced into your study and what steps you took to minimise them, thus showing that you appreciate the limitations of your work and the strength of your conclusions. You should also consider the implications of the findings for future research and for clinical practice. Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. Avoid claiming priority or alluding to work that has not been compared.

5. Referencing: The references are the foundation on which your report is built. Literature searches and reading of references should always be the starting point of your project. This section must be accurate and in¬clude all the sources of information you used.

In the Vancouver format, references are numbered consecutively as they appear in the text and are identified in the bibliography by numerals.

List all authors when there are six or fewer; when there are seven or more, list the first three, then add "et al." The authors' namer are fol-lowed by the title of the article; the title of the journal abbreviated ac-cording to the style of Index Medicus; the year of publication; the volume number; and the first and last page numbers.

References to books should give the names of any editors, place of publication, editor, and year.

In the text, reference numbers are given in superscript. Notice that issue number is omitted if there is continuous pagination through¬out a volume, there is space between volume number and page numbers, page numbers are in elided form (51-4 rather than 51-54) and the name of journal or book is in italics.The following is a sample reference:

Në tekst, numrat e referencave jepen me indeks të sipërm. Vëreni se çështja e numrave neglizhohet nëse ka numërtim të vazhdueshëm përg¬jatë gjithë vëllimit, ka hapësirë mes numrit të vëllimit dhe numrit të faqes, numrat e faqeve janë në këtë formë: 51-4 në vend të 51-54, dhe emri i revistës ose librit është në italic. Në vazhdim është një shembull i referencës:

Artikujt e revistave:

1. Lahita R, Kluger J, Drayer DE, Koffler D, Reidenberg MM. Antibodies to nuclear antigens in patients treated with procainamide or acetylpro¬cainamide. *N Engl J Med* 1979;301:1382-5.
2. Nantulya V, Reich M. The neglected epidemic: road traffic injuries in developing countries. *BMJ* 2002;324: 1139.
3. Murray C, Lopez A. Alternative projections of mortality and disability by cause 1990-2020: global burden of disease study. *Lancet* 1997;349: 1498-504.

Librat dhe tekste tjera:

4. Colson JH, Tamour NJJ. Sports in juries and their treatment. 2nd ed. London: S. Paul, 2006.
5. Department of Health. *National service framework for coronary heart disease*. London: DoH, 2000.

   www.doh.gov.uk/nsf/coronary.htm (accessed 6 Jun 2003).
6. Kamberi A, Kondili A, Goda A, dhe bp; *Udhërrëfyes i shkurtër i Shoqatës Shqiptare të Kardiologjisë për parandalimin e Sëmundjes Aterosklerotike Kardiovaskulare në praktikën klinike*, Tiranë, 2006
7. Azemi M, Shala M, dhe bp. *Pediatria sociale dhe mbrojtja shëndetësore e fëmijëve dhe nënave*. Pediatria, Prishtinë 2010; 9-25

Shmangni përdorimin e abstrakteve si referenca; "të dhëna të papub-likuara" dhe "komunikime personale". Referencat e pranueshme, por ende të papublikuara lejohet të merren, vetëm nëse shënoni se janë "në shtyp".

6. Mirënjohjet: Ju mund të keni dëshirë të falënderoni njerëzit që ju kanë ndihmuar. Këto mund të rangohen prej atyre që ju kanë përkrahur me teknika eksperimentale deri tek ata që ju kanë këshilluar deri në bër¬jen e dorëshkrimit final.

7. Formati i fajllit të të dhënave për **ilustrimet** (**figurat**): JPG

Nëse përdoren fotografitë e pacientëve, qoftë subjekti, qoftë fotografitë e tyre nuk duhet të jenë të identifikuara, ato duhet të shoqërohen me lejen e shkruar nga ta për përdorimin e figurës. Format e lejuara janë në dispozicion nga redaksia.

Nëse fajllet e të dhënave janë shumë të mëdha për t'u dërguar me e-mail, rekomandohet dërgimi me CD në adresën tonë.

8. Legjendat për Ilustrimet (Figurat)

Legjenda e tabelës duhet të vendoset mbi tabelë. Referenca e një tabeleje, e cila është marrë nga ndonjë publikim tjetër, duhet të vendoset poshtë tabelës. (Është përgjegjësi e autorit të sigurojë lejen e ribotimit nga botuesit e atij botimi) Legjenda e figurës duhet të vendoset në fund të faqes. Referenca e figurës e marrë nga ndonjë tjetër publikim vendoset në fund të legjendës. (Leja e ribotimit duhet të sigurohet nga botuesi i këtij botimi).

Journal articles:

1. Lahita R, Kluger J, Drayer DE, Koffler D, Reidenberg MM. Antibodies to nuclear antigens in patients treated with procainamide or acetylpro¬cainamide. *N Engl J Med* 1979;301:1382-5.
2. Nantulya V, Reich M. The neglected epidemic: road traffic injuries in developing countries. *BMJ* 2002;324: 1139.
3. Murray C, Lopez A. Alternative projections of mortality and disability by cause 1990-2020: global burden of disease study. Lancet 1997;349: 1498-504.

Books and other monographs:

4. Colson JH, Tamour NJJ. Sports in juries and their treatment. 2nd ed. London: S. Paul, 2006.
5. Department of Health. *National service framework for coronary heart disease*. London: DoH, 2000.

   www.doh.gov.uk/nsf/coronary.htm (accessed 6 Jun 2003).
6. Osler AG. *Complement: mechanisms and functions*. Englewood Cliffs: Prentice-Hall, 1976.

Avoid using as references abstracts; "unpublished data" and "personal communications". References to accepted but yet unpublished articles are allowed to be made, only if you note "in press".

6. Acknowledgements: You may wish to acknowledge people who have helped you. These can range from those who supported you with exper¬imental techniques to those who read or offered advice on your final manuscript.

7. Data file format for **illustrations** (**figures**): JPG

If photographs of patients are used, either the subjects should not be identifiable or their pictures must be accompanied by written permis-sion to use the figure. Permission forms are available from the Editor.

If data files are too big for transmission as an Email attachment submis¬sion of a CD to our address is recommended.

8. Legends for Illustrations (Figures)

The legend of a table has to be placed above the table. The reference of a table, which has been taken from another publication, must be placed below the table. (It is the author's responsibility to obtain the permission of reproduction from the publishers of the publication.) Figure legends are to be placed at the end of the paper. The reference of a figure taken from another publication stands at the end of the legend. (Permission of reproduction must be obtained from the publishers of this publication).