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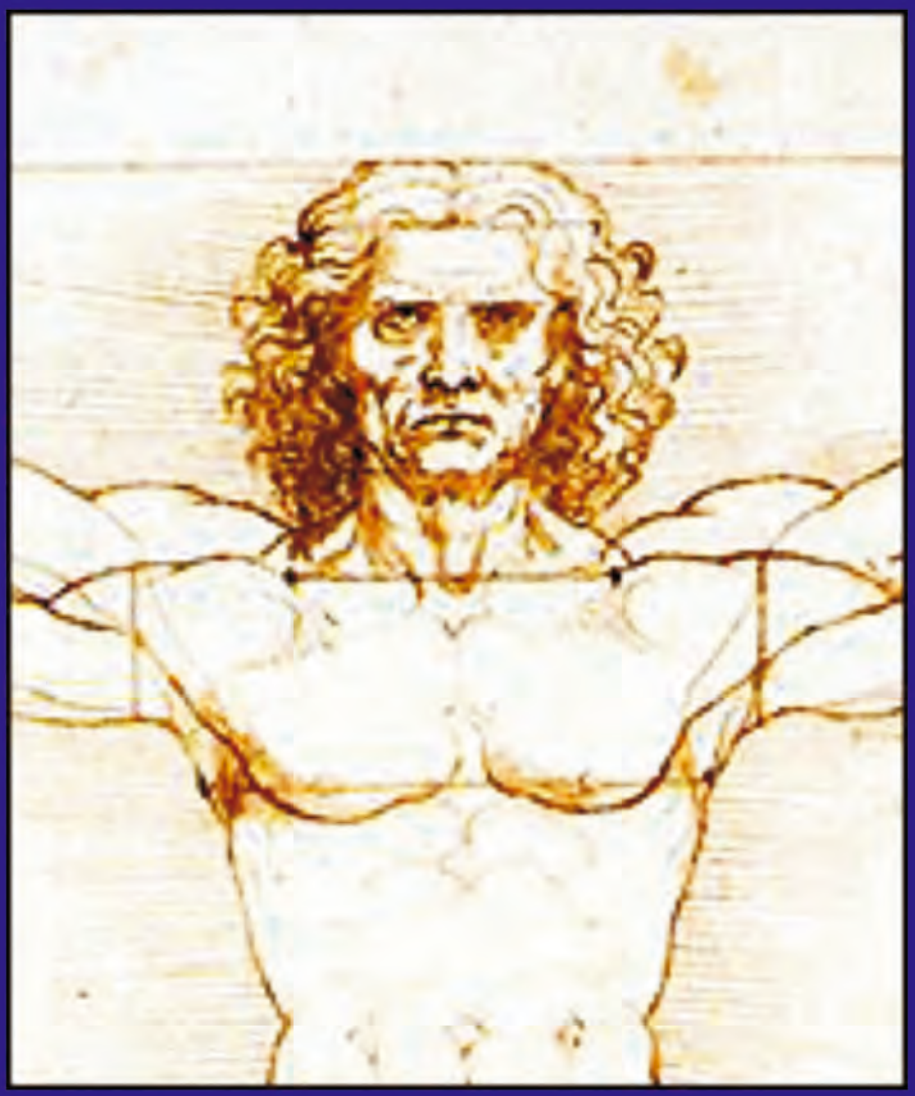

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SADRŽAJ

Čitaj da shvatiš

Piši da preneseš

Uradi da te pamte

* * *

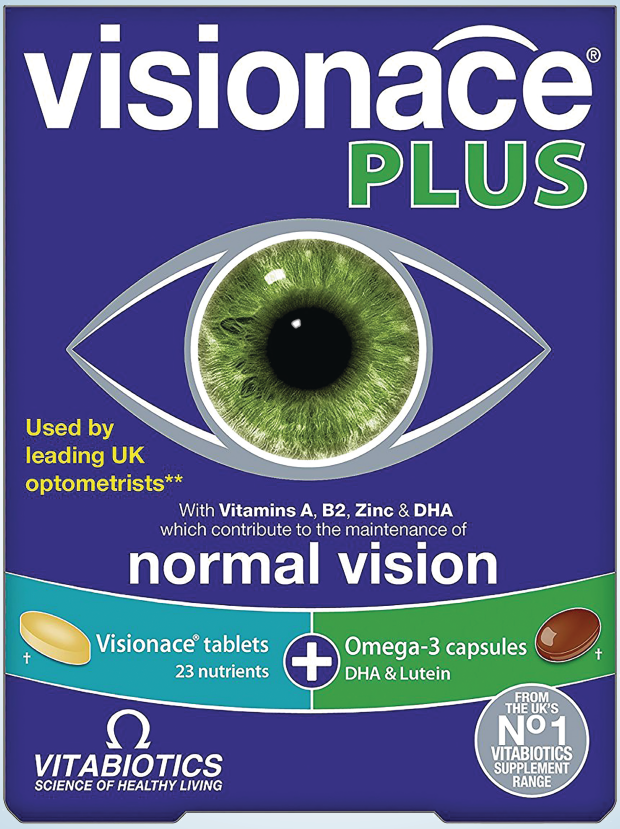
Read to understand

Write to impart

Work to be remembered

Avdo Ćeranić

BOLJI POGLED NA SVET!



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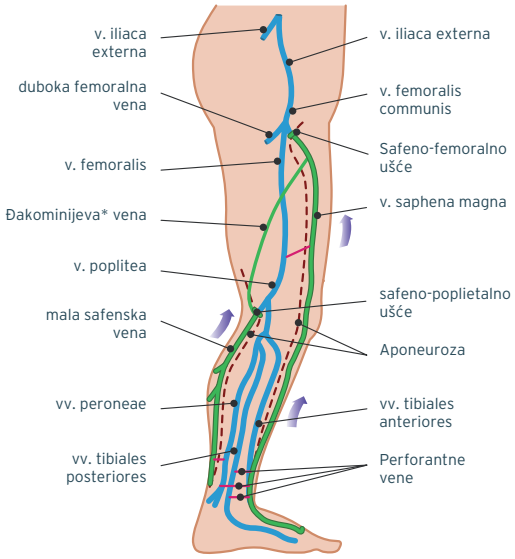
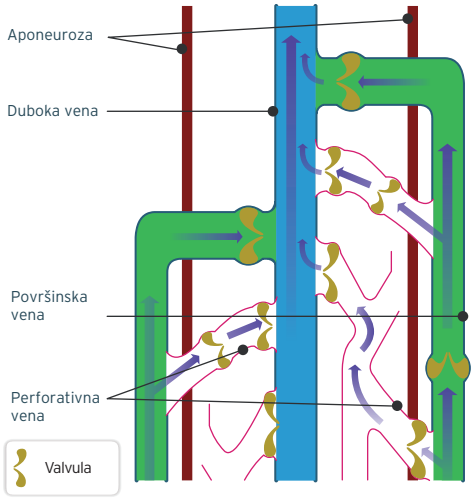


Anatomija dubokih i površinskih vena

2 kompartmenta :
- duboki
- površinski

3 sistema :
- Duboki venski sistem
- Površinski venski spletovi
- Perforantne vene

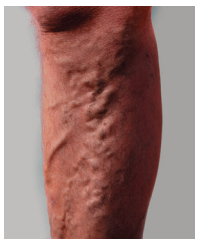


Perforantne vene povezuju površinski i duboki venski sistem

CEAP* klinička klasifikacija venske bolesti [1]

C0
Bez vidljivih i palpabilnih znakova venske bolesti

C1
Retikularne vene
Teleangiektazija



C2
Varikozne vene >3mm

C3
Edem

C4a
Hiperpigmentacija ili ekcem

C4b
Lipodermatoskleroza ili bela atrofija

C5
Zatvoreni venski ulkus

C6
Aktivni venski ulkus

* CEAP: Međunarodna klasifikacija hronične venske insuficijencije uzimajući u obzir etiološke, kliničke, patofiziološke, anatomske i morfološke manifestacije hronične venske insuficijencije.

Funkcionalni simptomi kao što su bol ili osećaj težine u nogama, mogu biti prisutni kod svih kliničkih stepena CEAP klasifikacije od C_0 do C_6

POBOLJŠANJE SIMPTOMA VENSKE INSUFICIJENCIJE SA SAMO 1 TABLETOM DNEVNO [2,3,4]

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(1) EKLÖF B, et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. J Vasc Sur 2004;40:1248-52
(2) CAZAUBON. M, *et al.* - Etude comparative d'acceptabilité, d'efficacité et de tolérance de deux formes galéniquesde disomine 600 mg, dans le traitement des symptômes de la maladie veineuse chronique. Angiologie, 2011, vol. 63, n°2
(3) R. BARBE Etude de la durée d'action du Diovenor avec contrôle par pléthysmographie. Tribune médicale, n°270, p 49-50, 1988.
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Original article

FACTORS AFFECTING ANAESTHESIA PREFERENCES OF THE GRAVID WOMEN WHO ARE TO DELIVER BY CAESAREAN SECTION

Sahinturk Helin,[*] Turhan Cakar Sanem, Can Selvi Ozlem, Yilmaz Abbas Ali, Uysalel Asuman

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Abstract: **Objectives:** In recent years, a significant increase has been observed in the prevalence of caesarean sections (CS). Although as in many other countries, CS rates in Turkey are higher than the targeted rate. This increase in the prevalence of CS also affects obstetric anaesthesia.

In this study, we investigate the choice of anaesthesia among pregnant women who are scheduled for CS, as well as general anaesthesia and regional anaesthesia rates, the reasons for choosing general anaesthesia or regional anaesthesia, and the factors that affect their choices.

Methods: A questionnaire consisting of 20 questions were applied to pregnant women applying for delivery by elective caesarean operation, between November 2011 to November 2012, in order to study the anaesthesia technique they prefer and the reason behind their preferences.

The questionnaire was applied to pregnant women during the visit, on the day before the operation or while they were waiting in the waiting room before the CS procedure.

Results: Our study revealed that age, gravida, previous type of delivery, previous anaesthesia experience, employment status, monthly income level, educational status, being given information about anaesthesia in advance, the source of information, and being diagnosed with panic disorder were all found to be influential in the decision of which type of anaesthesia to opt for.

Conclusion: We have found out that the reason why pregnant women who have higher educational status, who work and have high level of monthly-income prefer regional anaesthesia method more depends on the fact that they have more information on anaesthesia method, they have more common use of the internet and the information they obtain from the people around them is not prejudiced against regional anaesthesia method. We believe that as the education levels rise in the future and the patient population becomes more aware, which will direct them to do more research, their preference rates will change.

Key words: Caesarean, Anaesthesia Preferences, Questionnaire Study.

INTRODUCTION

In recent years, a significant increase has been observed in the prevalence of caesarean sections (CS). The World Health Organization (WHO) recommends that the rate of CS should be limited to 15% (1, 2), although as in many other countries, CS rates in Turkey are higher than the targeted rate. According to 2016 data published by the Turkish Statistical Institute, the CS delivery rate in Turkey was reported to be 21% in 2002, which increased to 51% in 2014 and 53% in 2015 (3). This increase in the prevalence of CS also affects obstetric anaesthesia, as a highly requested sub-branch of anaesthesiology that is reported to provide satisfactory results. The common acceptability and use of regional anaesthesia for childbirth have raised the importance of obstetric anesthetics in the field of anesthetic applications (4).

In this study, we aimed to investigate the choice of anaesthesia among pregnant women who are scheduled for CS, as well as general anaesthesia and regional anaesthesia rates, the reasons for choosing general anaesthesia or regional anaesthesia, and the factors that affect their choices.

MATERIAL AND METHODS

This study was registered at clinical trials.gov. (Registration number: NCT02026284). After obtaining Institutional Ethics Committee approval and written informed patient consent, a total of 750 pregnant women scheduled to undergo elective CS between November 2011 and November 2012 were included in this study, and were asked to fill out a questionnaire investigating the anaesthesia choice and the reasons that affected their choices. The pregnant women who agreed to take part and were included in this study were informed about the questionnaire, and both verbal and written approval was obtained. The questions were asked by the anaesthesiologist, and the patients' answers were recorded by the same physician. The women were informed that they were not obliged to answer every question, and could choose to "pass" if they did not want to answer, and also that they could discontinue the questionnaire whenever they wanted.

The questionnaire was applied to 26-week to 40-week pregnant women during the visit, on the day before the operation or while they were waiting in the waiting room before the CS procedure. Patients who underwent emergency surgery, patients with communication problems, patients who lacked the mental capacity to answer the questions, and patients who did not want to take part were excluded from the study. Twenty questions included in the questionnaire, which are given in Appendix 1, were asked verbally by the anaesthesiologist.

The first four questions in the questionnaire were designed to determine the demographic characteristics of the respondent, which inquired about the age, obstetric anamnesis (gravida, parity, the number of live births, abortion and curettage) and gestational week, respectively. Women within the high-risk pregnancy age ranges, being younger than 20 years of age and over 35 years of age, were grouped together (5, 6). The respondents were asked about their previous types of delivery, the number of normal deliveries (if any) and the number of CS deliveries. They were asked further whether their previous delivery experiences had affected their choice of anaesthesia, and the respondents who gave an affirmative answer were asked how their choices had been affected. The following question was about the type of anaesthesia chosen in any previous deliveries, and how the experience had affected the current choice of anaesthesia. The next three questions garnered information on the respondents' employment status (employed, unemployed, housewife), monthly income (grouped as TRY 500–1000, TRY 1000–2000, TRY 2000–4000 and TRY 4000 and above) and education level (uneducated, primary school graduate, high school graduate, university graduate). Then, they were asked that whether they had been informed about the optional delivery and anaesthesia methods before the operation. Patients who were thought to be informed before the delivery were asked who had informed them, or how they had been informed. A question was asked that included 13 sub-items listing the factors that affected the patients' choice of anaesthesia, their previous anaesthesia experiences, their feelings about previous anaesthesia experiences (whether they satisfied or not), the reasons related to the baby (desire to see the baby immediately after delivery, and the desire to initiate breastfeeding earlier), and their concerns about the anaesthesia method in relation to their choice of general or regional anaesthesia, and their reasons for choosing accordingly. The patients were also asked whether anyone had influenced their anaesthesia choice, or if anyone had made the decision on their behalf, with an affirmative answer being followed by an additional question related to who had made the decision. The final six questions of the questionnaire were prepared considering the opinions and recommendations of the psychiatry clinic and inquired of the respondents whether they suffered from any underlying psychiatric disorders, such as anxiety or panic attacks. Respondents were asked further whether they had any attacks accompanied by palpitations lasting about 10 minutes, shortness of breath, shivering, sweating, high blood pressure, discomfort, anxiety, fear and concerns from time to time. They were then asked whether they had applied for psychiatric assistance as a result of such complaints and whether they had been diagnosed with any anxiety disorder (i.e. panic disorder or generalized anxiety disorder) in the past. In cases where the patient was observed to have an anxiety disorder, regardless of whether or not a diagnosis had been made, it was asked that whether these negative experiences had affected the choice of anaesthesia. In the last two questions, it was asked that whether the patient had suffered any involuntary experiences that have harmed bodily integrity (sexual abuse/harassment), and if the answer was in the affirmative, it was asked that whether this experience influenced their choice of anaesthesia. For this part of the questionnaire, it was ensured that the patient was able to answer this question when she was alone.

The patients were given no guidance while the questions were being asked. It was stated that their choice of anaesthesia would be applied, as long as there were no conditions precluding the chosen anaesthesia, such as systemic disease, upper respiratory tract infection or impaired bleeding profile. In cases where a medical problem may exist, the most appropriate method of anaesthesia would be used for the health of both the mother and baby.

The SPSS 15.0 package program was used for the evaluation of the statistical data obtained from the questionnaire, which was prepared to evaluate the choices of anaesthesia and related factors. No normality tests were applied, and non-parametric test methods were chosen. A Chi-square or Fisher's exact test was used to test the distribution of categorical variables between the groups, while continuous variables were analysed with Mann-Whitney U or Kruskal Wallis variance analysis tests to determine the differences between groups. Continuous variables were expressed as a median (Minimum-Maximum), and categorical variables were expressed as frequency distributions and percentages in the summary of the results. For the same purpose, graphs were created using percentages and frequencies. A p-value of < 0.05 was considered statistically significant.

RESULTS

The respondents were divided into three age groups: < 20 years of age, which is considered as a risky age group for pregnancy; 21–34, which is considered the ideal age range for pregnancy; and 35–44. The majority of respondents were found to be in the 21–34 year age range (78.3%). While the gravida rates of the majority of patients (39.5%) were determined as 2, the parity rate was determined as 0 (45.9%).

Of the participants included in this study, 55.9% were unemployed, while education levels were defined in four groups, being uneducated, primary school graduate, high school graduate and university graduate. Considering the level of education of the patients included in our study, 0.04% were uneducated, 27.9% were primary school graduates, 28.8% were high school graduates, and 42.9% were university graduates. When the monthly income levels of the respondents were asked, 23.6% of the patients were found to be in the TL 500–1,000 income group, 32.8% in the TL 1,000–2,000 income group, 9.3% in the TL 2,000–4,000 income group and 34.3% in the > TL 4,000 income group.

The socio-demographic characteristics of the women who participated in this study are presented in Table 1.

When asked whether they had been informed about different delivery and anaesthesia methods, the pati-

Table1. *Demographic characteristics of the pregnant women*

		n	%
Age of the mother	**< 20 years old**	25	3.3
	21–34	587	78.3
	35–44	138	18.4
Gravida	**1**	267	35.6
	2	296	39.5
	3	104	13.9
Parity	**Nullipara**	344	45.9
	Multipara	406	54.1
Type of previous delivery	**First child**	339	45.2
	NVD	84	11.2
	C/S	310	41.3
	NVD+C/S	17	2.3
Previous anaesthesia type	**No anaesthesia experience**	421	56.1
	RA	198	26.4
	GA	116	15.5
	RA+GA	15	2
Employment status	**Employed**	331	44.1
	Unemployed	419	55.9
Level of monthly income	**TRY500–1000**	177	23.6
	TRY1000–2000	246	32.8
	TRY2000–4000	70	9.3
	> TRY4,000	257	34.3
Educational status	**Uneducated**	3	0.4
	PrimarySchool	209	27.9
	High-School	216	28.8
	University	322	42.9

ents who had been informed were asked who it was that had informed them. Of the 750 women, 438 women (58.4%) stated that they had not been informed about the different delivery and anaesthesia options, whereas 312 women (41.6%) stated that they had been informed, and 46% of those who had been informed reported being informed by the anaesthesiologist.

The respondents were asked which anaesthesia method they would choose in the absence of problems that would prevent their free choice of anaesthesia, to which 52.3% stated a preference for regional anaesthesia and 47.7% preferred general anaesthesia ($p < 0.05$) (Figure 1).

The factors that affected their choice between regional and general anaesthesia were asked under 14 items. Of the 392 patients who opted for regional anaesthesia, 186 (47.4%) said that their choice was based on their desire to see their baby immediately after the birth. The most common reason for choosing general anaesthesia was that the respondent did not want to see or remember anything. Of the 348 patients who stated a preference for general anaesthesia, 112 (32.1%) reported preferring this method for the above-mentioned reason (Figure 2 and 3).

Patients in the < 20 age group mostly opted for general anaesthesia, whereas the regional anaesthesia method was preferred in the other groups. Patients in these three groups preferred regional anaesthesia 28%, 53,5%, 51,4% respectively ($p < 0,05$).

When patients were evaluated according to gravida; 75% of patients in gravida 0 group, 56,6% of patients in gravida 1 group, 52% of patients in gravida 2 group, 50% of patients in gravida 3-4 group, 29% of patients in gravida 5 group preferred the regional anaesthesia method. When all gravida categories were evaluated, there was a significant difference between anaesthesia preference distributions ($p < 0,05$).

Participants in the study were divided into 4 groups according to the previous birth pattern. Patients were not delivered, had normal vaginal delivery, delivered caesarean section, and were classified as having both normal birth and caesarean delivery experience. When patients' anaesthesia choices were asked concerning the previous mode of delivery, the regional anaesthesia method was observed to be higher in the group of patients with no previous delivery experience (58,1% vs 41,9%), whereas the regional and general anaesthesia methods were observed to be preferred at similar rates in the other groups (45,2% vs 54,8%, 48,7% vs 51,3%, 35,3% vs 64,7% respectively). The general anaesthesia method was preferred more in the group of patients who had previously undergone a normal birth or a caesarean section than in the group of patients with no previous delivery ($p = 0.02$).

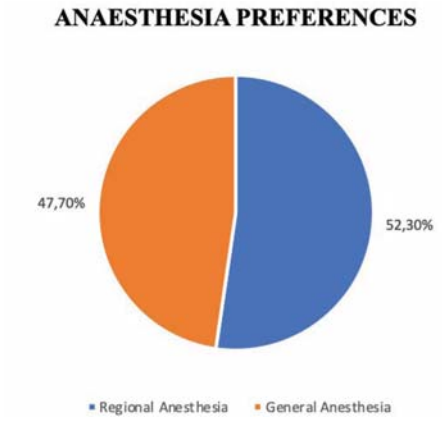

Figure 1. *Anaesthesia preferences*

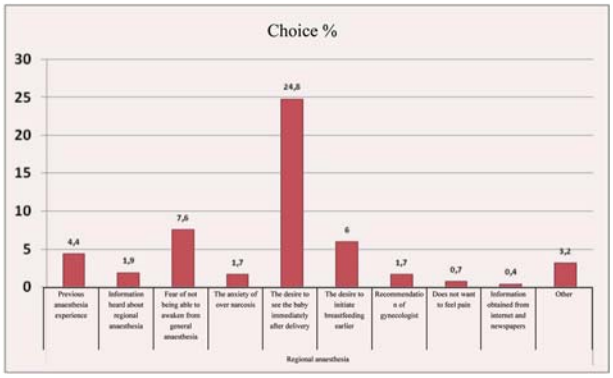

Figure 2. *Reasons for choosing regional anaesthesia*

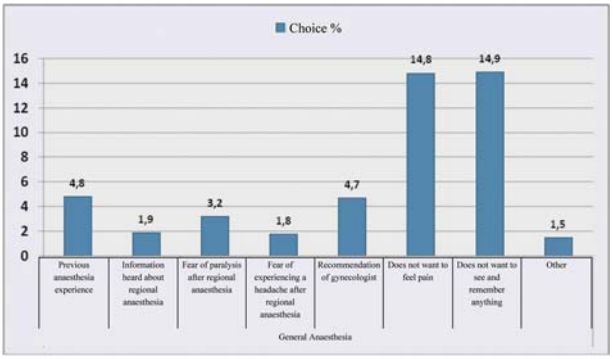

Figure 3. *Reasons for choosing general anaesthesia*

The patients in the study were divided into 4 groups according to the previous anaesthesia pattern. They were classified as having no experience of anaesthesia, having regional anaesthesia experience, having general anaesthesia experience, and having both regional anaesthesia and general anaesthesia experience. Of the patients with no anaesthesia experience, 55.6% of the patients preferred the regional anaesthesia method, whereas 44.4% were observed to prefer the general anaesthesia method. Of the patients who had regional anaesthesia experience in the past, 36.9% preferred the regional anaesthesia method, whereas 63.1% were observed to prefer the general anaesthesia method. Of the patients who had general anaesthesia experience in the past, 68,1% preferred regional anaesthesia whereas 31,9% preferred

Table 2. *Factors affecting the preference for anesthesia [n (%)]*

	Regional Anesthesia (n, %)	General Anesthesia (n, %)	*p*
Age groups			
< 20 age	7 (28%)	18 (72%)	< 0.01
21-34 age	314 (53,5)	273 (46,5%)	
35-44 age	71 (51,4%)	67 (48,6%)	
Gravida			
0	3 (75%)	1 (25%)	
1	151 (56.6%)	116 (43.4)	< 0.05
2	154 (52%)	142 (48%)	
3-4	78(50%)	78(50%)	
≥ 5	8 (29%)	19 (71%)	
Previous type of delivery			
None	197 (58,1%)	142 (41,9%)	
Normal vaginal delivery	38 (45,2%)	46 (54,8%)	0.02
Cesarean section (CS)	151 (48,7%)	159 (51,3%)	
Normal vaginal delivery + CS	6 (35,3%)	11 (64,7%)	
Previous anesthesia experience			
No experience	234 (55.6%)	187 (44.4%)	
Regional anesthesia (RA) experience	73 (36.9%)	125 (63.1%)	< 0.01
General anesthesia (GA) experience	79 (68,1%)	37 (31,9%)	
RA + GA	6 (42.9%)	9 (57.1%)	
Employment status			
Unemployed	182 (43.4%)	237 (56.6%)	< 0.01
Employee	210 (63.4%)	121 (36.6%)	
Monthly income level			
500-1000 TL	78 (44.1%)	99 (55.9%)	
1000-2000 TL	101 (41.2%)	145 (58.8%)	< 0.01
2000-4000 TL	39 (55.9%)	31 (44.1%)	
> 4000 TL	171 (66.5%)	86 (33.5%)	
Educational status			
Uneducated	1 (33.3%)	2 (66.7%)	
Primary school graduate	71 (33.8%)	138 (66.2%)	< 0.01
High school graduate	98 (45.4%)	118 (54.6%)	
University graduate	214 (66.5%)	108 (33.5%)	
Being given information about anesthesia in advance			
Not been informed	188 (42.9%)	250 (57.1%)	< 0.01
Been informed	204 (65.4%)	108 (34.6%)	
The source of information			
Anesthesiologist	114 (73.1%)	42 (26.9%)	
Internet-Newspaper	61 (68.5%)	28 (31.5%)	< 0.05
Gynecologist	27 (50.9%)	26 (49.1%)	
Friends	19 (51.4%)	18 (48.6%)	
Being diagnosed with panic disorder	13 (18.3%)	58 (81.7%)	< 0.01

the general anaesthesia. Of the patients who tried both methods, 42.9% preferred regional anaesthesia and 57.1% preferred general anaesthesia method. When all patient groups were evaluated, there was a statistically significant difference between the preference distributions of previous anaesthesia type and anaesthesia method ($p < 0,01$).

It was determined that 44.1% of the respondents were in the employed group while 55.9% were in the unemployed group. While 63.4% of the employed pregnant women preferred the regional anaesthesia method, this rate was 43.4% in the unemployed group ($p < 0,01$).

As the income level of patients increased, the preference rate of regional anaesthesia increased. The group with the highest preference for regional anaesthesia was the group with the highest income level (22,8%). The relationship between monthly income level of patients and preference of anaesthesia was statistically significant ($p <0.01$).

The general anaesthesia method was observed to be preferred at a high rate of 66.7% in the uneducated group, 66.2% in the primary school graduate group and 54.6% in the high school graduate group. In the university graduate group, 66.5% of the respondents were found to prefer regional anaesthesia ($p < 0,01$).

The respondents were asked about any sexual abuse or harassment that they were subjected to that may have damaged their physical integrity. The intention in this regard was to investigate whether such negative experiences were influential in the choice of anaesthesia type. Only three of the respondents admitted to having had such experiences in the past, and one stated that it had affected here the choice of anaesthesia.

Our study revealed that age, gravida, previous type of delivery, previous anaesthesia experience, employment status, monthly income level, educational status, being given information about anaesthesia in advance, the source of information, and being diagnosed with panic disorder were all found to be influential in the decision of which type of anaesthesia to opt for ($p < 0.05$) (Table 2).

DISCUSSION

Many factors may affect the choice of anaesthesia type as some of these can be modified during the pregnancy process, or even on the operating table. Our findings revealed that age, gravida, previous type of delivery, previous anaesthesia experience, employment status, monthly income level, educational status, and preoperative information related to anaesthesia and its source and presence of panic disorder all had significant effect on anaesthesia choice. Although with a little difference, most of our patients preferred regional anaesthesia (RA) to general anaesthesia (GA).

Our results are compatible with similar studies and showed that RA gained more popularity with the increasing knowledge in time. Kocamanoğlu et al. (7) found that rate of regional anaesthesia in C/S increased from 3% to 26.9% in five years which was attributed to increased experience and facilitated use of regional anaesthesia. Gülha} et al. (8) found regional anaesthesia as the choice of technique in a rate of 74%, but this study did not analyse the choice of the patient, but the technique used for C/S.

Age and level of education were the main predictors for the choice of anaesthesia. Patients aged below 20, mostly preferred general anaesthesia, probably based on concerns related to regional anaesthesia and birth. The respondents in this age group were mainly unemployed, primary school graduates which might be effective in their choice. Whereas pregnant women with high education level and in employed group, and women with easier access to information, choose regional aesthesia more. As gravida increased, we observed that patients were more likely to prefer general anaesthesia, which could be attributed to the thought that it would be a more comfortable and painless method than regional anaesthesia.

Patients with previous birth experiences preferred general anaesthesia more than the patients with no previous delivery experience and this can be attributed to the fears and concerns related to previous birth experiences. Patients with no birth experience had no concerns about themselves since they had had no negative experiences in this regard. Therefore, they focused on baby more and preferred regional anaesthesia.

It was observed that anaesthesia method in the previous births affected the choices oppositely. Patients with no anaesthesia experience and patients with previous GA experience preferred RA more than GA.The will of the patients to be conscious when they first saw their baby, and the negative experiences of GA such as nausea and vomiting lead patients to prefer RA. We believe that patients with no anaesthesia experience in the past tend to opt for RA because they are less concerned about being awake and lack the experience of both methods. Also, patients with previous anaesthesia experience tended to opt for the opposite of the previous method because of the dissatisfaction.

GA was more popular in unemployed group than the employed group (56,6% vs 36,6%), which can be attributed to the level of education and access to information. This result supports the effect of income on the RA preference. Büyükbayrak et al. (9) showed that education level, employment status and income have no effect on choice for type of delivery. But we observed

that presence of these parameters leads RA as anaesthesia type. Furthermore, they want their babies to be affected as less as possible by aesthetic drugs and want to see their babies after birth and begin breastfeeding.

In our study, regional anaesthesia was preferred more as if the patient required information about the technique. Kocamanoglu et al found 81.8% of obstetricians preferred general anaesthesia due to inadequate muscle relaxation, difficulties with position and delays, whereas only 15% of the anaesthetists opted for general anaesthesia (7). If the surgeon has prejudices against regional anaesthesia, this situation is reflected in the pregnant women who are being followed for nine months. However, in recent years, surgeons have tended to be less resistant to regional anaesthesia. Regional anaesthesia was observed to be more popular among women who have gained information from an anaesthesiologist, or even from internet (10). We think that obtaining information from a person with technical knowledge who has no prejudices about the method and obtaining information from a place in which all the details of the subject are available, like the internet, lead to a lifting of prejudices against and fear of regional anaesthesia methods.

Bukar et al. reported that general anaesthesia was preferred more than regional anaesthesia (70.1% vs 29.9%) for C/S (11). This was reported to be related to the anxiety and fear of being awake. In Bukar's study, reasons, such as not wanting to feel pain and to see or remember anything, which were among the rare reasons in the relevant literature, were found to be the most common reason behind the choice of general anaesthesia in our study. Pain is a subjective experience affected by socio-cultural factors, psychosocial factors, and biological factors (12), which plays a major role in anaesthesia choices of pregnant women in our study. In Bukar's study, women chose regional anaesthesia because they wanted to know what was happening, or they were afraid of not being able to wake up after the operation. However, in our study, all the patients chose regional anaesthesia because they wanted to see their babies immediately after birth. We believe that the difference between the results of Bukar et al. and our study is related to the different employment statuses of the two groups. In our study 44.1% of the respondents were in the employed group, compared to 16.5% in the study of Bukar et al.

Birth anxiety is associated with various factors, such as age, nulliparity, previous psychological problems and history of abuse (13, 14). Anxieties related to childbirth may manifest different aspects. It has been reported that 20% of the pregnant women have a fear of childbirth and 10% have severe fear of childbirth. Fear of pain, fear of being incapable of giving birth and fear of death are the most common causes of fear of childbirth (14). In our study 71 of 750 pregnant women (9.5%) had been diagnosed with panic disorder. A significant difference was observed in the choice of anaesthesia among the patients who were diagnosed with a panic disorder. Pregnant women who were diagnosed with panic disorders prefer general anaesthesia, which we believe was based on the desire to avoid the anxiety of being conscious during surgery, the fear of feeling pain and concerns about remembering this experience in the future, which they thought would be a bad experience.

The possibility that patients may have given false answers to certain questions (particularly regarding their private lives) is a limitation of our study. Given that only three of the 750 respondents admitted having a negative experience was considered an optimistic figure considering the conditions in our country.

In conclusion, our findings revealed that age, gravida, previous type of delivery, previous anaesthesia experience, employment status, monthly income level, educational status, and preoperative information related to anaesthesia and its source and presence of panic disorder all had significant effect on anaesthesiachoice. We believe that the choice of regional anaesthesia will be in line with the level that is required in women who at the ideal pregnancy age, that have had no negative experiences of childbirth or anaesthesia, that have a high sociocultural level, that have obtained information about anaesthesia from reliable sources, and that have not been diagnosed with a panic disorder.

Acknowledgement

This paper is a part of my dissertation "FACTORS AFFECTING ANAESTHESIA PREFERENCES OF THE GRAVID WOMEN WHO ARE TO DELIVER BY CAESAREAN SECTION", published on 03. 12. 2012.

Abbreviations

CS — caesarean sections
WHO — The World Health Organization
RA — regional anaesthesia
GA — general anaesthesia

DECLARATION OF INTEREST

The authors declare that there are no conflicts of interest.

Sažetak

FAKTORI KOJI UTIČU NA IZBOR ANESTEZIJE KOD TRUDNICA ZA POROĐAJ CARSKIM REZOM

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Uvod: Poslednjih godina primećeno je značajno povećanje učestalosti carskih rezova. Iako su povećane u mnogim zemljama, stopa carskih rezova u Turskoj je veća od ciljane. Ovo povećanje učestalosti carskih rezova utiče i na akušersku anesteziju. U ovoj studiji, istražujemo izbor anestezija koje su predviđene za trudnice kod kojih se planira carski rez, kao i stope učestalosti opšte i regionalne anestezije, ali i faktore koji utiču na njihov izbor.

Metode: Upitnik koji se sastojao od 20 pitanja, primenjen je na trudnicama za elektivni carski rez, u periodu između novembra 2011. god. i novembra 2012. god., kako bi se proučila vrsta anestezije koju preferiraju i razlog za njihove izbore. Upitnik je primenjen na trudnice tokom posete, dan pre operacije ili dok su čekale u čekaonici neposredno pre carskog reza.

Rezultati: Naše istraživanje je otkrilo da starost, gravidnost, prethodna vrsta porođaja, prethodno iskustvo sa anestezijom, radni status, mesečni nivo prihoda, obrazovni status, prethodno informisanje o anesteziji, izvor informacija i dijagnostikovanje paničnog poremećaja su uticali na odluku o tome koji tip anestezije će koristiti.

Zaključak: Otkrili smo trudnice sa višim stepenom obrazovanja, koje rade i imaju veći nivo mesečnih primanja, preferiraju oblik regionalne anestezije, a razlog leži u tome da imaju više informacija o samim metodama anestezije, češće koriste internet i informacije koje prikupljaju od ljudi oko sebe ne drže kao predrasude protiv regionalne anestezije. Smatramo da kako se nivo obrazovanja bude povećavao u budućnosti, a populacija pacijenata bude postajala sve svesnija, to će ih uputiti na više istraživanja, a njihove stope preferencija će se menjati.

Ključne reči: Carski rez, izbor anestezije, upitnik.

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Original article

EFFECT OF ANATOMO-TOPOGRAPHIC AND SONOGRAPHIC POLARITY OF THE THYROID NODULES ON THE THYROID MALIGNANCY BY EVALUATING ITS IMPRESSION ON THE RELATIONSHIP BETWEEN THE BETHESDA SYSTEM, TBSRTC, STRAIN ELASTOGRAPHY SCORE AND THE THYROID HISTOPATHOLOGY

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Abstract: **Background:** The goal is to evaluate the association between the topo-sonographic polarity of the thyroid nodules and the thyroid malignancy by analyzing its effect on The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), score of Strain Elastography (SE) for thyroid as Tsukuba Elasticity Score (TES), and histopathologic assessment.

Material and Methods: A preliminary single-center retrospective study was carried out by including the documents of 641 consecutive eligible patients, possessing 770 thyroid nodules which undergone neck ultrasonography (US), Doppler US, SE, and US-guided-fine needle aspiration (FNA) during April 2011 to April 2017. The stiffness had been measured by TES of SE. The ability of the prediction of the malignancy by the polarity of 770 thyroid nodules considering the association between; i) TBSRTC and histopathology and ii) TES and histopathology had been evaluated.

Results: Of the 770 thyroid nodules evaluated, 408 (53.0%) were located at the superior pole (Pol 1) while 362 (47.0%) were at the inferior pole (Pol 0) with 0.9046 AUC and 0.8171 AUC for the association between TBSRTC and histopathology and 0.9280 AUC and 0.7888 AUC for the association between TES and histopathology, respectively. However, those difference were not significant for Pol 1, topographically.

Conclusion: The topograghic and sonographic polarity of the thyroid nodules may not be useful for estimating the thyroid malignancy by using the association between TBSRTC and histopathology with TES and histopathology. However, the association with Pol 1, the superior thyroid pole, was stronger though the difference was not significant.

Key words: Polarity; Elastography; Fine-needle aspiration; Bethesda; TBSRTC; Thyroidectomy.

INTRODUCTION

Fine-needle aspiration (FNA), performed with or without local anesthesia, is an easy and confidential outpatient procedure. The sampling aspirates are get via 23- to 27-gauge, frequently 25- or 27-gauge, needle through the indicated thyroid nodule by repetitive movings (1). The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), a six-diagnostic-category system, is still currently the utilized and acquiesced worldwide, that offer an important interpretation system for reporting FNA cytology (FNAC). The first edition of TBSRTC was structured through a multidisciplinary concensus that was accepted at the Thyroid Fine Needle Aspiration State of the Art and Science Conference, National Cancer Institute (NCI), held in Bethesda, Maryland in 2007 (2). Nine years later, Ali and Vielh presented 'The Bethesda System for Reporting Thyroid Cytopathology: Past, Present, and Future' at The 19th International Congress of Cytology (ICC) in Pacifico Yokohama, Japan, on 30May, 2016 (3, 4). The related preparations for the symposium began 12

months earlier with the designation of international panel, including 16 cytopathologists (5).

Zhang et al presented a late-breaking abstract (6) in May 16-20- 2018, than reported a study (7) in November 2018 about the location of thyroid nodule in terms of both laterality and polarity as a predictor of malignancy. In the present study, it is purposed to evaluate the association between the polarity of the thyroid nodules and their ultrasonography-guided FNAC and its influence on TBSRTC vs. histopathology and Strain Elastography (SE) Score, Tsukuba Elasticity Score (TES), vs. histopathology.

To our knowledge, it is the first study in the English literature analyzing solely the efficacy of the polarity of the nodules as a topographical anatomic feature, forecasting the thyroid malignancy by investigating its impact on the association between i) TBSRTC and histopathology and ii) TES and histopathology in a large serial with the duration of six year.

MATERIAL AND METHODS

From April 2011 to April 2017, a retrospective study was designed by enlisting the data and documents of the patientswith the thyroid nodules with FNAC. To rule out the malignant formations in the thyroid nodules, all the cases had undergonetheneck US, Doppler US, SE application, and ultrasound-guided-FNA (US-g-FNA) to exhibit whether prediction with an anatomo-topographic polarity.

The Criteria for Enrolling into the Study

The inclusion criteria for being enrolled into the present study were possession of the thyroid nodules with the performed non-invasive, the neck US, SE, and invasive, US-g-FNA, applications and evaluation of FNACs based on TBSRTC with the histopathologic outcomes of the thyroidectomy procedures which had been performed for the indicated cases. Nevertheless, the exclusion criteria were the cases with the thyroid nodules, but had not indication for performing US-g-FNA and the cases with the purely cystic thyroid nodules.

Figure 1a: *An ovoid hypoechoic solid nodule, 21.1x8.3 mm, with the regular borders, possessing the minimal cystic apertures, located at the thyroid right lobe superior zoneextending along the isthmus, B-Mode US*

Figure 1b: *Some peripheral vascularization of the nodule in Figure 1a, Doppler US*

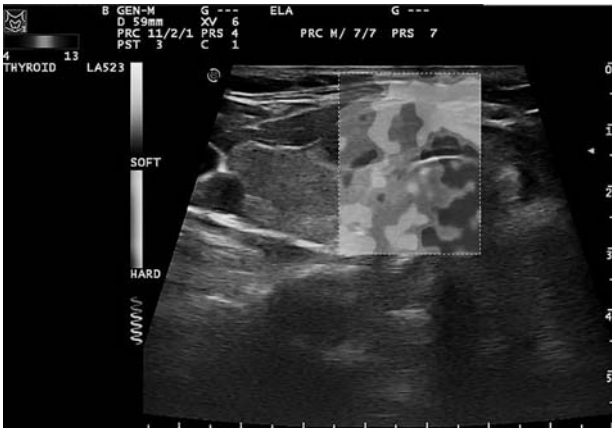

Figure 1c: *The Tsukuba Elasticity Score, TES, 2 of the nodule in Figure 1a, Strain Elastography*

Sonographic evaluation

The sonographic examination and evaluation had performed by using the neck US (Figure 1a), Doppler US (Figure 1b), and SE (Figure 1c) (Esaote MyLab 60, Geneva, Italy) with a linear probe of 4–13 MHz broadband,possessing the mean 12 MHz broadband.

Tsukuba elasticity score and coherent macroscopic/histopathologic characteristics

Sonoelastography of a thyroid nodule is evaluated by a 5-point-strain Itoh-Score or Elasto-Score, TES [8]. TES 1 and 2 (Figure 1c) are evaluated as soft benign nodules. TES 3, the medium consistency, is accepted as usually benign, while TES 4 and 5 are hard nodules and considered as malignant.

US-guided-FNA and FNAC

From each targeted and indicated thyroid nodule, three to eight smears had been prepared byusingthefine needle with 27-gauge (Hayat, 2 ml and 3P with 27G-0.40 x 50 mm, Istanbul, Turkey) by administrating the local anesthesic agent, Prilocaine hydrochloride 2%, i.v. 400 mg/20 ml. The smear materials had been implemented into the 95% alcohol for alcohol fixation and the technique of air fixation performed, then all the prepared materials had submitted to the cytopathologic assessment by haematoxylin-eosin (H&E), PAP, and May-Grünwald-Giemsa (MGG), respectively. Cytopathologic evaluation had been performed considering TBSRTC: (1) non-diagnostic, I (2) benign, II (3) atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), III; (4) follicular neoplasm/suspicious for follicular neoplasm (FN/SFN), IV; (5) suspicious for malignancy (SM), V (6) malignant, VI. Currently, Moss et al (8) reported a systematic review and meta-analysis, exhibitingthe application of FNA should be performed with the smallergaugesof needle (24-27 G). In the present study, all the applications of US-g-FNA had been administrated via the smallest needle with 27 G.

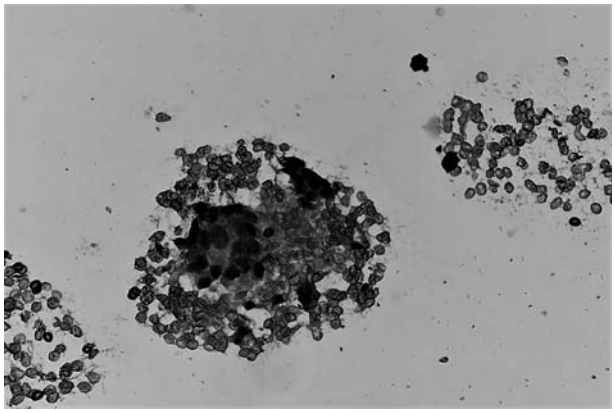

Figure 1d: A photomicrograph, revealing the cytopathology of TBRSTC Category III, (H&E; Original magnification, 20 x 0.40)

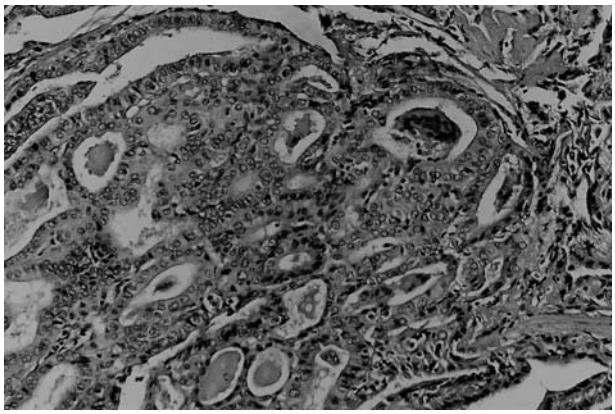

***Figure 2:** A photomicrograph, revealing the histopathology of PTC, (H&E; Original magnification, 20 x 0.40)*

Statistical Analysis

The statistical analyses of the present study were performed by utilizing SPSS 23.0 and NCSS 12.0 computer programs. The descriptive statistics and frequency tables were created to examine the data and variables in the statistical analyses. In addition, the receiver operating characteristic curves (ROC curves) and hyphothesis tests for the diagnostic tests were performed to compare and analyze the diagnostic test performances. ROC curve is a graph showing the performance of a classification model at all classification thresholds. The Z-tests were performed by NCSS 12.0 computer program for comparing the area under the ROC curves (AUCs) for the independent groups. AUC measures the whole two-dimensional area underneath the complete ROC curve, an integral calculus, from (0,0) to (1,1). In addition, AUC provides an aggregate measure of performance across all possible classification thresholds.

RESULTS

An application of US-g-FNA had been performed for a sum of 641 cases with the mean age of 51 ± 2,499 (77.8%) women and 142 (22.2%) men, with 770 indicated thyroid nodules with the mean size of 19 ± 9 mm in diameter which had been exhibited on the sonograghic evaluation during six years. On the basis of polarity, the thyroid nodules located at the superior pole, polarity 1 (Pol 1), and inferior pole, polarity 0 (Pol 0), were detected as 408 (53.0%) and 362 (47.0%), respectively. Cytologically, Bethesda Category I, II, III, IV, V, and VI were detected as 31 (4.0%), 515 (66.9%), 145 (18.9%) (Figure 1d), 41 (5.3%), 37 (4.8%) and 1 (0.1%), respectively. Histopathologically, benign, 191 (85.7%); PTC (Figure 2), 20 (9.0%); FTC, 7 (3.1%); HCC, 5 (2.2%) had been revealed. Of the 770 thyroid nodules examined, 408 (53.0%) were locates at the superior pole while 362 (47.0%) were at the inferior pole. Sonographically, SE Scores, TES 1, 2, 3, 4, and 5, were detected as 187 (24.3%), 368 (47.8%), 164 (21.3%), 39 (5.1%), 12 (1.6%), respectively for 770 thyroid nodules.

The ROC curve of Pol 1 for TBSRTC and histopathology was superior to the one of Pol 0 (Figure 3), indicating the association between TBSRTC and histopathology had been stronger in Pol 1, the thyroid nodules located at the superior poles. However, the significancy of that difference was analyzed by using Z-test ($Z = 1.025$) and it was revealed that the association between TBSRTC and histopathology was not significant with regard to the different groups of the polarity, Pol 0

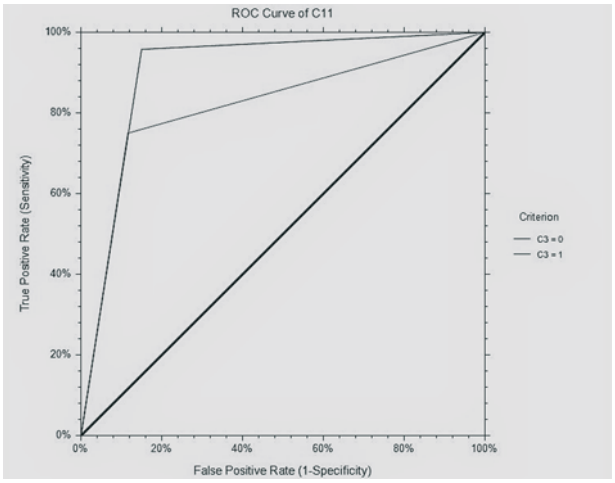

Figure 3: *The Sensitivity, Specificity, TPR, FPR, AUC, and ROC curves of Pol 1 and Pol 0fot comparing the association between TBSRTC and histopathology of the thyroid nodules.*
TPR: True positive rate; FPR: False positive rate; Pol 1: Group of Polarity 1, superior pole; Pol 0: Group of Polarity 0, inferior pole

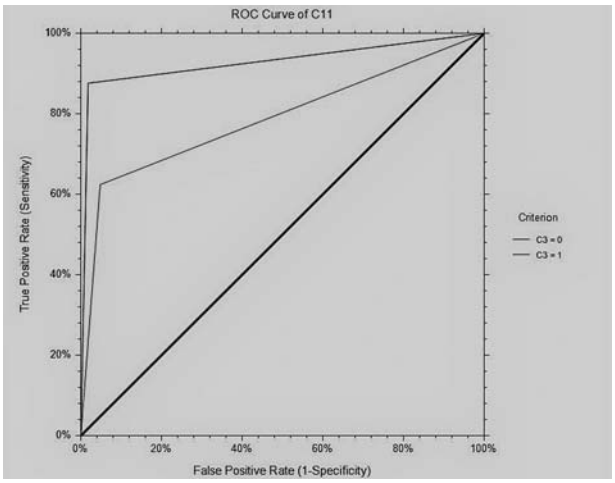

Figure 4: *The Sensitivity, Specificity, TPR, FPR, AUC, and ROC curves of Pol 1 and Pol 0 fot comparing the association between TES and histopathology of the thyroid nodules.*
TPR: True positive rate; FPR: False positive rate; Pol 1: Group of Polarity 1, superior pole; Pol 0: Group of Polarity 0, inferior pole; TES: Tsukuba Elasticity Score

and 1 ($p > 0.05$) (Table 1). Similarly, the ROC curve of Pol 1 for SE score, TES, and histopathology was superior than the one of Pol 0 (Figure 4), indicating the association between TES and histopathology had been stronger in Pol 1, the thyroid nodules in the superior poles. Nevertheless, the significancy of that difference was analyzed by using Z-test ($Z = -1.421$) and it was appeared that the relationship between TES and histopathology was not significant according to the different groups of the polarity, Pol 0 and 1 ($p > 0.05$) (Table 2).

DISCUSSION

The incidence of thyroid cancer, the most frequent endocrine cancer, has significantly increased, recently at higher rate than any other cancer and that increase in its detection is estimated mainly due to common use of

Table 1. *The Z-test for comparing the association between TBSRTC and histopathology with regard to the different groups of the Polarity, Pol 0 and 1*

The Test, Comparing Two AUCs (Empirical Estimation)

H0: AUC 0 = AUC 1
H1: AUC 0 ≠ AUC 1
Total Sample Size: 770

Polarity	AUC	(AUC 0-AUC 1)	Std. Error	Z value	p value
0	0,8171	-0,0875	0,0854	1,025	0,3055
1	0,9046				

TBRSTC: Thyroid Bethesda System for Reporting Thyroid Cytology; AUC: Area under the ROC curve

Table 2. *The Z-test for comparing the association between SE score, TES, and histopathology with regard to the different groups of the Polarity, Pol 0 and 1*

The Test, Comparing Two AUCs (Empirical Estimation)

H0: AUC 0 = AUC 1
H1: AUC 0 ≠ AUC 1
Total Sample Size: 770

Polarity	AUC	(AUC 0-AUC 1)	Std. Error	Z value	p value
0	0,7888	-0,1393	0,0980	-1,421	0,1554
1	0,9280				

SE: Strain elastography; TES: Tsukuba Elasticity Score; AUC: Area under the ROC curve

diagnostic methods such as ultrasound worlwide (9–12). The percentage of clinical ascertaining of the thyroid nodules are 5% for females and 1% for males in non-endemic areas, 50% in autopsy series, and 19-68% by using US as a diagnostic tool in a wide range of of the studied populations (13, 14). US-g-FNAC is rapid, reliable, minimally invasive, cost-effective, and out-patient procedure, used in the determining the surgical indication or follow-up procedures for the suspicious thyroid nodules and attenuating the risk of unnecessary surgery, with approximately 62% to 85% diagnostic accuracy (15, 16). Moss et al (9) propunded that FNA should be performed without aspiration and with smaller needle gauges, 24- to 27- Gauge needles. In the present study, all the FNA performed as US-g-FNA via 27 G, to our knowledge.

Considerable investigations, such as clinical parameters, US patterns of the nodules, Doppler US, repeated US-g-FNA practices, US elastography, core-needle biopsy, intraoperative frozen sections, TBSRTC, TBSRTC II, cytological subclassifications, molecular mutational analyses, and diagnostic thyroid lobectomy, have been performed to be able to distinguish the malign thyroid nodules from the benign ones to refrain from an unnecessary surgical procedure and its possible complications. Unfortunately, any diagnostic tool among them or the other diagnostic methods can precisely warrant the malignant formation of a thyroid nodule to date. Therefore, the clinical management of the indeterminate cytology remains challenging and a non-invasive application, i.e. elastography for the mentioned purposes is still debated. SE is a quasi-static strain imaging, working by the policy of Hooke's law of elasticity which was discovered by the Robert Hooke in 1660. It aims to differentiate the tissues in accordance with their stiffness or elasticity as defined in guidelines of EFSUMB (European Federation of Societies for Ultrasound in Medicine and Biology) (17). SE is applied by comparing the stiffness of the thyroid nodule and paranchyma via Hooke's law. Any pathologic processes change the structure of the related tissues, finally their elasticity.The meta-analyses with the mean sensitivities of 82-92% and mean specificities of 67-92%, considering SE in terms of prediction of malignant thyroid nodules were reported (18, 19, 20).

Currently, Zhang et al (6) presented their study, as a late-breaking abstract, entitled thyroid nodule location on ultrasonography as a predictor of malignancy at the 27th American Association of Clinical Endocrinologists (AACE) meeting, which was held in Boston, MA, May 16-20, 2018. They presented a retrospective study for the period of July 2016 to June 2017 and analyzed the thyroid nodules from 188 patients who had undergone FNA in terms of the laterality (left versus isthmus versus right), polarity (upper versus middle versus lower), microcalcifications, and multi-nodularity.To our knowledge, Zhang's study (6) was the first of its kind to purpose for demonstrating whether an association between the location of thyroid nodule and the likelihood of the malignancy. Afterwards, Zhang et al (7) reported as a publication, entitled "Thyroid nodule location on ultrasonography as a predictor of malignancy" in 1st of November 2018, very recently. They retrospectively reviewed the data of 219 cases with the thyroid nodules who underwent US-g-FNA during one year. In the mentioned study, the demographic features of the cases as well as the laterality, polarity, morphology and multinodularityof the thyroid nodules were analyzed. Majority of the nodules, 79.3% were in the lower pole, while 9.6% in the upper pole and 6.9% in the middle pole. A significantly higher ratio of the thyroid malignancy was recognized in upper pole, 22.2%, comparing the lower, 4.7% and middle pole,15.4%. In the present study, 53.0% of the nodules were recognized at the superior pole, Pol 1, while 47.0% were at the inferior pole, Pol 0. The association between TBSRTC and histopathology had been stronger for the nodules located at the superior poles, however, that difference was not significant with regard to the different groups of the polarity, Pol 0 and 1, which was the anatomo-topographic situation of the thyroid nodules.

Zhang et al studied the laterality of the nodules for predicting the malignancy with the polarityretrospectively from 219 cases with thyroid nodules who underwent FNA in one year. In the present study, 641 cases with 770 thyroid nodules had been investigated retrospectively for the period of 6 years whether the polarity had effected the association between i) TBSRTC and histopathology and ii) TES and histopathology, separately.

To our knowledge, it is the first study in the English literatute, investigating solely the efficacy of the polarity of the nodules as a topographical anatomic feature, forecasting the thyroid malignancy in terms of having influence upon TBSRTC vs. histopathology and TES vs. histopathology. It is also an extended study with 770 thyroid nodules, had undergone US-g-FNA, with a single-center experience of six years.

CONCLUSION

Of the 770 thyroid nodules evaluated, 408 (53.0%) were Pol 1 while 362 (47.0%) were Pol 0 with 0.9046 AUC and 0.8171 AUC for the association between TBSRTC and histopathology and 0.9280 AUC and 0.7888 AUC for the association between TES and histopathology, respectively. However, those difference were not significant for Pol 1.

In conclusion, the topograghic and sonographic polarity of the thyroid nodules had not been useful for estimating the thyroid malignancy by using the association between TBSRTC and histopathology with TES and histopathology. However, the association with Pol 1, the superior thyroid pole, was stronger though the difference was not significant.

Abbreviations

FNA — Fine-needle aspiration
TBSRTC — The Bethesda System for Reporting Thyroid Cytopathology
FNAC — Fine-needle aspiration cytology
SE — Strain Elastography
TES — Tsukuba Elasticity Score
US — Ultrasound
US-g-FNA — Ultrasound guided fine-needle aspiration
H&E — Haematoxylin-eosin
MGG — May-Grünwald-Giemsa
AUS/FLUS — Atypia of undetermined significance/follicular lesion of undetermined significance
FN/SFN — Follicular neoplasm/suspicious for follicular neoplasm
SM — Suspicious for malignancy
ROC curve — The receiver operating characteristic curve
AUC — Area under the ROC curve
PTC — Papillary thyroid carcinoma
FTC — Follicular thyroid carcinoma
HCC — Hürthle cell carcinoma
US-g-FNAC — Ultrasound guided fine-needle aspiration cytology
EFSUMB — European Federation of Societies for Ultrasound in Medicine and Biology
AACE — American Association of Clinical Endocrinologists

Conflict of interest

No conflict of interest relevant to this article has been declared.

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Sažetak

EFEKAT ANATOMSKO-TOPOGRAFSKOG I SONOGRAFSKOG POLOŽAJA TIROIDNIH ČVOROVA NA MALIGNITET TIROIDNE ŽLEZDE EVALUACIJOM IMPRESIJE NA ODNOS IZMEĐU BETESDA SISTEMA, TBSRTC, REZULTATA ELASTOGRAFIJE I HISTOPATOLOGIJE

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Uvod: Cilj je da se proceni povezanost između topo-sonografskog polariteta tiroidnih čvorova i maligniteta tiroidne žlezde analizom njihovih efekata na Betesda sistem za izveštavanje o tiroidnoj citopatologiji (TBSRTC), rezultate elastografije (SE), rezultate Tsukuba elasticiteta (TES skor) kao i histopatološke procene.

Materijal i metode: Preliminarna unicentralna retrospektivna studija je sprovedena analizom medicinske dokumentacije 641 pacijenta koji ispunjavaju uslove, koji imaju 770 čvorova tiroidne žlezde, a kojima je urađen ultrazvuk vrata, dopler, SE, kao i aspiraciju finom iglom pod kontrolom ultrazvuka, u periodu od aprila 2011. do aprila 2017. Krutost je merena pomoću TES i SE. Sposobnost predviđanja maligniteta polaritetom 770 tiroidnih čvorova, je evaluirana, obzirom na povezanost između: i) TBSRTC i histopatologijei ii) TES i histopatologije.

Rezultati: Od 770 evaluiranih tiroidnih čvorova, 408 (53,0%) je bilo locirano u gornjem polu (Pol 1), dok je 362 (47,0%) bilo u donjem polu (Pol 0) sa 0.9046 AUC i 0.8171 AUC za vezu između TBSRTC i histopatologije i 0.9280 AUCi0. 7888 AUC za povezanost između TES i histopatologije. Međutim, te razlike nisu bile značajne za Pol 1, topografski.

Zaključak: Topografski i sonografski polaritet tiroidnih čvorova možda nije koristan za procenu malignosti štitne žlezde analizom povezanosti između TBSRTC i histopatologije sa TES i histopatologijom. Međutim, povezanost sa Polom 1, gornjim tiroidnim polom, bila je evidentna iako razlika nije bila značajna.

Ključne reči: polaritet, elastografija, aspiracij afinom iglom, Betesda, TBSRTC, tiroidektomija.

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Original article

ZOLEDRONIC ACID ADMINISTRATION ENHANCES FRACTURE HEALING IN THE OSTEOPOROTIC FRACTURES IN OVARIECTOMIZED RABBITS

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Abstract: **Objectives:** To evaluate the radiological, histological and mechanical effects on osteoporotic fracture healing of single-dose zoledronic acid (ZA) applied to an animal model with an experimentally created osteoporotic bone fracture.

Methods: A total of 14 adult, female New Zealand rabbits, aged 5-6 months were used in the study. Bone mineral density (BMD) values were calculated from bone densitometry measurements and recorded. Bilateral ovariectomy was then applied to all the rabbits. At 10 weeks after ovariectomy, bone densitometry was again performed on all the animals and the BMD values were compared. Osteoporosis was accepted as having developed in animals determined with a reduction of 28% in BMD values. After the placement of a K-wire intramedullarly in the femurs of the rabbits, a closed fracture was created with the standard method. The animals were then randomly separated into 2 groups as the zoledronic acid group (ZAG) and the control group (CG). An infusion of 0.1 mg/kg ZA was administered to the ZAG animals from the ear vein. With visualisation of bone union rabbits were sacrificed by decapitation. Radiological, mechanical and histological assesments were then applied.

Results: In the histological evaluation, the mean histological score was determined as 5.00 in the ZAG and 3.00 in the CG. The difference between the groups was found to be statistically significant ($p < 0.001$). In the radiological evaluation, the mean score was 7.00 in the ZAG and 6.25 in the CG. Even though higher points were obtained by the ZAG in the inter-observer evaluations, the difference between the groups was not statistically significant ($p = 0.073$). In the mechanical evaluation, the elasticity collapse in negative proportion to rigidity was measured as 2.91 mm in the ZAG and 3.96 mm in the CG ($p = 0.686$). The rigidity data of the ZAG were higher in the mechanical tests but the difference between the groups was not statistically significant ($p = 0.086$).

Conclusion: As the results of the study showed that the ZAG had higher values than those of the CG in all the histological, mechanical and radiological evaluations, the application of a single dose of ZA can be considered to increase the healing of osteoporotic fractures.

Key words: Bone healing; Osteoporosis; Ovariectomy; Zoledronic acid; Animal Model.

INTRODUCTION

Bisphosphonates, which are the most commonly used medications in the treatment of osteoporosis, inhibit bone resorption, creating an anti-catabolic effect. Zoledronic acid (ZA) is the most potent of these medications (1). Due to this anti-catabolic property, the ZA effect on bone healing has been examined in many experimental studies (2, 3, 4). However, the healing of an osteoporotic bone is different from normal fracture healing (5). Therefore, it should be remembered that even after an excellent operation, success will be determined by the strength and quality of the newly formed bone. Although the available clinical evidence is insufficient, the slowdown in bone mechanism in osteoporosis is considered to possibly be responsible for delayed callus maturity and the retardation in bone healing (6). However, although ZA, which is frequently used in osteoporosis treatment, is known to reduce the risk of new fracture formations, its effect on fracture healing in osteoporotic patients is as yet unknown.

AIM

The aim of the present study was to evaluate the effect of ZA, which is commonly used in the treatment of osteoporosis, on the healing of bones with osteoporotic fractures created experimentally in rabbits using radiological, histological and mechanical methods.

METHODS

14 adult female New Zealand rabbits, aged 5-6 months, were obtained from a local laboratory animal application and research center for use in the study. Approval for the study was granted by the Local Ethics Committee for Animal Research. To take the bone densitometry measurements at the beginning of the study, all the animals were administered intramuscular 40 mg/kg ketamine hydrochloride (Ketalar, Pfizer Inc., Istanbul, Turkey) and 5 mg/kg xylazine (Rompun, Bayer Turkish Chemical Inc., Istanbul, Turkey) then positioned prone while under general anaesthesia. The device was calibrated for the animals and the 2^{nd}, 3^{rd} and 4^{th} lumbar vertebrae were scanned. The bone mineral density (BMD) values were calculated as milligram / square centimeter (mg/cm^2) and recorded.

First operation (Ovariectomy)

Under general anesthesia, for surgical prophylaxis, each rabbit was injected 50 mg/kg cefazolin sodium (Sefazol, Mustafa Nevzat Medical Inc. Istanbul, Turkey) intramuscularly. The abdominal cavity was opened with a 4 cm laparotomy incision along the abdominal midline. After reaching the ovaries, the mesovarium and tuba uterina were ligated and ovarian tissues were bilaterally excised. After a 10-week waiting period, the presence of osteoporosis was confirmed by repeated BMD measurements showing a decrease of at least 28% from the previous values.

Second operation (Intrameduller fixation)

A vertical 3 cm incision was made on anterior of the knee. Medial parapatellar arthrotomy was performed to reach the joint. The patella was transferred to the lateral. The knee joint was put in flexion and a 2.5 mm intramedullary K-wire was advanced retrograde so as to center the femur intercondylar area from the patellofemoral joint line level. The end of the K-wire was cut off to avoid contact with the joint (Figure 1). Following the intramedullar placement of a K- wire, a standard closed fracture was applied to the femur using the the three-point technique with the device described by Bonnerans et. al (7). All procedures were applied in the laboratory while the animals were under anesthesia. The fractures produced were confirmed with standard femur antero-posterior and lateral (Shimadzu, Kyoto, Japan) radiographs taken while the animals were still anesthetized. The animals were then randomly separated into 2 groups as ZAG and CG. Animals in CG were administered intravenous saline placebo of 0.9% in the ear vein and the ZAG subjects were administered zoledronic acid (Zometa®, 4mg Flacon, Novartis, Istanbul, Turkey) as 0.1 mg/kg diluted in 10 ml saline using an infusion pump over 15 minutes.

Radiological Evaluation

10 weeks after the second operation radiographic union was observed. All animals were euthanatized by decapitation. The femurs with the implants were disarticulated from the knee and hip joints. All soft tissue was

Figure 1. *Incision, patellar tilt, entrance point of the implant sent for fixation into the femur and its appearance in the intramedullary canal*

removed from the bone. Union evaluation was made from 2 site radiographs using a radiological scoring system of remodelling, bone healing findings and periosteal reactions in the union area (8) (Table 1), Evaluations of the samples were made by two separate radiologists.

Mechanical Tests

4 samples were taken from each group for mechanical evaluation. K-wires were removed from the intramedullar canal before testing. In the three-point bending test, the sample was placed between two supports at L distance and P force was applied on the midpoint. A universal testing device of 250 kN load capacity (ALERGE®, Istanbul, Turkey) was used for the test. To assess the relationship between the force and the amount of collapse at the midpoint, force was applied at 10 mm/minute and the data of the force applied and the amount of collapse were recorded.

Histological Evaluation

Histological evaluation was applied to all samples. For histopathological examination bone tissues were cut into 2-3 mm sections using a spring-saw in order to include the callus tissues formed after the union and these then were put into the decalcification solution (Biodec®, Biooptica, Milano, Italy). We observed that bone tissues have decalcified on the sixth day. The samples were put through alcohol and xylol series with the routine automatic follow-up system (Shandon® Waltham, Massachusetts, USA), and were then embedded in paraffin blocks and cut into circular sections of 4-5 microns. Samples were stained with hematoxylin-eosin. Histological classification of healing was made in accordance with the histological healing scale defined by Huoet. al (9) (Table 2). In the 16th week of the study, one of the subjects in the control group was lost through natural causes and was excluded from the study.

Table 1. *Radiological Scoring system for fracture healing*

Categories	**Scores**
Periosteal reaction	
Full	3
Moderate	2
Mild	1
None	0
Bone Union	
Union	3
Moderate bridge (> %50)	2
Mild bridge (< %50)	1
Nonunion	0
Remodeling	
Full remodeling cortex	2
Intramedullary canal	1
No remodeling	0
Maximum total score	**8**

Statistical Evaluation

Statistical data analysis was carried out using SPSS 22.0 software. Conformity of the data to normal distribution was evaluated with the Shapiro-Wilktest. For the non-normally distributed data, the Mann-Whitney U test was used to compare two groups. In the comparison of dependent groups, the Paired Samples t-test was applied to normally distributed data. The interclass correlation coefficient was used to determine inter-rater reliability. The level of statistical significance was accepted as $\alpha = 0.05$.

RESULTS

In bone densitomentry, pre-ovariectomy mean BMD value was found 354 ± 16 mg/cm^2. At 10 weeks after ovariectomy, bone densitometry was again performed

Table 2. *Histological evaluation scale for fracture healing histological state*

Histological State	Score
Mature (lamellar) bone	10
Immature bone and small amount of mature bone	9
Completely immature (woven) bone present	8
Mostly immature bone and little cartilage present	7
Cartilage and immature bone of equal amounts	6
Mostly cartilage and small amount of immature (woven) bone	5
Cartilage tissue present	4
Fibrous tissue and cartilage tissue of equal amounts	3
Mostly fibrous tissue and small amount of cartilage tissue	2
Fibrous tissue is present in the callus tissue of the histological section examined	1

and mean BMD value found as 255 ± 25 mg/cm^2. 28% fall was observed between the initial BMD values of the rabbits and the BMD values at the 10th week following the ovariectomy. These changes between the preoperative and postoperative 10th week data were found to be statistically significant ($p < 0.001$).

For the radiological evaluation, the radiographs taken at 10 weeks after the formation of the fracture (Figure 2) were scored by 2 independent observers using the previously-mentioned scoring system.

Inter-rater reliability was found to be high at the end of the scorings (ICC = 0.908; 95% CI (0.737-0.970)). Although the ZAG scores were higher than those of CG, the statistical analyses showed no significant difference between the groups ($p = 0.073$) (Table 3).

Following the mechanical evaluation the change in the load applied in relation to the amount of collapse in the CG samples and the values obtained are presented in Table 4. This table also shows the results concerning rigidity. When these results were assessed statistically, the differences between the groups were not found to be significant ($p = 0.086$).

In the histological evaluations, a large amount of connective tissue and newly formed capillary vessels

Figure 2. *The view of anteroposterior and lateral radiographs of closed fractures that were created by standard methods and the view of bone union after 10 weeks*

Table 3. *Bone healing values of the groups*

Control Group				**Zoledronicacid group**			
	Observer 1	Observer 2	Mean		Observer 1	Observer 2	Mean
Sample 1	3	4	3.5	Sample 1	7	7	7
Sample 2	6	6	6	Sample 2	6	6	6
Sample 3	7	7	7	Sample 3	8	8	8
Sample 4	6	6	6	Sample 4	7	7	7
Sample 5	7	6	6.5	Sample 5	8	7	7.5
Sample 6	7	7	7	Sample 6	7	7	7
Sample 7	-	-	-	Sample 7	7	7	7
Median	**6.25**			**Median**	**7.00**		**P = 0.073**

Table 4. *Biomechanical results of the samples pertaining to control and zoledronic acid groups*

Sample name	**Elastic force (N)**	**Bending Moment (Nmm)**	**Elastic collapse (mm)**	**Rigidity (Nmm2)**
C1	304	7.223	5,38	1.009.104
C2	167	3.961	2,96	1.005.347
C3	128	3.029	2,43	936.652
C4	334	7.505	4,97	1.019.859
Mean	235	5.592	3,96	1.007.225
ZA 1	196	4.415	3,45	862.706
ZA 2	216	4.856	2,37	1.380.693
ZA 3	392	8.829	6,06	983.428
ZA 4	255	5.739	1,87	2.070.403
Mean	235	5.297	2,91	1.182.060
p value	**0,686**	**0,686**	**0,686**	**0,886**

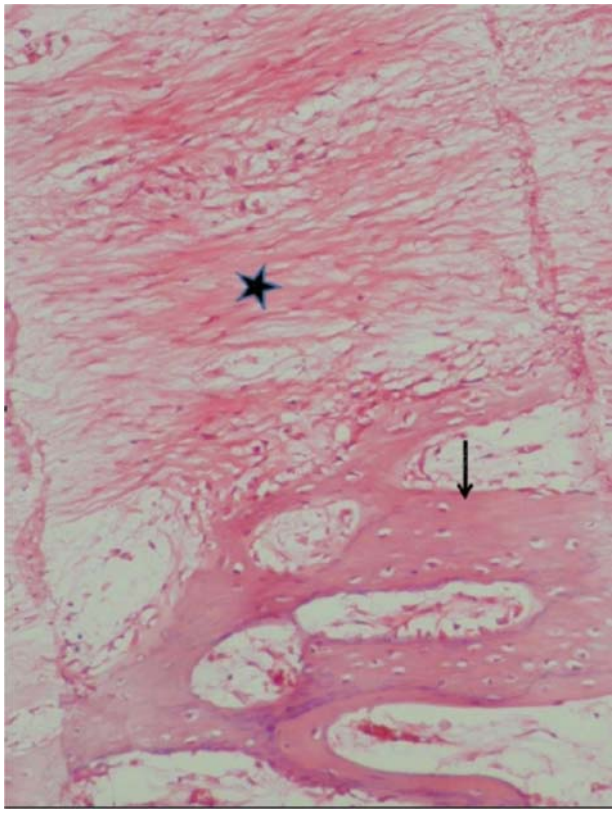

Figure 3. *CG, ligament cells along the fracture healing line (star) and cartilage cells (arrow) healing score: 3 (x10, Haematoxylin-Eosin)*

were observed in the CG samples (Figure 3), and immature bone tissues composed of chondrocytes and chondroblasts were dominant in the ZAG samples (Figure 4). As a result of the microscopic scorings, the difference between the two groups was found to be statistically significant ($p < 0.001$) (Table 5).

DISCUSSION

In this study of the effect of zoledronic acid, which is commonly used in the treatment of osteoporosis, the results showed a positive effect of the administration of a single-dose on experimentally produced osteoporotic fractures in a rabbit model.

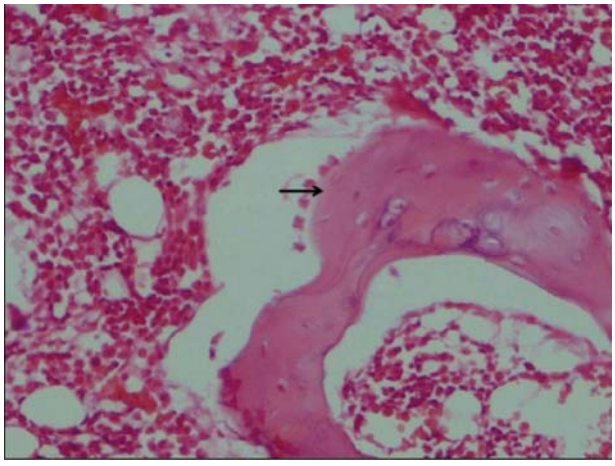

Figure 4. *ZAG, Arrow showing the formation of immature bone in the fracture healing line. Healing score: 5 (x 20, Haematoxylin -Eosin)*

There is a complex relationship between osteoporosis and bone healing. Although available clinical evidence is insufficient, the slowing down of bone metabolism has been considered to be responsible for the delayed maturity of callus and the slowdown in bone healing (6). A review of the literature shows that in general the effects of bisphosphonates on bone healing in animal models are controversial. While some studies have stated that bisphosphonates delay and decrease callus formation but do not affect bone healing quality (10, 11), others have reported an increase in the amount of callus on the fracture line and accordingly, an improvement in fracture resistance (12). Still other experimental studies have shown that although ZA administration increases callus volume and improves mechanical endurance in the callus area, it causes delays on normal bone healing (2, 3, 4). With currently gradually increasing use in the treatment of osteoporosis, the effect of ZA on bone healing following fracture in osteoporotic patients is not yet exactly known. In experimental stud-

Table 5. *Histological healing scores pertaining to control and zoledronic acid groups*

Rabbit	Control Group		Zoledronic acid Group	
	Macroscopic Appearance	**Microscopic score**	**Macroscopic appearance**	**Macroscopic score**
1	Midpoint	3	Distal 1/3	5
2	Distal 1/3	3	Distal 1/3	7
3	Midpoint	3	Distal 1/3	4
4	No callus	3	Midpoint	5
5	Distal 1/3	3	Distal 1/3	5
6	Midpoint	3	Proximal 1/3	5
7	-	-	Midpoint	4
Median		**3,00**		**5,00** $p < 0,001$

ies, methods such as bilateral ovariectomy applications, low calcium diets along with ovariectomy, corticosteroid administrations following ovariectomy, denervation of the local skeletal area, gravity-free environment and stabilization of the bone with different techniques are used for the production of osteoporotic animal models (13, 14, 15). In the current study, all the animals were ovariectomized bilaterally to produce experimental osteoporosis. Prior to the ovariectomy, the BMD of all the rabbits was measured and recorded. In studies carried out to produce experimental osteoporosis in literature, rabbit bones have been examined in biomechanical and densitometrical aspects after bilateral ovariectomy and osteoporotic changes have been observed to occur in at the end of 6-8 weeks (13, 16). In a study by Baofeng et al., it was stated that human osteoporosis is defined as a decrease of > 2.5 standard deviation (SD), which corresponds to an approximate 25% fall in BMD. At the end of week 10 in that study, a 36% decrease was observed in the BMD of the rabbits which had been applied with ovariectomy and methylprednisolone (15). Similarly, in the current study, a 10-week period was waited for the development of osteoporosis following ovariectomy in rabbits. BMD was measured again in all the rabbits and the values were compared to the preoperative values. A 28% fall was observed in the bone mineral densities after the ovariectomy in comparison with the previous values. This difference between the two measurements was also found to be statistically significant ($p < 0,001$).

In a study that examined the effects of bisphosphonates on fracture healing, Madsen et al. produced closed fracture models in rat tibias by giving the subjects clodronate and no significant difference was seen in the amount of callus and bone bridging along the fracture line in the direct radiographic assessments carried out in the 4th week of fracture healing (10). It was stated that this could have been due to the short healing period of 4 weeks. In another study, Tarvainen et al. examined the effect of clodronate on fracture healing in osteopenic and normal rats (15, 17). Callus endurance was not determined to be affected by drug administration in the osteopenic group, but it decreased at the end of 8 weeks in the non-osteopenic group. With these findings, it was concluded that bisphosphonates could have different effects on the healing of normal and osteopenic fractures. Accordingly, in the current study, which aimed to examine the effects of ZA on osteoporotic fracture healing, the periosteal reactions in the area of union, the bone healing findings and remodeling were based on the radiological evaluation of healing. Union was present in all 13 of the preparates included in the evaluations. In the analysis of the direct radiographs, it was concluded that remodelling was better in the area of the fracture in the ZAG samples and that bone union was better in this group since more periosteal reactions were present along the fracture line. The ZAG scores were higher than those of the CG and the averages were also higher. That the scorings were applied by two different observers also strengthened this argument. However, these findings were not found to be statistically significant ($p = 0.073$).

In the assessment of the biomechanical test results of the study, no statistically significant difference was found between the analyses of the samples of ZAG and CG ($p = 0.086$). However, the finding that the amount of collapse was lower and the values of rigidity were higher in the ZAG samples suggested that the resistance in this group was higher than the samples in the control group and therefore ZAG was more resistant.

In a study by Y. Hao et al. ZA was applied to femur fractures of osteoporotic rabbit models on the postoperative 1st day, 1st week and 2nd week and evaluations were made of bone healing (18). As a result of biomechanical tests, the strongest group was found to be the one that had been given the drug on the 1st day while the least strong group was the drug-free control group. The biomechanical findings of the current study are compatible with the related literature, and ZA administration was shown to have a positive effect in biomechanical terms. However, although the elastic collapse and rigidity values of ZAG were found to be higher in the analyses, the differences between the groups were not statistically significant ($p = 0.086$). Histological evaluation of fracture healing was applied according to the histological healing scale developed by Huo et al (9). According to the evaluation results, fibrous tissue, cartilage tissue, immature (woven) bone and mature (lamellar) bone were found in the section examined and the preparates were assessed based on the amounts. Although partial cartilage tissue and newly formed capillary veins were present in the callus tissue of the CG samples, the fact that fibrous tissue was much more prevalent in comparison to ZAG samples, and that cartilage tissue, mature and immature bone tissues were relatively less indicated that less microscopic healing occurred in the control group. Based on these findings, the healing scores were higher in ZAG and the difference between the groups was found to be statistically significant ($p < 0.001$). In another study which examined the effects of ZA on osteoporotic rat models following ovariectomy, it was found that ZA inhibited excessive bone resorption, and increased callus development and mineralization, although it prevented endochondral and fibrocartilage callus from developing into immature bone (18). In yet another study in which the effect of alendronatewas evaluated on fracture healing in dogs, it was observed that bone formation was

not affected in the alendronate group while the amount of callus formation was twice or three times higher compared with the control group (19).

Limitations of the current study can be said to be that radiological evaluations were applied with a subjective assessment scale rather than an objective assessment method such as Micro CT, and that biomechanical tests were applied to only 8 of the 13 animals. This was because of concerns that samples required for the histological examinations might have been damaged.

CONCLUSION

According to the findings obtained from this study, in histological assessment of bone healing in ZAG and CG, better healing was observed in ZAG and the data were found to be statistically significant. However, although ZAG values were higher in mechanical and radiological evaluation, there was no statistically significant difference between the two groups. On the basis of these data, zoledronic acid administration can be considered to have a positive effect on fracture healing in osteoporotic fractures. Conflicting results in the related literature can be attributed to the differences in subject types examined, the variety of drugs used, methods of drug injection, drug amounts and differences in timing.

Abbreviations

ZA — zoledronic acid
BMD — Bone mineral density
ZAG — zoledronic acid group
CG — control group

DECLARATION OF INTEREST

The authors declare that there are no conflicts of interest.

Licensing

Sažetak

PRIMENA ZOLEDRONIČNE KISELINE UNAPREĐUJE ZARASTANJE OSTEOPOROTIČNIH FRAKTURA KOD OVARIJEKTOMISANIH ZEČEVA

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Cilj: Evaluacija radioloških, histoloških i mehaničkih efekata primene mono-doze zoledronične kiseline na zarastanje osteoporotičnih fraktura kod životinja kod kojih je eksperimentalno izazvana osteoporotična fraktura kosti.

Metode: Ukupno 14 odraslih, zečeva ženki sa Novog Zelanda, starosti 5-6 meseci, je ispitivano u studiji. Mineralna gustina kosti (BMD) je određivana densiometrijom i memorisana. Potom je izvršena obostrana ovariektomija kod svih zečica. Desete nedelje nakon ovariektomije je ponovo urađena densiometrija kod svih zečica i BMD je poređena. Osteoporosa je potvrđena kod životinja kod kojih je došlo do redukcije od 28% u BMD vrednostima. Nakon plasiranja K-žice intramedularno u femur zečica, bliska fraktura je izazvana standardnom metodom. Životinje su potom nasumično podeljene u 2 grupe: zolendroična kiselina grupu (ZAG) i kontrolna grupa (CG). Infuzija od 0,1 mg/kg zolandreične kiseline je data ZAG životinjama kroz ušnu venu. Nakon što su životinje dekapitirane, radiloške i mehaničke procene su izvedene.

Rezultati: U histološkoj evaluaciji, srednji histološki skor je bio 5.0 u ZAG grupi i 3,0 u CG grupi. Razlike među grupama su statistički značajne ($p < 0,001$). U radiološkoj evaluaciji srednja vrednost je bila 7,00 u ZAG i 6,25 u CG grupi. Iako je ZAG grupa dobila više bodova tokom evaluacije, razlika između grupa nije bila statistički značajna ($p = 0,073$). U mehaničkoj evaluaciji kolaps elastičnosti u negativnoj proporciji sa krutošću je izmeren i to 2,91 mm u ZAG i 3,96 mm u CG grupi ($p = 0,686$). Podaci o rigidnosti ZAG su bili viši u mehaničkim testovima, ali razlika između grupa nije bila statistički značajna ($p = 0,086$).

Zaključak: Kako su rezultati studije pokazali da ZAG ima veće vrednosti od CG u svim histološkim, mehaničkim i radiološkim procenama, može se smatrati da primena jedne doze ZA povećava zarastanje osteoporotskih fraktura.

Ključne reči: zarastanje kostiju, osteoporoza, ovarijektomija, zolendronična kiselina, životinjski model.

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Original article

THE USE OF THE THIOL-DISULFIDE HOMEOSTASIS AS AN INDICATOR OF OXIDATIVE STRESS IN PEDIATRIC ADENOID HYPERTROPHY PATIENTS

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Abstract: **Background:** To the best of our knowledge, no study has yet focused on the association between the adenoid hypertrophy (AH) and the thiol-disulphide balance.

Objectives: The purpose of this study is to evaluate the relation between AH and the thiol-disulphide balance, which is used as a marker of oxidative stress (OS), by measuring its exchange using a novel technique.

Study design: Non-randomized and prospective clinical study.

Material and methods: The present study consisted of 25 patients who presented to the otolaryngology outpatient clinic of our hospital with AH. An age- and sex-matched control group was composed of 24 healthy children. The effect of AH on the thiol-disulphide balance in children was evaluated. We also evaluated the total antioxidant status (TAS), total oxidant status (TOS), oxidative stress index (OSI), ferric reducing/antioxidant power (FRAP), glutathione (GSH), lipid hydroperoxide (LOOH) and advanced oxidation protein products (AOPP) to assess the OS status of children.

Results: The TOS was significantly higher in the AH group and the TAS was significantly higher in the control group (all p values < 0.05). The mean values of OSI, LOOH and AOPP were significantly higher in the AH group than the control group (all p values < 0.05). Native thiol and total thiol levels were lower in the AH group than those of the control group (p < 0.05). Disulphide level and disulphide/native thiol and disulphide/total thiol ratios were higher in the AH group than that of the control group (all p values < 0.05).

Conclusion: In conclusion, we observed decreased thiols with increased disulphide values in children with AH compared with the controls. Thiol/disulphide homeostasis can be used as an indicator of OS in children with AH.

Keywords: thiol-disulphide balance, adenoid hypertrophy, oxidative stress.

INTRODUCTION

Pediatric upper airway obstruction is majorly caused by adenoid hypertrophy (AH). The most common clinical manifestations of AH include breathing through the mouth, blockage in nasal airways, speech with a nasal voice and obstructive sleep apnea. These patients are also at high risk for developing chronic sinusitis and middle ear infection (1). As the airways are congested, the patient may experience sleep deprivation or snoring, and sleep apnea. The manifestations are more severe for the pediatric cases, where the congested airways may lead to chronic sleep apnea and hypoxia. In more severe cases, the patient may develop pulmonary hypertension together with unilateral heart failure (majorly right-sided) (2, 3). There may be hypoxic metabolic changes in the cellular level; that include dissolution of cellular compartments (including the lysosomes), which leads to the discharge of free oxygen radicals.

In the homeostatic state, the human body can stabilize the free radical formation by producing antioxidants (4). There are several suggested mechanisms for oxidative stress (OS) formation. They include increased formation of ROS (reactive oxygen species) and free radicals, and diminished ability to manage the oxidative stress. As the radicals are very unstable reactants, they are likely to cause injury to the tissue by reacting with the cellular molecules such as proteins, nu-

cleic acids, fats (specifically in the cell membrane), and carbohydrates. The purpose of antioxidant production is to prevent the possible negative effects of the free radicals. If they are not counterbalanced, the radicals may cause extensive damage, various diseases, or even death (5-9).

The thiol-disulfide homeostasis is one of the major mechanisms to prevent OS in the body (9). An automated process is used for the measurement of the thiol and disulfide levels (individually or cumulatively). With the help of this new method, the thiol-disulfide homeostasis can easily be used as an indicator of OS. The literature reports several different disorders that are associated with the thiol/disulfide balance (10-15); however, there are no studies that have examined its association with AH. Therefore, this study was planned to investigate the association of the thiol/disulfide homeostasis with AH, through the aforementioned newly developed method. The study will mainly focus on the thiol-disulfide and pediatric AH cases. The study includes the application of several other indicators such as total antioxidant status (TAS), total oxidant status (TOS), oxidative stress index (OSI), ferric reducing/ antioxidant power (FRAP), glutathione (GSH), lipid hydroperoxide (LOOH) and advanced oxidation protein products (AOPP)] in order to correctly determine the OS among the subjects.

MATERIAL AND METHODS

The Study Sample

The study was conducted in accordance with the principles of the Declaration of Helsinki, applicable regulatory requirements and Good Clinical Practices. This study was approved by the Ethical Committee of the Hospital (17-11-13). An informed consent form was obtained from the parents of the participants prior to being included in the study.

The study was conducted in a non-randomized and prospective manner. The experimental group (AH) consisted of 25 subjects that were chosen among the patients of the Otolaryngology Outpatient Clinic of the Hospital (7 females and 18 males; mean age, 5.20 ± 1.70 years). The control group (C) consisted of 24 healthy children without sleep related complaints and AH (using flexible endoscopy) that were chosen to match the study group regarding gender and age (7 females and 17 males; mean age 5.25 ± 1.75 years).

The subject's airways were transnasally/transorally examined with a flexible endoscope. Following the endoscopic examination, the subjects were graded according to the blockage in the choanal space as follows: Grade 1, 25% blockage; Grade 2, 25 to 50% blockage; Grade 3, 50 to 75% blockage; Grade 4, 75 to 100% blockage. The subjects in the experimental group had Grade 3 or 4 adenoid hypertrophy, and all of these subjects underwent transoral cold curettage adenoidectomy (with general anesthesia). The exclusion criteria were as follows: presence of nasal septal deviation, sinonasal infection, hematological disease, chronic inXammatory diseases, major craniofacial abnormalities, chromosomal syndromes, previous adenotonsillectomy or adenoidectomy; and taking any kind of medication two weeks prior to the study.

Blood sample collection

Blood samples were collected between 8 and 10 a.m. Ten milliliters of venous blood was collected from all participants into vacuum biochemistry tubes. The blood samples were centrifuged for 10 minutes at 4000 rpm; after waiting for 30-45 minutes, the sera were separated and stored at -80 °C in Eppendorf tubes until analysis.

Measurement of the Parameters

The thiol-disulfide assay

The modified Ellman reagent was used to determine the total thiol content of the samples. The dynamic disulfide amount was calculated as follows: [(total thiol content-native thiol content)/2]. The disulfide/thiol ratio was calculated by the obtained results as stated by Erel and Neselioglu (16).

The glutathione (GSH) assay

The glutathione (GSH) level was assessed through its reaction with OPA (1mg/ml o-phthaldialdehyde in methanol) as per the modified technique of Koyuncu et al. (17). The obtained GSH level was used as a benchmark. The samples were assessed via the microplate reader (Spectra max M5, USA), with excitation at 345 nm and emission at 425 nm. The results were expressed in nmol/mL (for the serum) and nmol/g (for the wet tissue).

Ferric Reducing Antioxidant Power (FRAP) Assay

The FRAP assay is a colorimetric method that measures the ferric-reducing ability of the plasma. It is easily determined through a computerized method, which makes it a practical indicator of "antioxidant power". In an acidic medium, ferric ions are reduced to ferrous form, leading to the formation of a colored ferrous-tripyridyltriazine complex (18). In the FRAP assay, the antioxidants are used as reducing agents against

Fe(III). The ferric tripyridyltriazine complex [Fe(III), colorless] is reduced to ferrous-(2,4,6-tripyridyl-s-triazine)2 [Ferrous(II), blue]. Subsequently, the color change is quantitatively measured through spectrophotometry at 593 nm. The absorption values are positively correlated with the antioxidant power of the sample. Thus, the FRAP assay can be used to quantitatively measure the reducing/antioxidant power of a given sample. A mixture of 1000 μL (100 μL of sample + 900 μL of diluted water) was prepared and mixed with 2 mL of FRAP reagent. After being thoroughly mixed, the mixture was kept in dark for 30 min. It was subsequently analyzed with a spectrophotometer at 593 nm. The following formula was used to calculate the FRAP value: FRAP value μM = [Abs. (sample) × FRAP value of Std (μM)] / Abs. of Std.

Assay of advanced oxidation protein products

The advanced oxidation protein products (AOPP) were spectrophotometrically determined through a modified version of the Witko, Nguyen, and Descamps-Latscha method (19). Samples were prepared as follows: 100 μL of supernatant was diluted with phosphate-buffered saline (1:5), 5 μL of 1.16 M potassium iodide was then added to each tube, followed by 10 μL of acetic acid two minutes later. The new mixture was analyzed with the spectrophotometer at 340 nm (blank reference: 1000 μL of PBS, 50 μL of Potassium Iodide (KI), and 100 μL of acetic acid). The chloramine-T absorbance was linear at 340 nm within the range of 0 μmol/L to 100 μmol/L. AOPP concentrations were expressed as micromoles per liter of chloramine-T equivalent.

Total oxidant status (TOS) Assay

The TOS levels were measured with the fully automated Rel Assay kit (Rel Assay Diagnostics kit, Turkey) and an autoanalyzer (Thermo Scientific Multiskan GO, ThermoFisher Scientific, Vartaa, Finland). The results were expressed in ìmol H2O2 equivalent/L.

Total antioxidant status (TAS) Assay

The TAS measurements were made with the fully-automated RL0031 Rel Assay® kit (Rel Assay Diagnos-tics kit; Mega T2p, Gaziantep, Turkey) and an autoanalyzer (Thermo Scientific Multiskan GO, ThermoFisher Scientific, Vartaa, Finland). The results were expressed in micromolartrolox/L.

Oxidative stress index (OSI) Assay

OSI indicated the degree of OS by comparing the TOS and TAS values. The OSI value was calculated using the following formula: OSI (arbitrary unit) = TOS (ìmol H2O2 Eq/l)/TAS (mmol Trolox Eq/l) × 100 (20).

Lipid hydroperoxide (LOOH) Assay

Serum lipid hydroperoxide (LOOH) concentrations were spectrophotometrically measured (SpectraMax M5, Molecular Devices, USA) using automated iron oxidation-xylenol orange test (21).

Statistical analysis

The data were analyzed with SPSS for Windows, version 21.0. Descriptive statistics (mean ± standard deviation, median, interquartile range) were used to interpret the data. The differences between the two groups were analyzed with the student's t-test and the differences between the median values were analyzed with the Mann-Withney U- and the chi-square tests. The qualitative data were analyzed using the Pearson χ^2 test and Fisher's exact test. *p*-value < 0.05 was considered to be statistically significant.

RESULTS

The biochemical values and demographic characteristics of all patients are presented in Table 1. It was determined that the groups were not significantly different regarding their demographic data ($p > 0.05$). Compared to the control groups, the AH group's TOS values were higher and TAS values were lower ($p < 0.05$). Also, the mean OSI, LOOH and AOPP levels were found to be significantly higher among the AH patients ($p < 0.05$ for all variables). However, the FRAP and GSH values were lower in the AH group ($p < 0.05$).

The native thiol and total thiol levels were lower and the disulfide levels were higher in the AH group (AH), compared to the control group(C) [native thiol = 367.1 ± 47.5 lmol/L (AH) vs 476.9 ± 63.5 lmol/L (C), $p < 0.05$; total thiol = 412.2 ± 48.3 (AH) lmol/L vs 525.8 ± 64.4 lmol/L (C), $p < 0.05$; disulfide = 28.67 ± 7.97 lmol/L (AH) vs 20.91 ± 3.83 lmol/L (C), $p < 0.05$]. Consequently, the disulfide/native thiol and the disulfide/total thiol ratios were found to be higher for the AH group [disulfide/native thiol ratio = 7.96 ± 2.59% (AH) vs 4.44±0.88 % (C), $p < 0.05$; disulfide/total thiol = 7.05 ± 2.14 % (AH) vs 4.01 ± 0.77% (C), $p < 0.05$]. The difference between native thiol/total thiol ratios of the two groups was not statistically significant ($p = 0.07$).

Table 1. *Comparison of biochemical values and demographic characteristics of groups*

	Patients with AH (n = 25)	**Controls (n = 24)**	**P**
Age, years	5.20 ± 1.70	5.25 ± 1.75	0.920[m]
Male gender, n (%)	18 (72.0)	17 (71.0)	0.928[m]
TAS (mmol Trolox equiv./lt)	1.2 ± 0.23	1.42 ± 0.26	0.004[m]
TOS (μmol H2O2 equiv./lt)	16.8 ± 2.31	12.16 ± 2.77	< 0.001[m]
OSI (AU)	1.42 ± 0.25	0.87 ± 0.23	< 0.001[m]
FRAP (μmol/l)	686.1 (150.0, 974.0)	897.5 (877.2, 964.2)	< 0.001[m]
GSH (nmol/ml)	2.34 (0.64, 4.75)	4.98 (4.87, 5.36)	< 0.001[m]
LOOH (nmol/l)	7.21 ± 2.34	4.78 ± 2.24	0.001[m]
AOPP (μmol/liter)	50.31 ± 15.94	39.29 ± 15.27	0.017[m]
NATIVE THIOL (SH)	367,1 ± 47,5	476,9 ± 63,5	< 0,001[m]
TOTAL THIOL	412,2 ± 48,3	525,8 ± 64,4	< 0,001[m]
DISULPHIDE (SS)	28,67 ± 7,97	20,91 ± 3,83	< 0,001[m]
% SS/SH	7,96 ± 2,59	4,44 ± 0,88	< 0,001[m]
% SS/TOTAL THIOL	7,05 ± 2,14	4,01 ± 0,77	< 0,001[m]
% SH/TOTAL THIOL	88,97 ± 3,74	90,55 ± 1,92	0,070[m]

[m] Mann–Whitney U-test

All variables are showed as n(%) for categorical data or as mean ± SD or median (minimum, maximum) for continuous data with or without a normal distribution, respectively. AH, adenoidal hypertrophy; TAS, total antioxidan status; TOS, total oxidan status; OSI, oxidative stres index; FRAP, ferric reducing/antioxidant power; GSH, glutathione; LOOH, lipid hydroperoxide; AOPP, advanced oxidation protein products.

DISCUSSION

It was observed that the disulfide/native thiol and the disulfide/total thiol ratios were significantly higher among the pediatric AH patients compared to the healthy controls. To the best of our knowledge, this is the first study to show that the thiol/disulfide homeostasis can be used as an indicator of OS among pediatric AH cases.

Thiols are a group of organic compounds with a sulfhydryl group (-SH) that is bound to a carbon (C) atom. The sulfhydryl groups can be oxidated to form disulfide bonds and later be reduced back to thiol groups, thus creating the thiol/disulfide homeostasis. The thiols play an important role in maintaining the oxidative condition of the body. They act as a defense mechanism against the reactive oxygen species that cause oxidative stress. Their other functions include apoptosis, detoxification, antioxidant protection, and regulation of cellular enzymatic activity (16, 22). Most organs and systems are sensitive to oxidative stress and redox products. Hence, the disturbance of the oxidative balance can lead to pathologies in structural and functional levels. Previously, it was only possible to measure the thiol/disulfide homeostasis. It is currently possible to separately measure both compounds with the Erel & Neselioglu method (16). Several studies have used this method to evaluate different acute and chronic conditions (6, 9-15).

Insufficient thiol levels may lead to several disorders; such as bipolar disorder, atopic dermatitis, cardiovascular disorders, neurological disorders and cancer (9-15, 23-26). Thus, it is important to be able to determine the state of the thiol/disulfide balance.

The current literature indicates that the thioldisulfide homeostasis can be used as an indicator of OS for various otorhinolaryngological diseases. Simsek et al. (27) have applied this method to nasal polyposis patients. Kara et al. (24) have similarly used the disulfide/native thiol and disulfide/total thiol ratios to determine the OS state of pediatric tonsillopharyngitis patients.

It is also used to demonstrate the OS status of pediatric adenotonsillar hypertrophy patients (5). These studies were used as the basis of our research regarding the application of the said method for the pediatric AH patients. Gul et al. (28) have found that the serum disulfide levels had increased among adult AH patients. This oxidative shift is due to the obstructed airways. Several other studies also indicated that adenoid hypertrophy is positively correlated with OS. There are different possible OS indicators for AH patients. However, the thiol-disulfide homeostasis has not been previously used to evaluate the OS of children with AH. We

have found that the children with AH had an increased thiol-to-disulfide ratio, and the OS parameters had significantly increased.

It should be noted that the oxidant molecules may interact and affect the measurements. The TOS measurement is required to determine the general OS state of a patient, as it provides more information compared to the antioxidants' individual measurements (29). Indeed, the TAS measurements are more commonly used compared to individual measurements of antioxidants. In this study, we evaluated TOS, TAS, FRAP, LOOH, AOPP, OS¤ and GSH levels of the experimental (AH) and control (C) groups. It was determined that among AH patients, the OS parameters (TOS, OSI, LOOH and AOPP) had increased and antioxidant parameters had decreased (GSH, TAS, FRAP). This indicates increased generation of free radicals due to increased exposure to external pathogens. These findings indicate the need for adenoidectomy among these patients to prevent OS. If left untreated, OS may lead to various diseases such as diabetes mellitus, cancer, chronic kidney disease and liver disorders.

We should be noted that our study has several limitations: the small sample size and the lack of post-adenoidectomy data. However, the initial post-adenoidectomy findings may not be reliable, as anesthesia and surgical treatment lead to operational stress. This leads to short-term changes in the OS status of the patient (30). It is also certain that the direct effects of the surgical procedure, together with the effects of tissue repair after adenoidectomy, are followed by an acute and long-lasting systemic oxidative stress. Nevertheless, the inXuence of this treatment could not be estimated as the oxidative parameters were not measured immediately after adenoidectomy. However, the samples should be collected at a later point during follow-up. Another limitation of study was the lack of information on the severity of the sleep disordered breathing. Polysomnographic evaluation can be difficult in small children and the correlation between the severity of the sleep disordered breathing and OS parameters in small children is limited.

CONCLUSION

It was determined that the AH patients had decreased thiol and increased disulfide levels compared to healthy controls. Increased oxidative stress may cause serious disorders in children with AH. The thiol-disulfide homeostasis can be used as an easy method to determine the OS status of patients. These initial findings should be confirmed through further prospective studies with larger samples.

Abbreviations

OS — oxidative stress
AH — adenoid hypertrophy
TAS — antioxidant status
TOS — total oxidant status
OSI — oxidative stress index
FRAP — ferric reducing/antioxidant powe
GSH — glutathione
LOOH — lipid hydroperoxide
AOPP — advanced oxidation protein products

Conflict of Interest

No author has any potential conflict of interest.

Financial Disclosure

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Sažetak

KORIŠĆENJE TIOLDISULFIDNE HOMEOSTAZE KAO INDIKATORA OKSIDATIVNOG STRESA KOD PEDIJATRIJSKIH PACIJENATA SA ADENOIDNOM HIPERTROFIJOM

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Uvod: Do sada nijedna studija se nije fokusirala na povezanosti adenoidne hipertrofije i tioldisulfidne homeostaze.

Cilj: cilj naše studije bio je da se proceni povezanost između adenoidne hipertrofije i tioldisulfidne homeostaze, koja se koristi kao jedan od markera oksidativnog stresa (OS), tako što smo merili njegovu raznemu koristeći novel tehniku. Dizajn studije: nerandomizovana i prospektivna klinička studija.

Materijal i metode: U studiju je uključeno 25 pacijenata, koji su lečeni u ambulanti otorinolaringologije u našoj bolnici, a koji su bolovali od adenoidne hipertrofije. Kontrolna grupa je mečovana prema polu i godinama života, a brojala je 24 zdrava deteta. Ispitivali smo efekat adenoidne hipertrofije na balans tiol-disulfida. Takođe smo ispitivali ukupni antioksidativni status (UAS), ukupni oksidativni status (UOS), indeks oksidativnog stresa (OSI), redukujuća/antioksidativna snaga gvožđa (FRAP), glutation (GSH), lipidnu hidroperoksidazu (LOOH) i produkte viših oksidativnih proteina (AOPP) prilikom određivanja OS statusa kod dece.

Rezultati: UOS je bio statistički značajniji u AH grupi, kao i UAK koji je bio statistički značajno viši u kontrolnoj grupi ($p < 0,05$). Srednja vrednost OSI, LOOH i AOPP bile su statistički značajno više u AH grupi u odnosu na kontrolnu grupu ($p < 0,05$). Nativni tiol a i ukupni nivoi tioldisulfida bili su viši u AH grupi u odnosu na kontrolnu grupu ($p < 0,05$). Disulfidni nivoi, odnos disulfid/nativni tiol, kao i disulfid/ukupni tiol odnos je bio statistički značajano viši u AH grupi u odnosu na svoju kontrolnu grupu ($p < 0,05$).

Zaključak: U zaključku možemo istaći da smo u ovoj studiji dobili rezultate koji ukazuju na snižen nivo tiola, kao i povećan nivo disulfidnih vrednosti kod dece sa AH u odnosu na svoje kontrole. Tiol/disulfid homeostaza može biti indikator oksidativnog stresa kod dece sa AD.

Ključne reči: tiol-disulfid balas, adenoidna hipertrofija, oksidativni stres.

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Original article

ANALYSIS OF THE EFFECT OF THE ANTIDEPRESSANT SERTRALINE ON THE LENGTH OF QT INTERVAL IN PATIENTS WITH DEPRESSION AND ALCOHOL DEPENDENCE

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Abstract: **Introduction and Aim:** Depression in psychiatry covers a large area of mental pathology and it is one of the most complex problems of modern medicine with broad implications for the health of the individual and the society as a whole. Depression is also a frequent companion of alcohol addiction. The aim of this study was to investigate the effect of the antidepressant drug sertraline on the length of QT interval in depressed patients with alcohol dependence. **Patients and methods:** This research included male patients (older than 18 years of age) suffering from alcohol addiction, who were also diagnosed with depression, that is, depressive disorder, at the beginning of hospitalisation, on the basis of DSM-IV (Diagnostic and statistical manual of mental disorders) criterion and positive Hamilton Rating Scale for Depression (HRSD). The study included 49 patients treated with antidepressant sertraline for 20 days. In our study, the global QTc interval (12 leads) was determined automatically by applying ECG device of the producer and type "Schiller Cardiovit AT-1", which uses "SCHILLER ECG Measurement and Interpretation Software for Children and Adult ECGs". Measured/empirical values of data were statistically processed in SPSS 16.0 programme package for Windows. Methods of descriptive statistics and methods of statistic testing of hypotheses were used. **Results:** In our study, in spite of the vulnerability of patients due to the heart damage and the liver dysfunction arising from alcohol consumption, as well as altered patients' drugs metabolism, no elongation of QTc interval resulting from the application of sertraline was established ($p = 0.735$). The average prolongation of QTc interval of 1.633 ms was observed (95% CI = 8.005 ms, 11.270 ms). **Conclusion:** Our study does not indicate that the antidepressant drug sertraline has a statistically significant effect on the prolongation of the QT interval of depressed patients with alcohol dependence.

Key words: alcohol addiction, depression, comorbidity, QT interval, sertraline.

INTRODUCTION

Depression in psychiatry covers a large area of mental pathology and it is one of the most complex problems of modern medicine with broad implications on the general health of the individual as well as on the society as a whole. Major depressive disorder is more frequent for alcohol addicts than in the general population (1). **The aim** of this study was to investigate the effect of antidepressant drug sertraline on the length of the QT interval of depressed patients with alcohol dependence.

PATIENTS AND METHODS

This researched included male patients (older than 18 years of age) suffering from alcohol addiction and treated at the Department of Addictive Diseases of the Banja Luka Psychiatric Clinic of the University Clinical Centre of the Srpska Republic and the Psychiatric

Clinic of the University Clinical Centre in Novi Sad, in whom depression, that is, depressive disorder, was diagnosed at the very start of hospitalisation, on the basis of DSM-IV criterion (2) and positive Hamilton Rating Scale for Depression (3). The study included 147 patients, out of which 49 by a method of random selection were treated by the antidepressant sertraline. Due to the necessity of applying anxiolytics in relieving and preventing the symptoms of alcoholic abstinence syndrome in patients, anxiolytic in equal doses (bromazepam a 3 mg: 1,1,2) was applied in the course of research. Values of gamma-glutamyltransferase (GGT), as indirect indicators of the intensity of alcoholism and liver cell lesions (hepatocytes), as well as electrolyte status (Sodium, Potassium, Calcium and Magnesium) and values of creatine kinase isoenzyme MB (CK-MB) were determined in these patients at the beginning of the study and on the twentieth day upon admission to treatment. These parameters were determined in serum by applying Olympus AU680 chemical analyser (Olympus America Inc.; Centerville, Pa., USA).

In order to be included in the study, patients had to satisfy the following criteria: to have a clinically diagnosed alcohol addiction and to satisfy the criteria under DSM-IV for depressive disorders. It was also necessary for them to have normal referential values in electrolyte findings (Na, K, Ca, Mg), not to have heart rhythm disorders or diagnosed heart diseases. The referential values of electrolytes were the working referential values that are used at the Clinical Centre Banja Luka: Na 130-147 mmol/L; K 3.2-5.2 mmol/L; Ca 2.2-2.7 mmol/L, and Mg 0.5-1.1 mmol/L.

Patients who do not satisfy the above-stated criteria, patients with diagnosed congenital Long QT syndrome, Brugada syndrome, acute infective diseases, autoimmune and malign diseases, as well as patients who take the drugs which prolong QT interval, were not included in the study. The research was approved by the Ethical Committee of the Clinical Center Banja Luka, and the patients gave their written consent for participating in the study.

The existence of alcohol addiction and depression was assessed on the basis of autoanamnestically obtained data and clinical observation. DSM-IV criteria were used for the purpose of diagnosing alcoholic addiction and depression (2). Hamilton scale (HRSD: Hamilton Rating Scale for Depression) (3) was used for quantifying the weight of depression. The version containing 17 items was used. The weight of depression was determined pursuant to the following scoring system: a) 0-7 score is an indicator that depression is not present; b) 8-15 score speaks in favour of the existence of minor (slight) depression; c) score ≥ 16 speaks in favour of existence of major (high) depression.

Antidepressive therapy, that is, sertraline was applied with 49 patients during 20 days, whereby optimal doses of the antidepressant, i.e. doses recommended by the drug producer (sertraline a 50 mg 1,0,0) were used. Sertraline belongs to the group of selective serotonin reuptake inhibitors (SSRIs).

Long QT interval represents a marker of the development of ventricular arrhythmia (torsade de pointes-TdP) and sudden death. Electrocardiographic image (ECG finding) including the measurement of the length of QT interval was made with the patients in the course of hospitalisation in the stated time periods, namely: 1. at the beginning of the study, before the application of the relevant antidepressant at 11 a.m.; 2. on the 20th day after the application of the relevant antidepressant, at 11 a.m. The stated time matching the period of ECG check-up was done due to circadian changes in the electrophysiological changes of the heart (4). Due to the impact of the sine rhythm on the length of QT interval and for the adequate comparison between subjects, the QT interval is corrected by the value of the heart frequency, the so-called QTc interval (5). Because of deferred adaptation of the QT interval to the values of heart frequency, ECG measurement was done following the establishment of stable heart frequency (6). The measurement was done with patients in the resting (lying) position in the course of 20 seconds.

In our study, the global QTc interval (12 leads) (7, 8) was determined by an automatic application of ECG device of the producer and type "Schiller Cardiovit AT-1", which uses "SCHILLER ECG Measurement and Interpretation Software for Children and Adult ECGs" (developed by SCHILLER AG, Altgasse 68, CH-6341 Baar, Switzerland, see http://www.schiller.ch). Global QTc interval represents the interval with the earliest QRS onset and the latest T end in any lead. Global QRS complex in our study was shorter than 120 ms, which excludes the impact of extended depolarisation of ventricles on the length of QT interval. The analysis included patients with technically regular ECG findings (without interference, background noise, 'wondering' of the isoelectric line). Examination of automatic measurement by the coincidence of heart frequencies in V3 lead using the classical method was done. The patients with double and biphasic T waves were not included in the study, while the T wave amplitude was greater than 0.2 mV (7).

The measured/empirical data values were statistically processed in the SPSS 16.0 software package for Windows. Methods of descriptive statistics and methods of statistical hypothesis testing were used. As the methods of the first selection, parametric methods were used. In the case of a violation of the assumptions about the normality of the distribution and the homo-

geneity of the variance, the corresponding nonparametric methods were used. The control of variability and the confounding was performed by the repeated measures test and by the application of multifactor regression models with determining the degree of collinearity between the tested independent variables. Statistical conclusions are derived from 2-tailed p values, and significance levels $p < 0.05$.

RESULTS

The average values of HRSD score in depressed patients with alcohol dependence, depending on the administration of sertraline are shown in Table 1.

Statistically significantly lower HRSD score values were ascertained after sertraline administration ($p < 0.001$) (Table 1). To test the significance of the differences, the t test of the dependent samples was used, since the assumption about the normality of the differences was not disturbed (diff. HRSD score Shapiro-Wilk test: $p > 0.05$).

The average values of gamma glutamyl transferase (GGT) in depressed patients with alcohol dependence are shown in Table 2.

A statistically significant reduction in serum GGT values of patients on the 20th day of study with a significance level of $p < 0.001$ was ascertained. To test the significance of the difference, the sign test of pairs was used (Table 2). High values of standard deviation (SD) are the result of the presence of a large number of patients with high serum GGT values. The highest serum GGT was recorded in the group of patients before administration of the antidepressant (926.0 U / L).

The average values of creatine kinase isoenzyme MB (CK-MB) in depressed patients with alcohol dependence, depending on the administration of sertraline, are shown in Table 3.

A statistically significant decrease in the value of CK-MB, i.e. mitigation of the degree of myocardial damage was established on the 20th day of the study after administration of sertraline ($p = 0.032$). To investigate the significance of the difference, Wilcoxon's rank test with a sign was used (Table 3).

Table 4 shows descriptive QT interval data for depressed patients with alcohol dependence prior to administration of sertraline.

There was no statistically significant correlation between the length of the QTc interval (prior to the ad-

Table 1. *Average values of HRSD score in depressed patients with alcohol dependence, depending on the administration of sertraline*

Antidepressant	HRSD score before administration		HRSD score after administration		Sig. p
	Mean	SD	Mean	SD	
Sertraline	18.33	7.928	9.71	4.082	< 0.001*

HRSD: (Hamilton Rating Scale for Depression)
* t test of dependent samples

Table 2. *Average values of gamma glutamyl transferase (GGT) in depressed patients with alcohol dependence, depending on the administration of sertraline*

Antidepressant	GGT (U/L) before administration		GGT (U/L) after administration		Sig. p
	Mean	SD	Mean	SD	
Sertraline	115.655	146.2732	91.516	105.8785	< 0.001

Table 3. *Average values of creatine kinase isoenzyme MB (CK-MB) in depressed patients with alcohol dependence, depending on the administration of sertraline*

Antidepressant	CK-MB (ng/L) before administration		CK-MB (ng/L) after administration		Sig. p
	Mean	SD	Mean	SD	
Sertraline	15.00	4.730	14.47	4.686	0.032

Table 4. *Length of QTc interval in depressed patients with alcohol dependence before administration of sertraline (global QTc Base)*

Descriptive Statistics

	N	Minimum	Maximum	Mean	SD
Global QTc Base (ms)	49	375	449	409.29	19.210

ministration of sertraline) and the serum GGT values (alcohol intensity) (p = 0.230), serum CK-MB values (myocardial damage) (p = 0.869) and HRSD score (intensity of depression) (p = 0.128) (Table 5). The assumptions of the multiple linear models were satisfied: the normality of residual distribution (Shapiro-Wilk test p = 0.508), homoscedasticity of residuals (Figure 1), and the absence of collinearity between independent variables (high value of the tolerance parameter and the low value of the variance inflation factor VIF). However, due to the low eigenvalue of 0.037 and the highest condition index of 9.440, we still tested the correlation between independent variables. Since the CK-MB residuals deviate from the normal distribution and show a negative asymmetry (skewness), they are transformed into a positive asymmetry (gamma distribution) by reflection. This was taken into account when interpreting the coefficients of the independent variables which have had reflected CK-MB (R_CK-MB) for the dependent variable. The reflection was done in such a way that the CK-MB empirical value was subtracted from the maximum value of CK-MB enlarged for one unit (max CK-MB + 1). To test the significance of the difference, a generalized linear model of the gamma with long linkand robust estimator was used. A statistically negative correlation of GGT and R_CK-MB was ascertained (regression coefficient B = -0.0014, p < 0.001). That is, higher values of GGT are associated with higher values of CK-MB i.e. greater degree of damage to the myocardium. HRSD / R_CK-MB correlation (p = 0.900) and HRSD / GGT correlation (p = 0.980) have not been ascertained.

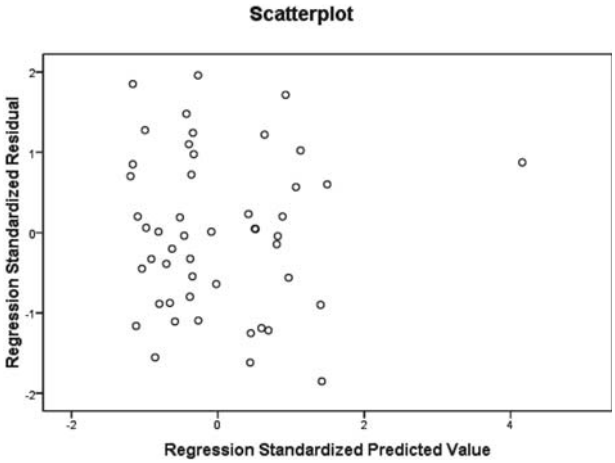

Figure 1. *Diagram of dissipation of standardized residuals of multiple linear regression model of dependence of QTc interval length in depressed alcoholic patients before the application of sertraline. The graph does not show dispersion of residuals to the side (fan out or fan in), and eo ipso heteroscedasticity*

Table 6 shows descriptive QT interval data for depressed patients with alcohol dependence after administration of sertraline.

The generalized linear model (subclass gamma with a log link- robust estimator) was used to test corre-

Table 5. *Multiple linear regression model of the dependence of QTc interval length in depressed patients with alcohol dependence prior to administration of sertraline*

Coefficients[a]

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig. p	Collinearity Statistics	
	B	Standard Error	Beta			Tolerance	VIF
(Constant)	395.262	11.176		35.366	< 0.001		
GGT	0.023	0.019	0.179	1.216	0.230	0.944	1.060
CK-MB	0.099	0.597	0.024	0.166	0.869	0.943	1.060
HRSD score	0.536	0.346	0.221	1.549	0.128	1.000	1.000

GGT: gamma glutamyl transferase (U/L)
CK-MB: creatine kinase isoenzyme MB (ng/L)
HRSD: Hamilton Rating Scale for Depression
VIF: variance inflation factor
a. Dependant variable: Global QTc Base (ms)

Table 6. *Length of QTc interval in depressed patients with alcohol dependence after administration of sertraline (global QTc on the 20th day)*

Descriptive Statistics

	N	Minimum	Maximum	Mean	SD
Global QTc 20th Day (ms)	49	362	483	410.92	27.498

lationof the QTc interval length in depressed patients with alcohol dependence after administration of sertraline (in alcoholic abstinence). There was no statistically significant correlation between the length of QTc interval (after sertraline administration) and serum GGT (alcohol intensity) (p = 0.437), serum CK-MB (myocardial damage) (p = 0.896) and HRSD score (intensity of depression) (p = 0.309) (Table 7). There was no statistically significant correlation between independent variables: GGT / R_CK-MB (p = 0.295), HRSD / R_CK-MB (p = 0.990), and HRSD / GGT (p = 0.502). In thosecases, a generalized linear model of the gamma with the log link and robust estimator was also used.

Since there is no statistically significant differences in patients' QTc intervals before and after administration of sertraline from the normal distribution (diff. QTc Shapiro-Wilk test: p = 0.182), the t-test of the dependent samples (Paired-Samples T Test) was used. There was no statistically significant difference in QTc interval length after sertraline administration (p = 0.735) (Table 8, Figure 2). The average QTc interval prolongation was 1.633 ms(95% CI = -8.005 ms, 11.270 ms). Therefore, prolongation of the QTc interval length greater than 11.270 ms in depressed patients with alcohol dependence after administration of sertraline can be expected in 2.5% of cases.

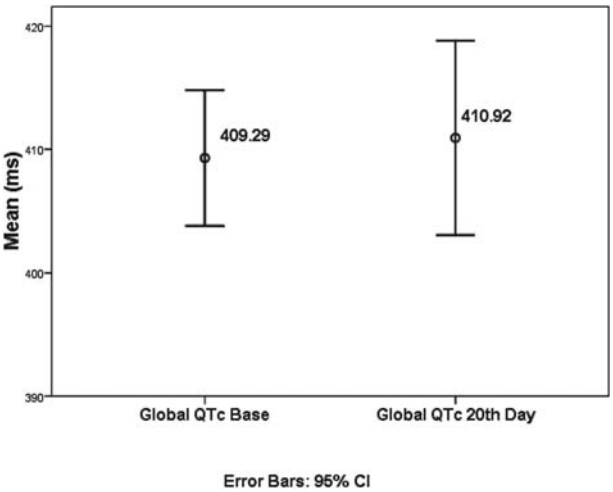

Figure 2. *Length of QTc interval in depressed patients with alcohol dependence depending on the administration of sertraline*

DISCUSSION

After administration of sertraline, a statistically significant decrease in the creatinine kinase value of

Table 7. *Generalized Linear Model of the dependence of the QTc interval length in depressed patients with alcohol dependence after administration of sertraline (in alcoholic abstinence)*

Parameter Estimates

Parameter	B	Standard Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	Sig. p
(Intercept))	6.028	0.034	5.962	6.095	31516.763	1	< 0.001
GGT	0.00006	0.00007	- 0.00008	0.0002	0.603	1	0.437
CK-MB	0.0002	0.0017	- 0.003	0.004	0.017	1	0.896
HRSD score	- 0.0019	0.0019	- 0.006	0.002	1.036	1	0.309
(Scale)	0.005[a]						

GGT: gamma glutamyl transferase (U/L)
CK-MB: creatine kinase isoenzyme MB (ng/L)
HRSD: Hamilton Rating Scale for Depression
Dependent variable: Global QTc 20th Day (ms)
Model: (Intercept), GGT, CK-MB, HRSD score
a. Computed Based on the Pearson Chi-Square.

Table 8. *Significance of difference in length of QTc interval in depressed patients with alcohol dependence, depending on the administration of sertraline*

Paired Samples Test

	Paired Differences					t	df	Sig. p (2-tailed)
	Mean (ms)	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
Global QTc 20th day – Global QTc base	1.633	33.553	4.793	-8.005	11.270	0.341	48	0.735

isoenzyme MB (CK-MB) on the 20th day of the study was observed ($p = 0.032$) (Table 3). This result would indicate the cardio-protective effect of sertraline on the reduction of myocardial damage of depressed patients with alcohol dependence. It should be kept in mind that the reduction of myocardial damage may also be due to the abstinence from alcohol of the patient group examined in hospital conditions. However, this information certainly requires further analysis and research.

Given the effect on the QTc interval, Sicouri et Antzelevitch (9) classify sertraline into a group of drugs that are poorly associated with torsade de pointes (TdP) and QTc prolongation (group 4), and venlafaxine, e.g. in group 2 (drugs for which there are reports that they are affiliated with TdP, but so far there is no reliable evidence that they cause TdP). For further clarification, group 1 belongs to drugs that can be claimed to cause TdP. Authors (10) indicate the safety of the use of sertraline, and negate their effect on the length of the QTc interval. They also highlight the safety of sertraline in patients who have suffered a myocardial infarction, which could also be explained by the results of our own study on the reduction of myocardial damage after administration of sertraline. Wenzel-Seifert et al. (11) in meta-analysis confirm the occurrence of TdP on paroxetine and venlafaxine, but not sertraline. Okayasu et al. (12) using the multiple regression model indicate the dependence of the prolonged QTc interval on the sole use of tricyclic antidepressants (amitriptyline: $p < 0.05$ and clomipramine: $p < 0.01$), on the useof the same drugs in the combination with antipsychotic drugs ($p < 0.05$), and with the older age and female patients ($p < 0.01$). Sertraline and paroxetine in that study did not show a statistically significant influence on the length of the QTc interval. In the study of Sala et al. (13) antidepressants (sertraline, paroxetine, venlafaxine) in combination with antipsychotic drugs prolonged QTc interval (Fisher Exact Text, $p < 0.05$), but the monotherapy of antipsychotics did not. The limitation of that study is a small number of subjects (19 women in both groups) and the use of the other antidepressants in combination with antipsychotic drugs, which nevertheless do affect the length of QTc (other SSRIs e.g. citalopram, tricyclic clomipramine) (12, 14).

We see (from the presented literature) that sertalin is not associated with a significant prolongation of the QTc interval, that is, this effect is at least smaller than with other antidepressants from the SSRI group or tricyclics. Significant prolongation of the QTc interval occurs when sertraline is used in combination with other drugs known to prolong the QTc interval so that the isolated effect of sertraline remains unclear. The prolongation of the QTc interval is also due to poisoning or over dosage with sertraline. Thus PatanP et al. (15) cite TdP in a female person (72 years old) due to the use of sertraline in combination with digoxin, sotalol, and acenocoumarin. Boer et al. (16) present the case of prolongation of QTc interval after suicide over dosage with sertraline (2250 mg), diazepam (200 mg) and temazepam (400 mg). The QTc interval was 525 ms. Hoehns et al. (17) cite an example of a sudden death of a patient (26 years old), with symptoms of paranoid schizophrenia, obsessive-compulsive disorder, major depression, sleep apnea syndrome and akathisia. Patient therapy included clozapine 100 mg twice daily (therapy started four years before death), risperidone 3 mg twice daily, sertraline 200 mg once daily, atenolol 50 mg twice daily, and lorazepam 0.5 mg four times daily. The authors assume that the cause of death is clozapine-induced cardiomyopathy (which is confirmed by an autopsy finding) or clozapine and / or sertraline-induced arrhythmia.

There are also studies that say the opposite, that higher doses of sertraline have not been associated by significant QTc interval changes. Barbey et Roose in meta-analysis (18) indicate a much lesser toxicity of SSRI antidepressant to an ECG finding in isolated poisoning compared to tricyclic antidepressants. It is interesting that poisoning with thirty times higher doses than the usual therapeutic daily dose was not accompanied by more pronounced symptoms. However, what these authors did not emphasize, and should bear in mind, is the pharmacokinetic properties of the drugs (e.g., time of absorption), as well as the implementation of early therapeutic poisoning measures that can explain the milder symptomatology of high-dose SSRIs. In combination with alcohol and other medicaments, the toxicity of these drugs increases significantly. Alderman (19) also excludes significant effects of sertraline on the length of the QTc interval in case of overdose. High doses of sertraline (200 mg) in combination with pimozide and cisapride did not cause QTc interval prolongation, although these drugs do prolong the QTc interval. The limitation of that study would be a small sample (fifteen patients in both examined groups).

Unlike the previous ones, in our study we examined the isolated effect of sertraline on the length of the QTc interval in the population of patients with alcohol dependence, for which data in the literature are missing. We also emphasize that the results refer to the therapy doses of sertraline that are recommended by the manufacturer (50 mg, 1.0.0). In our study for the control of alcohol abstinence syndrome, bromazepam was used, for which no effects were confirmed to prolong the QTc interval (20). Although the examined patients are susceptible to the effects of drugs that prolong the QTc interval, either due to the direct effects of alcohol, liver damage, or concomitantdepression, no statisti-

cally significant difference in the QTc interval was observed after sertraline administration (p = 0.735) in our study (Table 8, Figure 2). An average prolongation of the QTc interval of 1.633 ms was observed (95% CI = -8.005 ms, 11.270 ms).

CONCLUSION

Higher serum gamma glutamyl transferase (GGT) concentrations (as a parameter that reflects the intensity of alcoholism) were statistically significantly associated with the higher creatine kinase isoenzyme MB (CK-MB) values, i.e. with the degree of damage to the myocardium. In depressed patients with alcohol dependence, after the administration of sertraline, a decrease in CK-MB was observed, what certainly requires further analysis and research. In our study a statistical probability of 2.5% indicates that the QTc interval prolongation will be greater than 11.270 ms after administration of sertraline in the depressed patients with alcohol dependence.

Abbreviations

GGT — gamma glutamyl transferase
CK-MB — creatine kinase isoenzyme MB
HRSD — Hamilton Rating Scale for Depression
SD — standard deviation
VIF — variance inflation factor

DECLARATION OF INTEREST

The authors declare that there are no conflicts of interest.

Licensing

Sažetak

ANALIZA DEJSTVA ANTIDEPRESIVNOG LEKA SERTRALINA NA DUŽINU QT INTERVALA KOD DEPRESIVNIH PACIJENATA SA ALKOHOLNOM ZAVISNOŠĆU

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Uvod i Cilj: Depresija u psihijatriji pokriva veliko područje mentalne patologije i predstavlja jedan od najsloženijih problema savremene medicine sa širokim implikacijama na opšte zdravlje pojedinca i na probleme društva u celini. Depresija je i čest pratilac alkoholne zavisnosti. Cilj ovog istraživanja je bio da se istraži dejstvo antidepresivnog leka sertralina na dužinu QT intervala depresivnih pacijenata sa alkoholnom zavisnošću. **Bolesnici i metode:** Ovim istraživanjem obuhvaćeni su pacijenti muškog pola (stariji od 18 godina), oboleli od alkoholne bolesti kod kojih je na početku hospitalizacije na osnovu DSM-IV (Diagnostic and statistical manual of mental disorders) kriterijuma i pozitivne Hamiltonove skale za procenu depresije (HRSD) dijagnostikovana depresija tj. depresivni poremećaj. Studija je obuhvatila 49 pacijenata muškog pola kod kojih je ordiniran antidepresiv sertralin tokom 20 dana. U našoj studiji globalni QTc interval (12-odvodni) određivan je automatski primenom EKG aparata proizvođača i tipa "Schiller Cardiovit AT-1" koji koristi "SCHILLER ECG Measurement and Interpretation Software for Children and Adult ECGs". Izmerene/empirijske vrednosti podataka statistički su obrađivane u SPSS 16.0 programskom paketu za Windows. Korišćene su metode deskriptivne statistike i metode statističkog testiranja hipoteza. **Rezultati:** Iako se radi o populaciji pacijenata osetljivoj na dejstvo lekova koji produžuju QTc interval, bilo zbog direktnog dejstva alkohola, oštećenja jetre ili intenziteta depresije, nije utvrđena statistički značajna razlika u dužini QTc intervala nakon ordiniranja sertralina (p = 0.735). Uočeno je prosečno produženje QTc intervala od 1.633 ms (95% CI = -8.005 ms, 11.270 ms). **Zaključak.** Naša studija nije ukazala da antidepresivni lek sertralin utiče statistički značajno na produženje QT intervala depresivnih pacijenata sa alkoholnom zavisnošću.

Ključne reči: alkoholna zavisnost, depresija, komorbiditet, QT interval, sertralin.

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THE RESULTS OF ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION WITH AUTOGENOUS HAMSTRING TENDONS

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Abstract: **Introduction:** Anterior cruciate ligament (ACL) injuries are the most common type of injury among knee ligament injuries. Despite the high success rates at ligament reconstruction with arthroscopic techniques, efforts for choosing the best grafts and fixation materials and appropriate post-operative rehabilitation are still ongoing. **Materials and Methods:** Between January 2007 and December 2010, 105 patients who underwent arthroscopic anterior cruciate ligament reconstruction using autogenous hamstring tendons were included in our study. The mean follow-up time was 16.3 months (7-46 months). The patients were evaluated according to physical examination findings like Lachman tests, Pivot-Shift, anterior drawer tests, thigh circumference measurement and clinical scores like Lysholm, IKDC score and VAS scores. Results: All patients underwent arthroscopy using standard arthroscopy portals. The residues of the ACL were cleaned and notchplasty was performed, and the semitendinosus and grasilis tendons were placed with transtibial technique in accordance with the trace of the natural ACL.

Preoperatively, the Lysholm score was 56.16 ± 17.4 and postoperatively, the score was 90.16 ± 6.6 and the result was statistically significant. Lachman was found to be 86.7% negative, pivot shift was 100% negative and the anterior drawer test was 95.2% negative. Preoperative VAS was 6.28 ± 1.9 and postoperative VAS was 3.41 ± 1.2. According to the IKDC score, 4,8% of the patients were A, 41% B, 41,9% C and 12,4% D groups, 54,8% of the patients in the postoperative evaluation. A, 36.2% B, 8.6% C and 1% D groups. 12% of the patients felt numbness around the graft site. No other complication was observed. **Conclusion:** When ACL surgery with hamstring tendons is performed with appropriate surgical technique, satisfactory results are obtained. Anterior knee pain and patella-related complications are frequently seen at patellar tendon grafts. This problem can be a reason for the preference of hamstring tendons in ACL repairs.

Key words: anterior cruciate ligament; reconstruction; hamstring; rehabilitation.

INTRODUCTION

The number of knee-related injuries are increasing nowadays due to the increase in sports awareness. Anterior cruciate ligament (ACL) injuries are the most common type of injury among knee ligament injuries. The efforts to make the diagnosis goes back to the years before Christ in the historical development. Until today's modern techniques many different surgical methods which began in the 1800's has been used in this type of injury.

Despite the high success rates at ligament reconstruction with arthroscopic techniques, efforts to achieve better understanding the etiological factors, choosing the best grafts and fixation materials and appropriate post-operative rehabilitation are still ongoing.

In this study, we aimed to evaluate the results of anterior cruciate ligament reconstruction with hamstring autogenous grafts according to the current literature.

MATERIAL AND METHODS

Between January 2007 and December 2010, a total of 112 patients underwent anterior cruciate ligament reconstruction. 7 patients were reconstructed with allografts and other 105 patients underwent arthroscopic anterior cruciate ligament reconstruction with autograft hamstring tendons. 105 patients with autogenous hamstring tendon graft were included in our study.

An informed consent form was signed by all patients. All patients included in the study were treated

Table 1. *Preoperative physical examination results*

PRE-OP	SCORE	PERCENT
LACHMAN	+1 +2 +3	% 72,4 % 22,9 % 2,9
PIVOT-SHIFT	Positive Negative	% 94,3 % 5,7
ANTERIOR DRAWER	+1 +2 +3	% 85,7 % 13,3 % 1

with endo-button method. 96.8% of the patients were male and 3.2% were female. 61% of the knees were right and 39% were left. The mean age was 28.76 ± 6,3 (16-43) years. The period between the anterior cruciate ligament injury and surgery was 13.3 ± 8.2 months (15 days-48 months). In the etiology of ACL, non-contact injuries were found to be 54.2%, contact injuries were 41%, and at 4.8 % of the patients the etiology was not fully demonstrated.

The diagnosis was made with physical examination findings and radiological evaluation in all patients. Lachman and Pivot-shift tests were performed on physical examination (Table 1). Direct radiography and magnetic resonance imaging were taken. The mean follow-up was 16.3 months (7-46 months).

Surgical Technique

All patients were given 1 g cefazolin intravenously for infection prophylaxis one hour before the operation. Patients were re-examined under anesthesia and clinical diagnosis was confirmed. Standard anterolateral, anteromedial portals were used. ACL and posterior cruciate ligament were examined. It was confirmed by the probe that the ACL was injured. ACL residues were removed with shaver. The femoral attachment of the ACL was revealed by making notchplasty. Then, arthroscopic procedure was interrupted, and grafting was started.

3 to 4 cm longitudinal incision was made from 1 cm medial of the tuberositas tibia and 3 to 4 cm below the medial joint space- gracilis tendon were palpated-to get hamstring autograft. Sartorial fascia was reached and cut. The sartorius tendon was located at the forefront under the sartorius fascia. Semitendinosus and gracilis tendons were followed from distal to proximal. Semitendinosus and the gracilis tendons were separated from the surrounding tissues and cut from the adhesion sites. Both tendons were sutured and marked. The tendon was passed through the tendon scraper and held with Kocher pens then the stripper was advanced with repetitive maneuvers until the tendon was pulled out. The long and thick tendon is placed outside, and the two tendons are intertwined and attached to each other with 2/0 rapid vicryl. Krackow sutures were thrown using ethibond from approximately 2/3-part of each end when the tendons were stretched with the special stretching apparatus. A guide wire was sent from the anteromedial portal when 55° adjusted tibial guide was located to the end of lateral meniscus posterior horn and 7 mm anterior of the ACL attachment. The tibial tunnel was opened over the guide tibial wire taking care of the thickness of the graft. For femoral tunnel, when knee was at 90° flexion, femoral aimer with a diameter appropriate to graft thickness was placed to posterior cortex of the intercondylar notch for right knee 11 clockwise and for left knee 1 clockwise with transtibial technique. The guide wire sent through the aimer was removed from the femoral anterior cortex. The knee was kept constant at 90° flexion to prevent damage to the guide wire. Femoral drill was sent over the guide wire according to the length of the graft desired to remain in the tunnel (average 25-35 mm). The endobutton drill was then advanced until the femoral anterior cortex was passed. The length of the endobutton tunnel was subtracted from the length of the femoral tunnel length and 5 mm endobutton length added to calculate appropriate endobutton size to be used. Endobutton free ends with attached graft were pushed through the hole in the back of the guide wire. The guide wire was pulled from the anterior cortex of the femur to allow the graft to enter the femoral tunnel. Four endobutton threads (2 in 2 different colors) were taken together with the guide wire from the femoral anterior cortex and the endobutton was placed in the femoral anterior cortex. Fixation was checked by pulling the graft from the tibial side. An interference screw and/or biodegradable screw were used for the tibial fixation. The knee was fixed to the tibia with interference screw while the knee was flexed 20°. Jones bandage was applied to the knee in full extension. After the operation, continuous ice was applied to the knee and 24 hours later the drain was pulled. Quadriceps exercises and exercises with CPM device were started in early period.

RESULTS

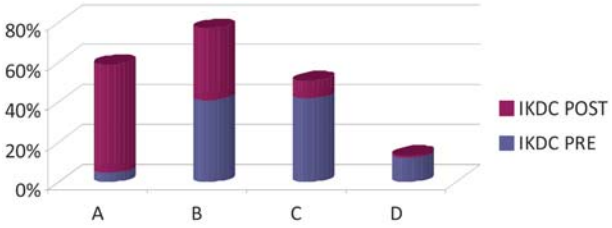
Medial meniscus rupture at 26 patients (24.8%), at 18 patients (17.1%) lateral meniscus and at 5 patients (4.8%) concomitant medial and lateral meniscus tears was observed and therefore partial meniscectomy was performed. There was chondral lesion in femoral medial condyle at 8 patients (7,6%).

The upper pole of the thigh was measured from the proximal 15 cm of the patella upper pole and compared with the postoperative third month measurements. T-test

Table 2. *The results of the patients were evaluated statistically according to the results of the 12th month*

POSTOPERATIVE	SCORE	PERCENTAGE
LACHMAN	Negative +1 +2	% 86,7 % 12,4 % 1
PIVOT-SHIFT	Negative	% 100
ANTERIOR DRAWER	Negative +1	% 95,2 % 4,8

Table 3. *IKDC scoring were performed at12 months*



was performed for the evaluation of thigh circumference measurement which was evaluated as a dependent group that conforms to the normal distribution. The mean preoperative thigh circumference was 45.37 cm and the post op thigh circumference was 43.35 cm. This result was statistically significant ($p < 0.001$).

The mean follow-up was 16.3 months (7-46 months). Lysholm and IKDC scoring were performed at 3-6 and 12 months. Lysholm scores in two dependent groups that did not conform to normal distribution were evaluated according to Wilcoxon test., Lysholm score was 56.16 ± 17.4 preoperatively and the postoperative score was 90.16 ± 6.6 and the result was statistically significant ($p < 0.001$). Pre- and postoperative VAS (Visual Analogue Scale) were performed. Preoperative VAS was 6.28 ± 1.9 and postoperative VAS was 3.41 ± 1.2. Lachman, Pivot-shift and Forward Drawer tests were performed at 3-6 and 12 months postoperatively. The results of the patients were evaluated statistically according to the results of the 12th month (Table 2). According to the International Knee Documentation Committee Evaluation Form (IKDC), 4,8% of the patients were included in the A group, 41 % B group, 41,9 % C group and 12,4% D groups. At postoperative evaluation (when the results of the 12th month of all patients were evaluated to ensure standardization), 54.3% of the patients were in A group, 36.2% B group, 8.6% C group and 1% D groups (Table 3).

DISCUSSION

The ACL lesion is the most common ligament injury among sports-related knee ligament injuries (1). The ACL injury mechanism may be sports-related or traumatic. Sports-related causes are also referred as non-contact injuries. In our study, the rate of non-contact injuries was 54.3% and the traumatic injuries was 41%.

There are still controversial issues in ACL surgery that have not been fully resolved. Discussion on the graft to be used in ACL reconstruction is ongoing. The ideal graft to be used should be easily accessible and easy to take, must be similar to natural ligament, and be able to allow aggressive rehabilitation. The graft should rapidly gain anatomical characteristics, should not cause morbidity in the donor field, should not cause disease transition or immune response. It should also not be expensive (2).

The graft is characterized by two anatomical features: Strength and stiffness. The strength of the graft should be equal to or greater than the natural ACL strength. The most commonly used autografts in ACL surgery are hamstring tendons and bone-patellar tendon-bone (BPB) grafts. Noyes et al in their study on BPB graft showed that the 14mm wide graft's strong was 164% of normal ACL, and 10 mm B graft' s strong was 107% of normal ACL strength. In the same study, they have reported that a single semitendinosus-free graft's (ST) strong was 70% of normal ACL, single gracilis grafts' strong (G) was 50% of normal ACL, double ST/G graft's strong was 250% of normal ACL of and quadriceps-patellar retinaculum-patellar tendon graft's strong (QT) was 14-21% of normal ACL reported 14-21% strength (3, 4).

Another feature of the graft is its stiffness. Insufficiency occurs early in hard grafts and late in soft grafts due to excess energy absorption. Therefore, the stiffness of the graft is important. While BPB is 3-fold harder than normal ACL, ST/G stiffness is equal to normal ACL (4).

Because of their high strength and stiffness and better fixation of bone-bone fixation, BPB grafts were preferred in ACL reconstructions. However, the disadvantages of this grafts are the problems such as anterior knee pain, patellar fracture, patellofemoral crepitation, numbness because of damage to infrapatellar branch of the saphenous nerve and loss of quadriceps strength (5). Since the strength and stiffness of the hamstring tendons were less than the normal ACL, this problem was prevented by forming a quadruple hamstring graft from these tendons.

In hamstring grafts donor site morbidity is less than patellar tendon grafts. Neuromas due to damage to the infrapatellar branch of the saphenous nerve are less common during hamstring graft harvesting. (6).

An interesting fact about the hamstring tendons is that they continue regeneration after the harvesting of these tendons.Ferretti et al. (7) showed in their study radiological signs of fibrous bands began to form in the remaining tendon path after removal of semitendinosus tendon.

In recent years, fixation of grafts to allow early rehabilitation of patients gained importance. The most com-

monly used fixation device for hamstring tendon fixation is endobutton. It has been shown that the endobutton fixation force is stronger than the interference screw. Endobutton transfers the force through the graft to the lateral cortex of the femur. The durability and survival of graft is so prolonged. However, due to the fact that the fixation is far from the joint, there are studies indicate that the endobutton does not prevent the piston movement in the tunnel and may eventually cause tunnel expansion (8, 9, 10).

The effects ofusing hamstring tendons on knee flexion or internal rotation are still a matter of debate. Hamstring tendons are the primary flexor of the knee andat the same time responsible for the internal rotation of the tibia. Some studies have stated that there is no hamstring weakness in the long term (11), but some studies have reportedmild hamstring weakness (12, 13).

Hamstring muscle weakness causes 2 problems. Hamstring muscle weakness first makes rehabilitation difficult after ACL reconstruction.In most rehabilitation programs, hamstring muscles have early and aggressive hamstring strengthening due to the synergistic study with ACL (14) in providing anterior knee stability. Secondly, weakness of hamstring muscles adversely affects athletic performance.

In a study to demonstrate the limitation of motion after the use of hamstring graft (15), postural stability with Biodex Balance system and flexion, extension, internal rotation and external rotation moment indexes and isokinetic extension/flexion moment measurements with Cybex dynamometer were performed. Measurements show that flexion-extension and internal rotation-external rotation forces are reduced in the operated extremity at the postoperative 1st year. This result demonstrates the importance of early and aggressive hamstring strengthening in the postoperative rehabilitation program in patients undergoing reconstruction with hamstring tendon.

There is still controversy about the time of ACL reconstructions. There is a risk of arthrofibrosis in acute reconstructions. Shelbourne (16) reported the rate of arthrofibrosis as 17% when reconstructed in the first three weeks after injury.On the other hand, this rate was 4% for those who were operated after three weeks. The rate of arthrofibrosis was decreased from 7% to 0.5% with the accelerated rehabilitation program. Waiting for the decrease of the edema and patient's regain mobilityand starting rehabilitation before surgery and reconstruction in the subacute period (4-6 weeks) is recommended (17). In addition, additional meniscus injuries and chondral damage have been reported in chronic repairs. In our study, the time between the patient's ACL rupture time and operation time was found as 13.3 ± 8.2 months (15 days-48 months).

Proper rehabilitation program after ACL reconstruction is one of the most important steps of treatment. This step directly affects the success of surgery. According to the literature results, the average time to return to active sport is 6 months (18). It was stated that early initiation of range of motion(ROM) exercises in early post-operative period and post-operative early mobilization positively affected rehabilitation and prevented quadriceps atrophy (18). We started passive ROM exercises with CPM after removing the drain and Jones bandage for our patients.

Debates on the post-surgery brace usingis also continuing. In a study conducted on healthy ACL volunteers using various brands of brace, none of the braces did not prevent any strain on the ACL in the normal activities of the knee but inhibited the anterior movement of the tibia at high forces and challenging movements (18). Chadwick et al. (19) reported that the use of a brace after the reconstruction using hamstring tendons did not alter clinical outcomes. In a study performed by Beynnon et al. (20) at patients with an ACL lesion and reconstructed ACL lesion, it has been shown that brace contributes to the development of knee proprioception. We applied brace for 6 weeks to the patients in our study.

CONCLUSION

As a result, if the ACL surgery using hamstring tendons is performed with appropriate surgical technique, satisfactory results may be obtained. The reason for the selection of hamstring tendons at ACL reconstructionsmay be the high incidence of knee pain and patellar complications at BPB grafts.

Abbreviations

ACL — Anterior Cruciate Ligament
IKDC — Score: International Knee Documentation Committee Score
VAS — Score: Visual Analogue ScaleScore
BPB Graft — Bone-Patellar Tendon-Bone Graft
ST Graft — Semitendinosus-Free Graft's
ST/G Graft — SemitendinosusGracilis Graft
ROM — Range Of Motion

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Founding

All authors declare that they have no founding.

DECLARATION OF INTEREST

The authors declare that there are no conflicts of interest.

Sažetak

REZULTATI REKONSTRUKCIJE PREDNJEG UKRŠTENOG LIGAMENTA KOLENA UZ UPOTREBU AUTOGENE TETIVE

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Uvod: Povrede prednjeg ukrštenog ligamenta kolena (ACL) su najčešće među povredama tetiva kolena. Uprkos visokoj stopi uspešnosti u rekonstrukciji pomoću artroskopskih tehnika, problemi oko odabira najboljeg grafta i fiksacionog materijala, kao i adekvatne postoperativne rehabilitacije i dalje postoje. **Materijal i metode:** Između januara 2007. i decembra 2010. godine izvedena je studija u kojoj je uključeno 105 pacijenata koji su podvrgnuti artroskopskoj rekonstrukciji prednjeg ukrštenog ligamenta koristeći autogene delove tetiva. Prosečna dužina praćenja bila je 16,3 meseca (7-46 meseci). Pacijenti su bili evaluirani na osnovu fizikalnog pregleda pomoću sledećih proba: Lahmanov test, Pivot-Šift, test prednje fioke, kao i pomoću merenja cirkumferencije butine i korišćenjem kliničkog skora kao što je Lysholm, IKDC skor i VAS skor. **Rezultati:** Svi pacijenti su podvrgnuti artroskopiji koristeći standardne artroskopske portove. Ostaci ACL su uklonjeni i izvedena je notch-plastika, a tetive semitendineusa i gracilisa su postavljene koristeći transtibijalnu tehniku u skladu sa prirodnom anatomskom pozicijom ACL. Preoperativno, Lisholm skor bio je 56,16 ± 17,4 , a postoperativno iznosio je 90,16 ± 6,6. Poređenje ove dve vrednosti pokazalo je statističku značajnost. Lahman je bio u 86,7% slučajeva negatvan, pivot šift test je bio negativan u 100% slučajeva, a test prednje fioke bio je u 92,5% slučajeva negativan. Preoperativni VAS bio je 6,28 ± 1,9, a postoperativni VAS bio je 3,41 ± 1,2. Prema IKDC skoru, 4,8% pacijenata bilo je tip A, 41% tip B, 41,9% tip C i 12,4% tip D; 54,8% pacijenata je u postoperativnoj proceni A, 36.2% B, 8.6% C i 1% D grupa. 12% pacijenata osećalo je utrnulost u predelu grafta. Nijedna druga komplikacija nije primećena. Zaključak: Kada se primeni odgovarajuća hirurška tehnika uz pomoć autogenih delova tetiva kod pacijenata obolelih od ACL, zadovoljavajući rezultati se dobijaju. Bolovi u predelu prednje strane kolena, kao i komplikacije vezane za čašicu se često viđaju kod patelarnog tetivnog grafta. Ovaj problem može da predstavlja razlog zbog kojeg se preferiraju autogeni delovi tetiva ACL.

Ključne reči: prednji ukršteni ligament, rekonstrukcija, rehabilitacija.

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EFFECTIVENESS OF COMPLETE BLOOD COUNT PARAMETERS FOR PREDICTING INTRACRANIAL INJURY IN CHILDREN WITH MINOR HEAD TRAUMA

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Abstract: **Objective:** We aimed to investigate the relationship between trauma severity and platelet indices (PI) and white blood cell (WBC) count to identify traumatic brain injury (TBI) in children with minor head trauma (MHT). **Materials and methods:** This prospective study included children with acute isolated MHT who underwent head computed tomography (CT) based on Pediatric Emergency Care Research Network (PECARN) criteria. Mean platelet volume (MPV), platelet distribution width (PDW), MPV to platelet ratio (MPV/PL), MPV to white blood cell ratio (MPV/WBC), and MPV to Neutrophil ratio (MPV/Neu) were evaluated.

Results: 86 children with MHT and 245 controls were included the study. WBC, Neu count, MPV, MPV/WBC, MPV/Neu and MPV/PI ratios were statistically different among patients with abnormal CT, patients with normal CT and healthy controls ($p < 0.05$). For predicting abbreviated injury score (AIS) > 1, the AUC values of WBC, neutrophil, MPV/WBC and MPV/Neu were 0.746, 0.739, 0.726 and 0.724, respectively.

Conclusion: In children with MHT who underwent CT, WBC, Neu counts, MPV/WBC and MPV/Neu ratios may be helpful for predicting the severity of trauma in pediatric emergency department.

Key words: children; complete blood count; head trauma; intracranial injury.

INTRODUCTION

Isolated minor head trauma (MHT) is a common cause of presentation at the paediatric emergency room, and includes the majority of all head trauma patients admitted to the paediatric emergency service. The most important mission of the clinician in the management of patients with MHT is to detect serious traumatic brain injury (TBI), which is estimated to represent one-third of all injury-related deaths (1). The most appropriate imaging technique for diagnosing TBI is head computed tomography (CT). Significant TBI is detected in < 1% of patients with MHT (1). In clinical practice we use The Paediatric Emergency Care Applied Research Network (PECARN) validated rule to identify children with MHT at very low risk for significant TBI without a head CT scan (2). Nevertheless, paediatric emergency physicians frequently face difficulties making a decision due to exaggerated concerns and insistent attitudes of parents, and usually disagree with neurosurgeons about requests for control head CT scans to detect possible TBI. While an unnecessary CT scan can lead to excessive radiation exposure and costs, bypassing a CT scan despite the insistence of the family may result in missing TBI.

Trauma acts as the trigger for a cascade of hemodynamic, metabolic, neuroendocrine, and immune responses leading to secondary tissue damage (3). Platelets, neutrophils, and lymphocytes are markers that reflect the inflammatory response which is required for subsequent restoration of homeostasis (4). Platelet count and platelet function are predictors of mortality, and the latter also contributes to detrimental cerebral bleeding in TBI (5, 6). The platelet volume indices (PVI) including mean platelet volume (MPV) and platelet distribution width (PDW) reflect the average size of platelets in the blood and correlate with platelet activity and function (7). These are parameters that can be derived inexpensively from a complete blood count (CBC). PVI and MPV have potential clinical utility, particularly in haematology and cardiovascular medicine (8, 9, 10). Until now, the diagnostic performance of MPV, WBC, and platelet count for determining trau-

ma severity and to identify TBI in patients with MHT have been investigated in few adult clinical studies (11, 12, 13).

To the best of our knowledge, no study has investigated CBC parameters in children with MHT; thus, we determined whether PVI and WBC count could be used as predictors of TBI in those patients. We researched how neutrophils, lymphocytes, platelets, and the PVI derived from a CBC result in changes in children with MHT; and if these parameters are useful to predict TBI.

MATERIAL AND METHODS

This prospective study was performed in patients with MHT who were admitted to the paediatric emergency and trauma centre of our university hospital between March and July 2017 with approval of the Ethical Committee of Katip Çelebi University. Patients with MHT were characterized as having a Glascow Coma Score (GCS) of 14 or 15, no abnormal findings on a neurological examination, and no signs of basilar skull fracture such as hemotympanum, oto- or rhinorrhoea, or a periocular or posterior auricular hematoma. The management of all patients and the head CT scan requirements were determined according to the PECARN guidelines. Unenhanced CT scans were performed on a 16-slice MX16 (Philips Medical Systems, Best, Netherlands) scanner with 1.5 mm slices of the cranial base and 2.5 mm for the brain parenchyma. Blood samples were drawn from every patient meeting the study criteria and who were willing to participate in the study within 10 min after they arrived in the emergency room. All head CT scans were evaluated by a neurosurgeon and a radiologist. The presence of a skull fracture (linear or depressed), acute epidural, subdural or parenchymal hematomas, subarachnoid haemorrhage, concussion, and cerebral oedema were considered positive CT results. Severe trauma was defined clinically by any of the following: admission to a ward for at least 48 h, admission to a paediatric intensive care unit (PICU), patients needing intubation, increased intracranial pressure treatment, transfusion, and exitus. Intracranial injury in a CT-positive patient was assessed using the abbreviated injury score (AIS, 2005) and ranked on a scale of 1 to 6, with 1 being minor and 6 being non survivable injury. The patient clinical and demographic characteristics (age, sex, vomiting, duration of loss of consciousness, presence of seizure or focal neurological deficit, presence of scalp hematoma and size, mechanism of trauma, and short outcome) were recorded. Patients whose GCS was < 14; those who had multiple trauma, penetrating injuries, anaemia, chronic disease, acute or chronic infection, bleeding diathesis, soft tissue injury; and patients who were admitted 24 h after trauma were not included in the study. Eventually, 86 children with acute isolated MHT who underwent a head CT scan and presented to the paediatric emergency room were included in the study. The control group consisted of 245 healthy children who had no trauma, no soft tissue injury, and no infection history during the 3 months before admission for a CBC exam. Written informed consent was obtained from the guardians of each patient before blood was taken.

CBCs were performed using a Coulter analyser (LH-780; Beckman Coulter, Brea, CA, USA) with the impedance method (intra-assay variation coefficient 1.6%, interassay variation coefficient 1.65%), which was routinely checked every month in the central laboratory of our hospital. Standard tubes with a constant amount of K3-EDTA were used. Blood samples of each patient were examined within 15 min to avoid any possible variation in the PVI. The PVI included MPV, PDW, and plateletcrit. Furthermore, we examined other platelet indices calculated based on CBC: MPV/platelets (MPV/PL), MPV/WBC (MPV/W), and MPV/Neu (MPV/N).

The statistical analyses were performed with SPSS for Windows software (SPSS Inc., Chicago, IL, USA). Quantitative data are presented as median with interquartile range. The Kruskal–Wallis test was used to evaluate the differences between study groups (head CT-positive and CT-negative) and healthy group for continuous variables. Differences in the means of continuous variables between groups (head CT-positive and head CT-negative) were analysed with the Mann–Whitney *U*-test. Differences in categorical variables were analysed with the chi-square test. Spearman's correlation test was used to assess the associations between laboratory parameters and the AIS score. The predictive ability of the laboratory data for the trauma severity was evaluated with receiver operating characteristic analyses. A p-value < 0.05 was considered statistically significant.

RESULTS

Of the 86 patients with MHT who underwent a head CT scan based on the PECARN criteria, 27 females (31.7%) and 59 males (68.6%) were included in the study. The median age of the patients with MHT was 3 years (1 month to 17 years). The median age of the control group was 6 years (1 month to 17 years) ($p > 0.05$). A total of 8 patients (9.3%) were injured by in-car accidents, 2 (2.3%) were injured by out-of-car accidents, 26 (30.2%) were injured by falling from a height, 1 (1.1%) was injured by a motor vehicle accident, and 49 (56.9%) were injured by low-energy impact. Sixty patients (69.7%) were discharged after emergency service observation, and eighteen (20.9%) were admitted to

the neurosurgery clinic after initial treatment. Five patients (5.8%) included in the study were in need of surgery, three patients (3.4%) were in need of the PICU, and no patients died.

The evaluation of the head CT scans showed that 36 patients (41.9%) had brain pathologies including skull fractures, whereas the head CT scans of 50 patients (58.1%) were normal. Among the head CT scan-positive group, 20 had isolated skull fractures, 18 of which were linear and 2 that were depressed fractures. Thirteen patients (15.1%) had intracranial haemorrhages (subdural or epidural hematomas). Of these patients, six had a linear skull fracture and one had a depressed skull fracture. Three of the patients (3.5%) had contusions with a linear skull fracture on a head CT scan. The clinical and demographic characteristics of the patients are shown in Table 1.

When we divided the cases into three groups based on the presence or absence on head CT scans and the control group, we found that WBC, Neu, MPV, MPV/PL, MPV/W, and MPV/N were significant variables (Table 2).

The WBC and Neu values increased progressively from the healthy controls (8.5/L and 3.3/L) to head CT-negative patients with MHT (10.4/L and 4.7/L), and further to patients with a head CT-positive scan (12.2/L and 7.1/L; $p < 0.01$). The MPV/W and MPV/N values decreased progressively from the healthy controls (1 and 2.5) to head CT-negative patients (0.74 and 1.5), and further to head CT-positive patients (0.64 and 1.16; $p < 0.01$) (Table 2). Significant differences were observed between patients who had clinically severe trauma and AIS scores ≥ 2 and those with no severe trauma and AIS scores < 2 in terms of WBC, Neu, MPV/W, and WBC/N (Table 3).

A negative correlation was detected between the AIS score and MPV/W ($r = –0.282$; $p < 0.05$) and MPV/N ($r =$

Table 1. *The clinical characteristics of the patients*

Patients n (%)	
Age (median, IOR)	3 (1-7)
Sex (male/female)	59/27 (68.6/31.4)
Symptoms/signs	
Vomitting	
< 3	13 (15.1)
≥ 3	9 (10.5)
headache	7 (8.1)
Loss of conciousness > 5 sn	7 (8.1)
seizure	1 (1.2)
Frontal hematoma	12 (13.9)
Occipital hematoma	10 (11.6)
Parietal/temporal hematoma	19 (22)
Clinically severe trauma +	13 (15.1)
Mechanism of injury	
fall from height	26 (30.2)
low energy injury	49 (56.9)
in car- accident	8 (9.3)
out-car accident	2 (2.3)
bike/motorcycle injury	1 (1.1)
Head CT +/ head CT-	36 /50
Isolated lineer / depressed fracture	18/2
lineer fracture + IC hemorrhage	6
IC hemorrhage + depressed fracture	1
Lineer fracture + contusion	3
IC hemorrhage without skull fracture	13
AIS score ≥ 2/< 2	14/72 (16.3/83.7)
discharge from pediatric emergency room	60 (69.7)
admission to the wards	18 (20.9)
admission to PICU	3 (3.4)
underwent operation	5 (5.8)

Table 2. *Comparison of CBC markers in the study groups and control group*

	Study group (min-max)		**Control group (min-max))**	**p**
Age (years)	3 (1-7)		6 (1-7)	,439
Sex (n) (female/male)	27/59		69/186	
	CT +	**CT -**		
WBC (/I)	**12.2** (9.7-18.7)	**10.4** (8.5- 12,4)	**8,5** (7.1-10,9)	**< 0,001**[a,b,c]
Neu (/I)	**7.1** (4.4-14.6)	**4,7** (2.9-6,3)	**3.3** (2.5-4.4.7)	**< 0,001**[a,b,c]
Plt (x10-^{3})	293 (237-393)	312.5 (257.5- 383.7)	290 (233.2-233.2)	0,440
PDW	16.4 (16.3-16.7)	16.4 (16,1-16.7)	16.5 (16.1-17)	0,607
Pct	,25 (,20-,29)	,24 (,20-,29)	,24 (,20-,29)	0,855
MPV (fl)	**7.7** (7.3-8.6)	**7.6** (7.2-8.1)	**8.4** (8.1-9.)	**< 0,001**[a,b,c]
MPV/WBC	**,64** (,42-,85)	**,74** (,62-,86)	**1** (,78-1,2)	**< 0,001**[a,b,c]
MPV/Neu	**1,16** (,57-1,6)	**1,5** (1,2-2,6)	**2,5** (1,8-3,4)	**< 0,001**[a,b,c]
MPV/Pl	**,026** (,018-,035)	**024** (,019-,029)	**,029** (,024-,037)	**< 0,001**[a,b]

a: CT+ vs control; b: CT- vs control; c: CT + vs CT –

Table 3. *Comparison of CBC markers regarding to trauma severity and AIS score*

	Sever trauma + (min-max)	Sever trauma - (min-max)	p	AIS < 2	AIS ≥ 2	p
WBC (/I)	**13.9 (10.7-22.9)**	**10.5 (8.60-12.4)**	**.020**	**9.8 (8.3-12.9)**	**18.2 (10.4-23.7)**	**.007**
Neu (/I)	**9.9 (6.4-16)**	**4.7 (3.2-6.9)**	**< 0.001**	**4.8 (3.1-7.5)**	**14.7 (6.1-16.9)**	**.002**
Plt (x10-^{3})	354 (290-388)	303 (246-383)	.193			
Pct	.27 (.24-.29)	.23 (.20-.28)	.069	.23 (.20-.28)	.25 (.17-.27)	NS
PDW	16.4 (16.3-16.5)	16.4 (16.2-16.8)	.840			
MPV (fl)	8 (7.05 -8.40)	7.6 (7.20-8.20)	.592	7.80 (7.50-8.45)	7.65 (6.97-6.97)	NS
MPV/W	.57 (.30-.78)	.73 (.61-.87)	**.020**	**.78 (.62-.91)**	**.45 (.30-.77)**	**.016**
MPV/N	.81 (.42-1.28)	1.52 (1.11-2.31)	**< 0.001**	**1.51 (1.10-2.60)**	**.56 (.42-1.27)**	**.005**

–0.335; p < 0.05) (Figure 1b, 1 d). By contrast, a positive correlation was observed between the AIS score and WBC (r = 0.316; p < 0.05) and the AIS score and Neu (r

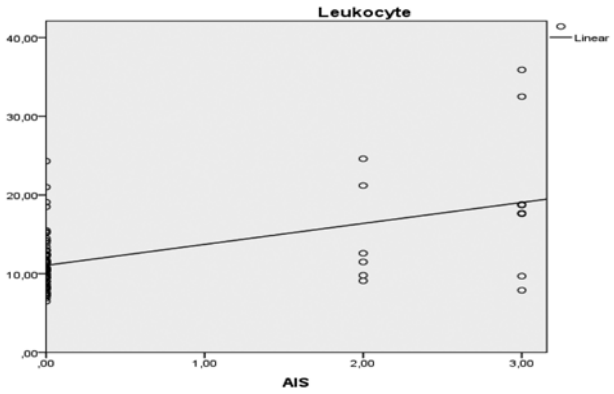


Figure 1a: *Correlation graph between WBC and AIS score*

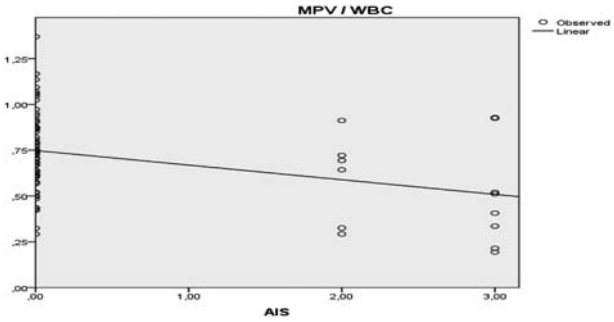


Figure 1b: *Correlation graph between MPV/W and AIS score*

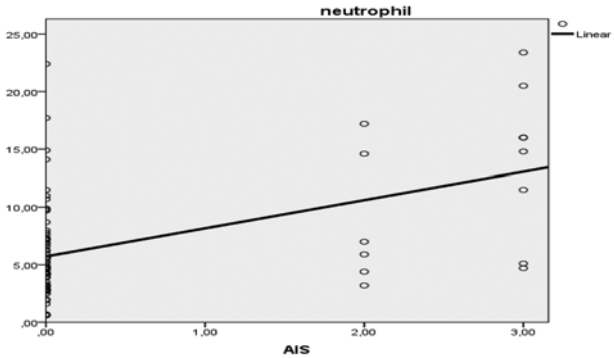


Figure 1c: *Correlation graph between Neutrophil and AIS score (p < 0.05, r = ,365)*

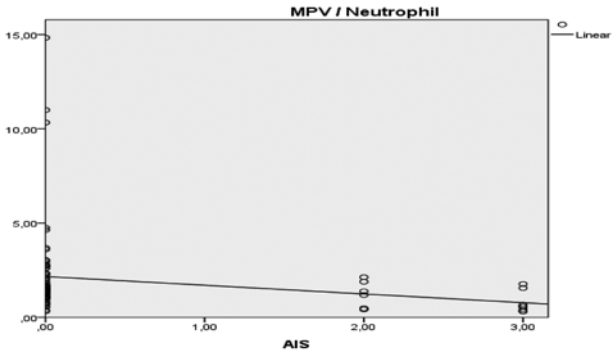
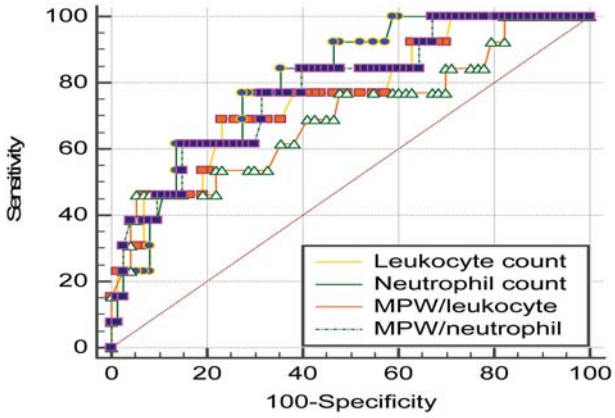


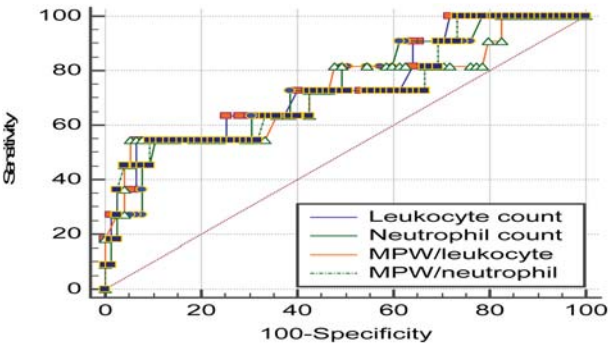
Figure 1d: *Correlation graph between MPV/N and AIS score*

= 0.365; p < 0.05) (Figure 1a, 1c). Neu and MPV/N exhibited area under the curve (AUC) values of 0.805 (95% confidence interval [CI], 0.70–0.88; p] and 0.782 (95% CI, 0.68–0.86; p) respectively for differentiating patients with MHT and severe trauma from those with no severe trauma (Figure 2a). Setting the WBC cut-off value to > 18.5 and the MPV/W cut-off value to ≤ 0.41 gave 99.33% and 94.67% specificity, respectively, for differentiating MHT patients with AIS scores > 1 from



Variable	AUC	SE[a]	95% CI[b]	Cut-off	sensitivity	specifity
WBC	0,761	0,0753	0,657 to 0,847	>12.5	69.23	76.21
Neu	**0,805**	0,0585	0,706 to 0,883	>6.9	76.92	72.60
MPW/W	0,701	0,0902	0,592 to 0,795	≤0.41	46.15	94.52
MPW/N	0,782	0,0701	0,680 to 0,864	≤0.9	61.54	84.93

Figure 2a: *The ROC curves of variables for the presence of severe trauma*



Variable	AUC	SE	95% CI	Cut-off	sensitivity	specifity
WBC	0,746	0,0899	0,641 to 0,834	>18.8	54.55	93.33
Neu	0,739	0,0857	0,634 to 0,828	>11	54.55	89.33
MPW/W	0,726	0,0989	0,619 to 0,817	≤0.41	54.55	94.67
MPW/N	0,724	0,0948	0,617 to 0,815	≤0.66	54.55	90.67

Figure 2b: *The ROC curves of varibales for AIS > 1*

those with AIS scores < 1 (Figure 2b). When differentiating the patients who had clinically severe trauma from patients who do not, setting the MPV/W cut-off value to ≤ 0.41 gave a specificity of 94.52% (Figure 2a).

DISCUSSION

This study demonstrated that WBC and Neu levels in children with MHT were significantly higher than those in healthy controls. Furthermore, a progressive increase in WBC and Neu levels occurred in parallel with the presence of head CT pathologies. The elevated levels of WBC, particularly Neu in children with MHT, indicated a post-traumatic inflammatory response (11, 14, 15, 16). It was clear from our sample that WBC and Neu levels were significantly higher in the head CT-negative MHT group than the healthy controls. This result suggests that the stress of trauma itself can result in marked demargination of leukocytes even in patients who do not sustain a significant injury. Furthermore, in the current study, WBC and Neu levels were positively correlated with trauma severity and the AIS score. Rovlias *et al.* reported that patients with a severe head injury have significantly higher WBC counts than those with moderate or MHT (14). In fact increased cortisol and catecholamine are responsible for the increase in the WBC count in patients with head trauma and patients with a higher WBC count on admission often have a poorer outcome (14, 17, 18). Our study provides evidence for the involvement of WBC and Neu after MHT. In particular, Neu counts could provide additional information about trauma severity and the presence of brain pathologies on head CT scans in children with MHT. Nevertheless, the increased WBC and Neu counts alone in parallel with the presence of brain injury and clinically severe trauma may reflect the stress response.

Could PVI alone or in combination with WBC count be of diagnostic value for brain injury after MHT? MPV and PDW represent platelet size and are potential biomarkers of platelet activity. However, only MPV values appeared to be of significance in patients with MHT in our study. This finding is compatible with the literature that among all variables produced by complete blood count analyses, MPV is better and well-standardized than PDW (19, 20). An increase in the MPV value suggests an increased released of a larger number of hyperactive platelets from the spleen, whereas a decrease in the MPV value may be due to consumption of larger platelets which occurs in sepsis, high-grade systemic inflammatory diseases, and an acute attack of familial Mediterranean fever in children (21, 22, 23). MPV values increase in some clinical situations such as cardiovascular disorders, stroke, and cancers (8-10, 24). The most important result of the current study was that within 24 h of injury MPV values decreased compared to healthy controls although there was no pathology on a head CT scan. Unlike the results of previous studies on head trauma, the decrease in MPV values was unexpected (11, 12). However, a similar finding was reported in a study of 54 adult patients with MHT (13). The results of that study also demonstrated that a progressive decrease in MPV occurs in parallel with the severity of MHT (13). A possible explanation could be the consumption of larger platelets at the site of leucocyte migration immediately after the trauma. An inverse relationship has been reported between platelet count and MPV under physiological and some pathological conditions to maintain haemostasis by preserving a constant platelet mass (25). We did not find any significant difference in the platelet count between the study and control groups. Although we cannot explain the pathology underlying the significant decrease in MPV with a normal platelet count, we believe that MHT without a brain injury would have a different effect on platelet biology, as physical damage may result in a higher prevalence of hypo reactive platelets than that in patients in other clinical situations (8-10, 24, 26). Our results also did not show any differences in MPV levels regarding trauma severity or the AIS score. However, if we investigated serial MPV measures in our study, we would have a better idea about the balance between selective consumption of larger platelets and the ability of the bone marrow to replace platelets in patients with acute isolated MHT.

When we examined the ratio of parameters that increased and decreased within 24 h after MHT, the results showed that the MPV/W, MPV/N, MPV/PL ratios of the study groups significantly decreased compared to the healthy blood donors. Moreover, the MPV/W and MPV/N ratios were significantly lower in patients with head CT pathologies than in those with a normal head CT scan.

The results of our study have some clinical implications. This study provides evidence for the involvement of WBC, Neu, and MPV within 24 h following

MHT. Although many markers have been studied and defined, CBC is easily accessible and inexpensive to perform in clinical practice. The MPV/W and MPV/N ratios provided additional information about trauma severity in children with isolated MHT and may be useful for patients with MHT who are being observed for possible traumatic brain injury.

Some limitations of our study should be mentioned. The study sample was small, and we did not conduct a serial CBC count for the patients. If serial CBCs were assessed, then possible changes in MPV and platelet count and the balance between thrombopoiesis and inflammation in patients with severe trauma after MHT would have been clearly revealed.

We suggest that the diagnostic performance of the MPV/N ratio for identifying clinically severe trauma in children with MHT (i.e., AUC of 0.78; $p = 0.01$) with sensitivity and specificity of 0.61 and 0.84, respectively for values < 0.9 provides a reliable basis for planning further investigations.

CONCLUSION

The MPV/W and MPV/N ratios can be used as markers for the severity of injury in patients with MHT presenting to the paediatric emergency room when the necessity for a head CT scan is unclear.

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The English in this document has been checked by at least two professional editors, both native speakers of English (18041804). This article presented orally on 5th Intercontinental Critical Care and Emergency Medicine Congress in Antalya, Turkey, 19 April 2018.

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Declaration of conflicting interests

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Availability of data and materials

The authors declare that no data have been fabricated or manipulated (including images) to support your conclusions. The authors declare that no data, text, or theories by others are presented as if they were the authors own.

Informed consent

Written informed consent was not necessary because no patient data has been included in the manuscript.

Human rights

All procedures performed in studies involving human participants 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.

Ethical approval

We confirm that Ethical Committee approval was sought where necessary and is acknowledged within the text of the submitted manuscript.

Sažetak

EFIKASNOST PARAMETARA KOMPLETNE KRVNE SLIKE ZA PREDVIĐANJE INTRAKRANIJALNE POVREDE KOD DECE SA MANJIM TRAUMAMA GLAVE

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Cilj: Cilj nam je bio da istražimo odnos između težine traume i broja trombocita (PI) i leukocita (WBC) za identifikaciju traumatske povrede mozga (TBI) kod dece sa manjim traumama glave (MHT).

Materijal i metode: Ova prospektivna studija obuhvatila je decu sa akutnim traumama glave koja su podvrgnuta kompjuterskoj tomografiji glave (CT) na osnovu kriterijuma Pedijatrijske istraživačke mreže hit-

ne pomoći (PECARN). Evaluirane su vrednosti srednjeg volumena trombocita (MPV), širina raspodele trombocita (PDW), odnos srednjeg volumena trombocita i trombocita (MPV/PL), odnos srednjeg volumena trombocita i leukocita (MPV/WBC), kao i odnos srednjeg volumena trombocita i neutrofila (MPV/Neu).

Rezultat: 86 dece sa MHT i 245 kontrola su uključeni u studiju. WBC, broj neutrofila, MPV, MPV/WBC, MPV/Neu kao i MPV/PI razmere bile su statistički drugačije kod pacijenata sa abnormalnim tomografijama glave, kod pacijenata sa normalniom tomografijama i u kontrolnoj grupi ($p < 0.05$). Za predviđanje skraćene ocene povrede (AIS) > 1, AUC vrednosti WBC-a, neutrofila, MPV/WBC i MPV/Neu bile su 0.746, 0.739, 0.726 i 0.724.

Zaključak: Kod dece sa MHT koja su podvrgnuta CT snimanju, WBC, Neu, MPV/WBC i MPV/Neu mogu biti korisni za predviđanje ozbiljnosti traume u pedijatrijskom odeljenju hitne službe.

Ključne reči: deca, kompletna krvna slika, povrede glave, intrakranijalna povreda.

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Original article

IS PREDICTION OF RENAL FAILURE WITH ITS INDICES FEASIBLE WITH PRESENCE OF HISTOPATHOLOGIC EVIDENCE FOR GASTRIC INTESTINAL METAPLASIA?

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Abstract: **Objectives:** Gastric intestinal metaplasia has traditionally been associated with gastric adenocarcinoma. Gastric intestinal metaplasia is usually related to the *Helicobacter pylori* infection, older ages, smoking history, and consumption of strong spicy foods, socioeconomic status presence of IL10-592 C/A. The purpose of the present research study was to evaluate the simple laboratory parameters in subjects with gastric intestinal metaplasia.

Findings: From May 2018 and October 2018, a total of 541, 281 male and 260 female, consecutive cases with gastric intestinal metaplasia with the mean age of 58.5 ± 15 years had been enrolled retrospectively with the exclusion of the cases with severe underlying disease, including the gastric cancer and gastric resection. The gastroscopy with the antral biopsy had been performed for all the cases and the biopsy samples had been evaluated for the presence of gastric intestinal metaplasia by Hematoxylin and Eosin and *Helicobacter pylori* status by Giemsa. The chi-squared test and independent *t* test were used for the comparison. The mean serum urea level detected as 34.2. ± 16.1 mg/dL in the gastric intestinal metaplasia and 31.2 ± 13.1 mg/dL in the control (95% CI from 32,3 to 34,6; $p = 0.013$), while the mean serum creatinin level 0.84 ± 0.28 mg/dL in the gastric intestinal metaplasia and 0.80 ± 0.26 mg/dL in the control (95% CI from 0,80 to 0,85; $p = 0.042$). The gastric intestinal metaplasia was detected mostly in elderly and male, regarding the multiple logistic regression ($p < 0.001$).

Conclusion: The serum urea and creatinin levels may serve as a simple clinical tool to predict the cases patients at risk for gastric intestinal metaplasia.

Key words: Metaplasia; Intestinal metaplasia; Endoscopy; Histopathology; Hematoxylin; Helicobacter pylori; Renal insufficieny; Urea; Creatinin.

INTRODUCTION

Gastric intestinal metaplasia (GIM), characterised by either the enteric or colonic mucosal immigration into the gastric mucosa, is prevalent in subjects, living in Asia and could lead to the gastric carcinoma at a rate of approximately 1%, annually (1). Both atrophic gastritis and GIM have been implicated in the gastric carcinogenesis and should be tracked by endoscopic screening programmes (2). The risk factors have been reported as the presence of *Helicobacter pylori* infection, older ages, smoking history, strong spicy food consupmtion, occupation status and presence of IL10-592 C/A (3). However, the role of facilitative laboratory tools to detect GIM remains largely unknown.

AIM

In the present study, it is purposed to explore the possible impact and association of established GIM on the basic laboratory parameters as well as the sociodemographic factors.

MATERIAL AND METHODS

Criteria for incorporation into the study

A sum of 541 (281 male and 260 female) consecutive cases with GIM with the mean age of 58.5 ± 15 years had been enrolled retrospectively, during the period between May 2018 and October 2018. The related documents and data had been collected and evaluated. Gastroscopy with the antral biopsy had been performed for all the cases at the enrollment of the present study. The control group (90 male and 90 female) with the mean age of 54.6 ± 13.5 years was selected from the dyspeptic cases without GIM. The exclusion criteria were the cases with severe underlying disease, including the gastric cancer and the gastric resection.

Endoscopic and Histopathologic evaluation

All the endoscopic examinations had been performed by using the propophol anestesia with Fujinon videoscope (Tokyo, Japan). The biopsy samples had been evaluated for the presence of GIM and *Helicobacter pylori* status. The gastric biopsy specimens had been fixed in a formalin and assessed for *Helicobacter pylori* by Giemsa and intestinal metaplasia by Hematoxylin and Eosin, and the intestinal metaplasia had been classified in two grades: absent and present.

Statistical analysis

All the statistical analyses were performed with the SAS software (SAS Institute, Cary, N.C.). The demographic clinical and radiologic characteristics of the cases were compared by the Student's t-test exact test to assess the difference in the proportions. All the p values were two-sided and the significance was indicated by a p value of less than 0.05.

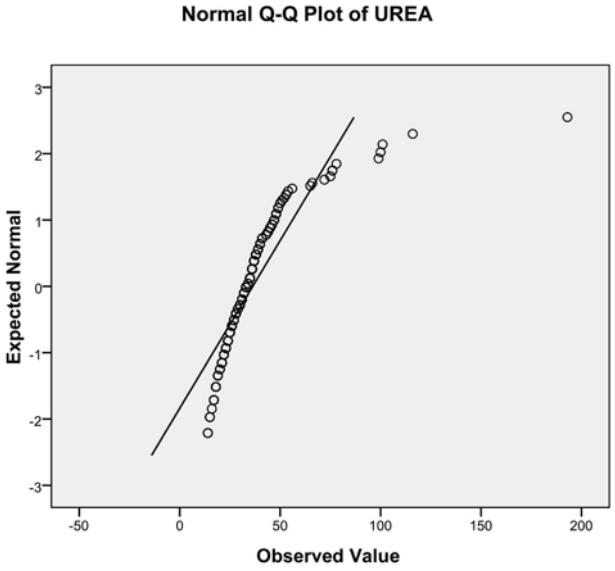

Figure 1a: *The normal Q-Q plot of serum urea*

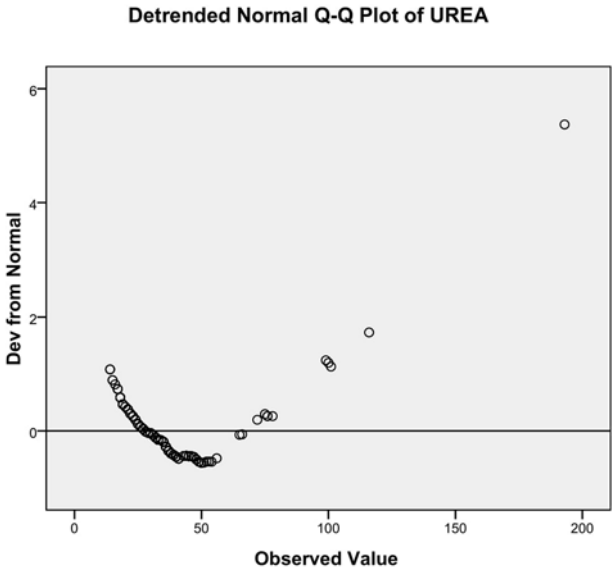

Figure 1b: *The detrended normal Q-Q plot of serum urea*

RESULTS

The characteristics of the cases at the baseline were well balanced between the studied cases and the control subjects with respect to age and gender (all $p > 0.05$). The baseline characteristics of the study subjects are depicted in Table 1. The mean serum urea level was 34.2 ± 16.1 mg/dL in the GIM group and was 31.2 ± 13.1 mg per deciliter in the control group (95% CI from 32.3 to 34.6; $p = 0.013$). The mean serum creatinin level was 0.84 ± 0.28 mg/dL in GIM group and was 0.80 ± 0.26 mg/dL in control group (95% CI from 0.80 to 0.85; $p = 0.042$). The further statistical analyses of those parameters for the serum urea levels (Figure1a, b) and serum creatinin levels (Figure 2a, b)

Table 1. *The baseline characteristics of the cases*

Group Statistics

	GIM	n	Mean	Std. Deviation	Std. Error Mean
Age	0	180	54,68	13,555	1,010
	1	541	58,58	15,077	,648
Urea	0	171	31,2339	13,16918	1,00707
	1	509	34,2224	16,11630	,71434
Creatinin	0	177	,8053	,26141	,01965
	1	514	,8486	,28824	,01271

GIM: Gastric intestinal metaplasia.

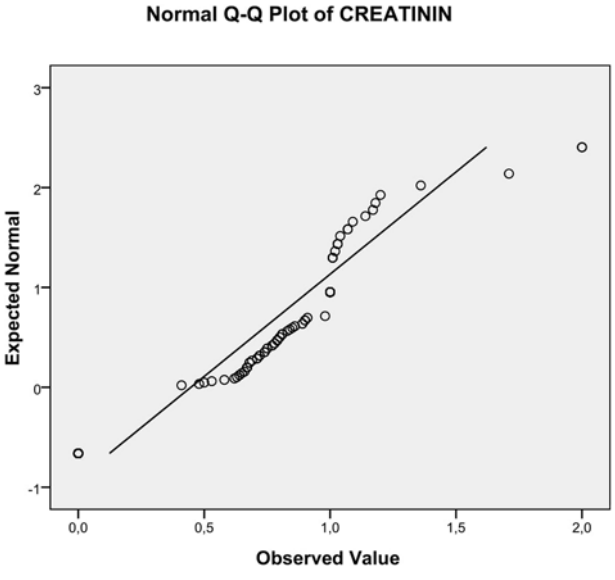

Figure 2a: *The normal Q-Q plot of serum creatinin*

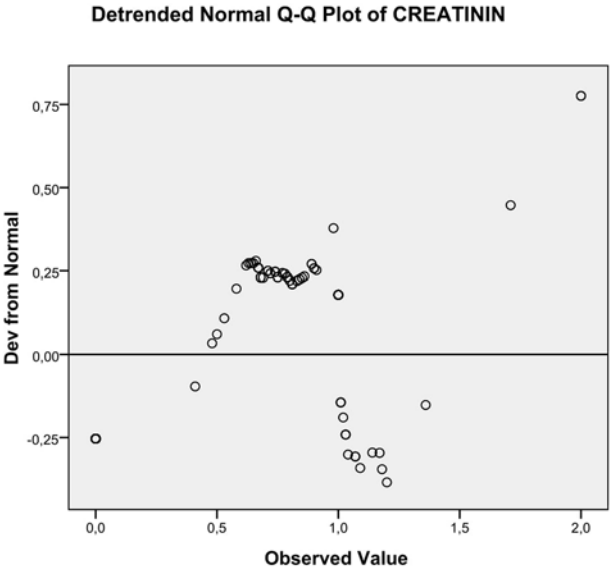

Figure 2b: *The detrended normal Q-Q plot of serum creatinin*

were depicted, seperately. According to the multiple logistic regression, GIM was more in elderly and male gender was a strong risk factor for GIM (all $p <$ 0.001). The other variables were similar across the groups (p = NS).

DISCUSSION

In the present study, the mean rate of *H. pylori* infection was 56% and did not differ between the groups (54% versus 58%). We also reported an original research study very recently, on December 2018, about frequency of *Helicobacter pylori* and association of location, six age groups, and assessment of borderline of 50-year base-age, based on the anatomic pilot region with the degree of helicobacter pylori colonization. We reported in our other study that the *Helicobacter pylori* positivity was 55.2% in general and observed mostly in the antrum and 45-64 age group. However, no any difference was detected between the location, age groups, subgroups with over and under 50 and the degree of *Helicobacter Pylori* colonization (4). Some other already published Turkish studies (5) have revealed the similar results, where as some reported the different, higher (6) and lower (7), ratios with our two research studies about *Helicobacter pylori*.

A recent study from the United States involving 4.146 individuals with the gastric intestinal metaplasia exhibited that the incidence rate of the gastric adenocarcinoma was 0,72/1.000 person-years in patients with the intestinal metaplasia, with a relative risk of 2,56 compared with the control group (8). The gastric cancer screening with the upper gastrointestinal tract endoscopy should be considered in persons who was born in the high risk areas for the gastric cancer (East Asia, Russia, and South America) or who had a family history of the gastric cancer. The gastric screening by endoscopy should be done every 1 to 2 years in the patients with the findings of atrophic gastritis or intestinal metaplasia on their histopathologic assessments (9). The emerging evidence also suggests that the preexisting GIM detected by histopathologic examination of the gastric mucosa confers a longterm risk of gastric cancer even after the *Helicobacter pylori* infection has been successfully eliminated (10). In a recent retrospective cohort study involving 923 patients with GIM showed that only family history (the hazard ratio, 3,8-95% and the confidence interval, 1,5–9,7; p = 0.012) and the extent of GIM (the odds ratio, 9.4-95% and the confidence interval, 1,8–50,4%) increased the risk for the gastric cancer (11). It was not obtained that data due to the retrospective nature of the present study.

It has been a well known fact that the tobacco smoking and many foods, including processed, salted or smoked meats are positively associated with a noncardia gastric cancer in a dose-dependent manner (12). To our knowledge, only few studies present in the English literature, regarding the intestinal metaplasia in the patients with the chronic kidney disease. The first study conducted a quarter century ago involving 80 patients with the chronic renal failure, revealing 50 patients (62.5%) had the intestinal metaplasia (13). In a study of Netto et al (14), 96 patients with the chronic kidney disease were endoscopied as the preparation for kidney transplantation. The most frequent found gastric disorder was a pangastritis (57,30%) and erosive pangastritis was found with 30,2%. The gastric metaplasia was found in 8,33%, which is much less than in the study of 1989. Another study with 50 chronic renal failure patients and 50 control patients revealed the intestinal metaplasia in 29,4% of the cases in the renal failure group. **In conclusion**, a higher urea concentration in the gastric juice and following metabolic disorders were regarded as a causative for the higher frequency of gastrointestinal alterations compared with the patients with a normal renal function (15). The data above suggest that the renal dysfunctional alter the gastric mucosal tissue with the formation of the toxic products, which may play a potential pathogenic role in GIM.

There are several important limitations of the study. First of all, in the present study was in a retrospective manner. Secondly, it was not obtained the serum bicarbonate levels among the study population. Thirdly, it was not assessed the renal functions through the sonographic assessment, and lastly, it was not collected the dietary behaviours of the subjects with GIM,

those lead to that disease. On the other hand, it is expected that the current study is large enough to assess the impact of GIM on the renal parameters.

CONCLUSION

Assessing serum urea and creatinin levels could serve as the simple clinical tool to identify the patients at risk for GIM as well as the further gastric cancer. Given the previously reported GIM prevalence, full biochemical screening may reveal the substantial numbers of cases with the previously unknown GIM.

Abbreviation

GIM — Gastric intestinal metaplasia

DECLARATION OF INTEREST

The authors declare that there are no conflicts of interest.

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Sažetak

DA LI JE UZ POMOĆ ODGOVARAJUĆIH INDEKSA MOGUĆA PREDIKCIJA BUBREŽNOG POPUŠTANJA KOD PACIJENATA SA HISTOPATOLOŠKOM POTVRDOM GASTROINTESTINALNE METAPLAZIJE?

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Ciljevi: Gastrointestinalna metaplazija je tradicionalno povezivana sa gastričnim adenokarcinomom. Gatrointestinalna metaplazija je obično povezana sa infekcijom Helicobacter pylori, starijom životnom dobi, pušenjem, konzumacijom jako začinjene hrane, socioekonomskim statusom i prisustvom IL10-592 C/A. Svrha ove studije bila je da se procene jednostavni laboratorijski parametri kod ispitanika sa gastrointestinalnom metaplazijom. **Rezultati:** Od maja 2018. do oktobra 2018. godine, ukupno 541 pacijent, od kojih su 281 muškarci, a 260 žene, sa gastrointestinalnom metaplazijom i srednjom starošću 58.5 ± 15, uključeni su retrospektivno u studiju, sa isključenjem pacijenata sa teškom osnovnom bolešću, uključujući rak želuca i resekciju želuca. Svim pacijentima je izvršena gastroskopija sa antralnom biopsijom, a uzorci biopsije su evaluirani na prisustvo gastrointestinalne metaplazije, korišćenjem Hematoksilina i Eozina, i statusa Helicobacter pylori (Giemza). Za poređenje i analizu su korišćeni hi-kvadrat test u nezavisni t test. Srednja vrednost koncentracije uree u serumu je bila 34.2 ± 16.1 mg/dL u gastrointestinalnoj metaplaziji i 31.2 ± 13.1 mg/dL u kontrolnoj grupi (95% CI od 32,3 do 34,6; p = 0.013), dok je srednja vrednost nivoa kreatinina u serumu 0.84 ± 0.28 mg/dL u gastrointestinalnoj metaplaziji i 0.80 ± 0.26 mg/dL u kontrolnoj grupi (95% CI from 0,80 to 0,85; p = 0.042).

Zaključak: Nivoi uree i kreatinina u serumu mogu poslužiti kao jednostavan klinički parametar za predviđanje slučajeva pacijenata sa rizikom od gastrointestinalne metaplazije.

Ključne reči: metaplazija, intestinalna metaplazija, endoskopija, histopatologija, hemotoksilin, helicobacter pylori, bubrežna insuficencija, urea, kreatinin.

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Professional article

EPIDEMIOLOGY OF OVERWEIGHT AND OBESITY OF TRAITORS OF THE MULTIMODAL FREIGHT MANAGEMENT OFFICE OF THE CITY PROVINCE OF KINSHASA

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Abstract: **Objective:** To determine the prevalence of overweight and obesity in the workplace. Methods: We conducted a cross-sectional study with 210 workers of which 119 male (56.7%) and 91 female (43.3%) selected in a simple random manner in a company in the city of Kinshasa province between November 2013 to January 2014. Overweight was determined by workers with a body mass index between 25 and 29.9 kg/m^2 and obesity by those with a body mass index ≥ 30 kg/m^2. **Results:** This study found a prevalence of 23.8% of overweight workers and 48.1% of workers suffering from obesity with predominance in women (65.5% in men vs. 80.2% in women, $p < 0.014$). The frequency of risk factors associated with obesity increased with the increase in weight status of BMI ($p < 0.001$). **Conclusion:** Obesity is a common pathology in the workplace and hypertension is the main modifiable risk factor. Sedentarity is the main determinant of overweight and obesity. Obesity is a public health problem in the workplace in the city of Kinshasa because of the command and collaboration frameworks are most affected.

Key words: overweight, obesity, associated risk factors, work environment.

INTRODUCTION

In the history of mankind, physical activity was essential to the survival of the species because it was necessary for foraging. Until the first half of the nineteenth century, the main daily occupations of man were characterized by a great physical activity: hunting, earthwork, handicrafts, etc. The human being did not just survive, he progressed until the arrival of the automobile, television, video games and internet (1, 2).

Technical progress has especially reduced opportunities for physical activity in the workplace. It is a fact that many employees today spend most of their work time sitting in front of the computer or watching television (3, 4).

Physical inactivity and sedentary behavior are two different and independent dimensions of movement behavior, respectively associated favorably and unfavorably with health status (5, 6). The World Health Organization (WHO), based on observations from around the world, shows that physical inactivity is responsible for two million deaths each year. Death rates for non-communicable diseases increase with body mass and more significantly with obesity (body mass index ≥ 30) (6). According to the same organization, the burden of overweight and obesity is growing so rapidly in Africa that these pandemics have become a public health problem throughout the African region that deserves study (6). Obesity affects 30% of adults, or 44 million Mexicans, and 40% are overweight (7). In 2002, China experienced a significant increase in obesity (2.6% of the population with a BMI ≥ 30) and overweight in general (14.7% of the population had a BMI ≥ 25), which affects about 215 million Chinese people (7). The 2008 figures confirmed the sharp rise in obesity in China: 90 million Chinese were obese and 200 million overweight. In the poorest countries, obesity is socially valued. For example, in Mauritania, girls of marriageable age are fattened to be more attractive and maximize their chances of finding a spouse. Unlike de-

veloped countries, it is about affluent populations, and is therefore a sign of success and wealth. Obesity, a multifactorial disease, is now considered a pandemic characterized by a metabolic disorder resulting from an accumulation of excess fat in the body and whose consequences can be harmful to health. It is a progressive chronic disease. It constitutes a serious risk factor that compromises the psychosocial functioning and the quality of life of patients who suffer from it (7). The prevalence overweight and obesity among Kinshasa workers is not very well known. It is to fill this gap that the present study was undertaken in a Multimodal Transport company in the Democratic Republic of Congo, in this case the Office of Management of Multimodal Freight, OGEFREM in acronym.

METHODS

Nature and period of study

We opted for the descriptive method and conducted a cross-sectional study that determined the prevalence of overweight and obesity among workers during a period from 2th November 2013 to 2th January 2014.

Framework of the study

This study took place at the Office of Management of Multimodal Freight, OGEFREM in acronym, of the city of Kinshasa, Democratic Republic of Congo.

Sample of the study

Our target population consisted of 400 male and female workers, aged 18 and over regardless of their rank and function. Our study sample was 210 randomly selected workers including 119 male (56.7%) and 91 (43.3%) female employees. Inclusion criteria included having freely agreed to participate in study, being between 18 and 59 years of age, being in apparent good health and working in one of the company's directorates for at least one year of service. Excluded were any worker who did not meet the inclusion criteria above.

Variables of the study

The morphological variables, level of physical activity and physiology used were as follows:

- Size (cm): It was rated with a SECA brand toe in lightly clad workers, was measured standing, heeled joints, head positioned so that the line of sight is perpendicular to the body,

- Weight (kg): It was measured using a calibrated SEC dry weight scale in kilograms (kg) to 100 g near him, the teenager stood on the scale, head up, looking towards the horizon with an undergarment. The body mass index (BMI) of workers was calculated using the following formula: BMI: mass (kg)/height (m). According to the World Health Organization (WHO) and the International Working Group on Obesity (8,9), overweight was defined for BMI values between 25 and 29.9 kg/m^2 and the obesity for the value greater than equal to 30 kg/m^2;

- Physical inactivity was measured by the number of steps per day ≤ 4999 recorded using an OMERON pedometer (10). The quality of life was assessed by the "Medical Outcome Study Short Form 36" (MOS SF-36) or "Short Form 36" (SF-36) questionnaire, is a generic questionnaire, robust, reliable, acceptable for the long-term. term measurement of quality of life, and validated in French. It contains 36 questions addressed to 9 dimensions: physical abilities, limitations related to the physical state, breads, perceived health, then vitality, relational life, psychic health, and finally evolution of the health perceived. Each item is weighted to obtain a score between 0 (zero quality) and 100 (maximum quality) for each of the 9 dimensions. The first 4 dimensions can be summarized in a Physical Summary Score and the following 4 in a Psychic Summary Score (10). Excessive alcohol consumption is defined as 21 grams of alcohol per day (11);

- Hypertension (HTA) was defined as BP ≥ 140/90 mmHg or the concept of antihypertensive therapy regardless of PA;

- Diabetes mellitus is defined as fasting blood glucose ≥ 126 mg/dl and dysglycemia or pre-diabetes (hyperglycemia or glycemic intolerance) with a blood glucose level of between 100 mg/dl and 125 mg/dl (11).

Statistical analyzes

The data collected was captured using Microsoft Excel 2013 Software and imported into the Social Science Statistical Package (SPSS) software version 21.0. Quantitative variables were presented as mean ± standard deviation and their extremes in the tables. The comparison of proportions was made using the Chi square test. The statistics the test results used were interpreted at the level of significance $p \leq 0.05$ for statistical decision making.

Ethical consideration

All workers had agreed to write for participation in the study according to the Helsinki Declarations. The information collected from the workers was kept confidential.

RESULTS

Socio-demographic characteristics workers are presented in Table 1. Of the 210 subjects in the study,

Table 1. *Socio-demographic and occupational characteristics of study subjects*

	n = 210	%
sex		
Male Female	119 91	56,7 43,3
Socio-professionnel level		
Commanders Collaboration frameworks Executing agents Age (X ± and, extremes) 18-39 years 40-59 years	89 71 50 45,1 ± 8,9 82 128	42,4 33,8 23,8 (27-59) 39 61
Level of study		
Superior Secondary Primary	173 18 19	82,4 8,6 9

there were 119 men (56.7%) and 91 women (43%), a sex ratio H/F of 1.3. The most represented age group was over 40 years of age (61.0%). The average age was 45 ± 8.9 years and the extremes at 27 and 59 years. Regarding the professional level, there were 89 (42.4%), 71 (33.8%) and 50 (23.8%) executives. 173 (82.4%) subjects studied had a higher level of education, 18 (8.6%) at the secondary level and 19 (9.0%) at the primary level.

The overall prevalence of overweight was 23.8 % and obesity was 48.1%. Overweight and obesity combined resulted in a prevalence of 71.9 %.

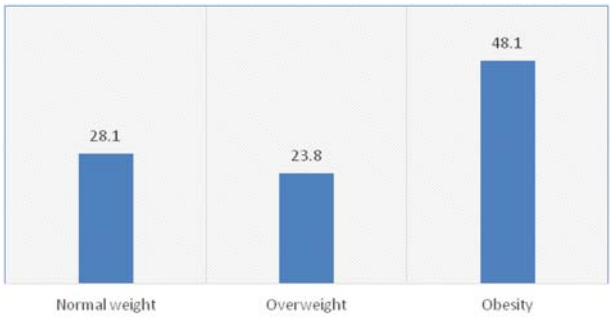

Figure 1. *Overall frequency of overweight and obesity*

According to sex, this prevalence is presented in Figure 2. When considering sex, Figure 2 shows that the specific prevalence is 80.2% for women and 65.5% for men. A statistically significant difference was found (P < 0.014). Compared to men, women have a high frequency of overweight and obesity (80.2% vs. 65.5%, (p < 0.014).

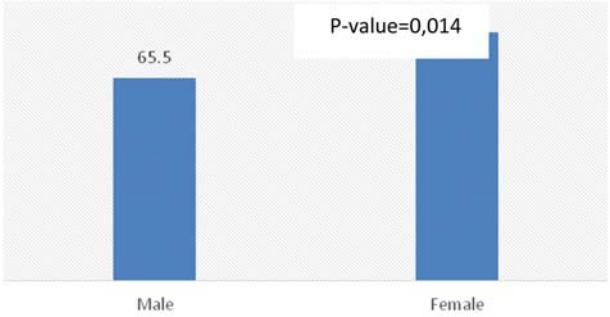

Figure 2. *Frequency of overweight and obesity by sex*

According to age, the frequency of overweight and obesity among the workers, Figure 3 shows us that workers aged 40 and over are most affected. The incidence of overweight and obesity increased significantly with age, so workers aged 40-59 were compared to those aged 18-39 (76.6%). vs 64.6%, p = 0.043).

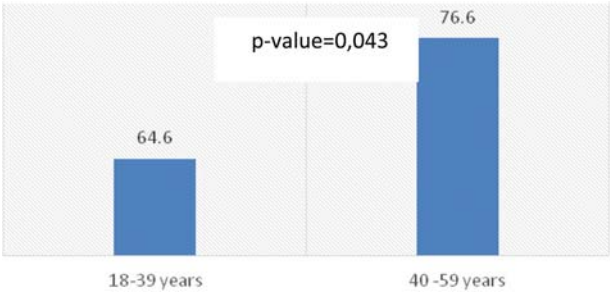

Figure 3. *Frequency of overweight and obesity by age*

Table 2 shows that the frequency of overweight and obesity increased significantly with high blood pressure (p = 0.0001) and the median daily energy expenditure was significantly higher among overweight workers than among workers obese 445 (111-1620) against 391 (118-1782).

Table 2. *Frequency, median and mean associated risk factors by nutritional status*

	BMI 18,5 à 24,9 Kg/m^2	BMI 25 à 29,9 Kg/m^2	BMI ≥ 30 Kg/m^2	p-value
Hypertension n (%)	7 (11,9)	23 (46,0)	58 (57,4)	0,0001
Diabetesmellitus n (%)	26 (44,1)	21 (42,0)	47 (46,5)	0,859
Physical inactivity	25 (50,0)	28 (47,5)	60 (59,4)	0,021
Energy expenditure (Kcal)	592 (132-1782)	445 (111-1620)	391 (118-1782)	0,007
Number of steps per day	5050 (234-12738)	4988 (254-12738)	4282 (100-11530)	0,003
Time spent sitting (min/day)	420 (60-780)	456 (60-900)	480 (60-840)	0,697

Table 3. *Determinants of overweight and obese in univaried and multivariate analysis*

Variables	analysis univaried			analysis multivariate		
	p-value	OR brut	IC 95%	p-value	OR aj	IC95%
Total sedentary time Physical inactivity	0,0001 0,000	8,928 5,31	1,865 10,087	0,001 0,000	8,422 7,33	1,852 1,972
Sex			1			
Male Female	0,008 0,000	0,998 4,756	0,996 2,029	0,011 0,003	0,697 4,334	0,994 0,451
Age			1			
18 to 39 years 40 years and over	0,000 0,000	6,521 4,926	2,724 3,987	0,881 0,004	1,093 3,599	0,341 0,395
Socioprofessional status			1			
Commanders Collaboration frameworks Executing agents	0,000 0,041 0,017	5,05 2,288 0,962	1,13 1,035 0,931	0,001 0,163 0,433	5,912 1,89 0,986	1,77 0,773 0,951
Quality of life			1			
Perception of physical health Perception of mental health	0,031 0,001	4,002 3,131	1,042 1,052	0,002 0,023	3,152 2,334	0,999 1,108

Table 3 identifies the determinants of overweight and obesity in univariate analyzes and multiple analyzes. In this regard, only the sedentary lifestyle expressed by the time spent sitting on the computer, physical inactivity, was the main determinant of overweight and obesity and increased the risk 8 times higher among sedentary employees.

DISCUSSION

This study aimed to determine the prevalence of overweight and obesity among workers in the city of Kinshasa. The prevalence of overweight and obesity among workers was 23.8% and 48.1%, respectively. Women and people aged 40 and over were the most affected with an associated risk, unlike men. This result corresponds to those observed by Gennus, Silander and combine in the world of work (11). According to the latest WHO global estimates, 38% of men and 40% of women over 18 are obese. In the workplace, obesity is very worrying, Koffi and alliers found a prevalence of 38.1% among port authority workers, both in Cameroon, Etoundi and ally found 37% in hotels and 57% observed by Fouda among shift workers working in the kitchen (12, 13, 14). The more you are in command, the more you become sedentary and change your eating behavior. This finding is consistent with those of Bergman, Burton and Barnett and colleagues who have found that high socio-occupational status is closely linked to physical inactivity, poor eating behavior and sedentary lifestyles (15, 16). However, Gardiner, Gao, Stamatakis and ally have shown that physical inactivity is related to an increase in nutritional status (17, 18, 19). This study can not allow us to generalize our results to all companies in Kinshasa and other national entities. Nevertheless, they show the extent of a public health problem hitherto poorly known in the professional world of Kinshasa. This is an interesting prospect for further studies that will allow employers to reduce costs related to staff health care and optimize business productivity.

CONCLUSION

Obesity is a common pathology in the workplace and hypertension is the main modifiable risk factor. Physical inactivity was the main determinants of overweight and obesity. Obesity is a public health problem in the workplace in the city of Kinshasa because of the command and collaboration frameworks are most affected. Awareness and behavior change education interventions to prevent these risks.

DECLARATION OF INTEREST

The authors declare that there are no conflicts of interest.

Sažetak

EPIDEMIOLOGIJA PREKOMERNE TEŽINE I GOJAZNOSTI ČLANOVA MENADŽMENTSKE SLUŽBE GRADSKE PROVINCIJE KINŠASA

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Cilj: Utvrditi učestalost prekomerne težine i gojaznosti na radnom mestu. **Metode:** Sprovedena je unakrsna studija sa 210 nasumično odabranih radnika sa liste osoblja kompanije u gradu Kinshasa, u periodu od novembra 2013. do januara 2014. god., a koja je uključivala 119 muškaraca (56,7%) i 91 ženu (43,3%). Prekomerna težina je označena kod radnika sa BMI između 25 i 29.9 kg/m^2, a gojaznost kod onih kod kojih je BMI ≥ 30 kg/m^2. **Rezultati:** Rezultati studije pokazuju da je učestalost prekomerne težine kod radnika 23.8%, dok 48.1% radnika pati od gojaznosti, i to sa većom učestalošću kod žena (65.5% kod muškaraca naspram 80.2% kod žena, $p < 0.014$). Učestalost faktora rizika povezanih sa gojaznošću raste sa porastom težine i BMI ($p < 0.001$). **Zaključak:** Gojaznost je česta na radnim mestima, a hipertenzija je glavni modifikujući faktor rizika. Sedentarni način rada je glavni uzrok prekomerne težine i gojaznosti. Gojaznost je problem javnog zdravlja na radnim mestima u Kinšasi, a najviše su pogođene rukovodeće službe.

Ključne reči: prekomerna telesna težina, gojaznost, pridruženi faktori rizika, radno okruženje.

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Case reports

PORCELAIN GALLBLADDER: A CASE REPORT

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Abstract: Porcelain gallbladder is an extremely rare variant of chronic cholecystitis. Previous studies have shown that the incidence of gallbladder cancer has reached 60% in patients with porcelain gallbladder, but in more recent studies, this incidence has been proven to be around 6%. Therefore, surgical intervention is not recommended for every patient. Although laparoscopic surgery is the preferred method of treatment, It is recommended that open surgery should be preferred in some publications because of high complication rates and technical difficulties of laparoscopic approach.

Keywords: Porcelain, gallbladder, cholecystitis, cholecystectomy, calcificaiton.

INTRODUCTION

Calcified gallbladder, calcified cholecystitis, cholecystopathia chronica calcarea or more commonly known as porcelain gallbladder (PGB) is a rare cholecystopathological condition in which the entire gallbladder wall is calcified (1). The relationship of this condition with gallbladder cancer was first pointed out by Brown in 1932 (2). In the literature, there are articles that do not routinely recommend prophylactic cholecystectomy. However, risk of carcinomatous transformation and need of long time follow-up is a disadvantage of non-surgical follow-up. Cholecystectomy is the recommended treatment for these patients (3).

CASE PRESENTATION

A 62-year-old male patient with a three-day history of abdominal pain was admitted to the general surgery outpatient clinic. The patient who had no history of previous surgery and who was using valsartan 320mg due to hypertension. The patient had tenderness in the right upper quadrant and epigastric region. In blood tests, leukocyte: 14500/mm^3 (4600-10200), hemoglobin: 15.6 g/dl (14.1-18.1), AST: 71 U/L (5-34), ALT: 68 U/L (0-55), total bilirubin: 1.2 mg /dl, crp: 12.3 mg/dl (0-0.5). Abdominal ultrasonography revealed a 4 x 3 x 3 cm hyperechogenic mass and fluid around sub-hepatic region. In intravenous contrast enhanced abdominal computed tomography, we revealed that the gallbladder wall was completely calcified, the wall thickness was 8 mm and the gallbladder was 43 x 35 x 27 mm in size. As a result of the radiological tests, we diagnosed the mass as PGB. Cholecystectomy was planned. The right subcostal incision was made to the abdomen and the wall of the gallbladder was yellow-colored and completely calcified as it was stained with bile. Gallbladder was completely dissected from the liver bed and there was a small amount of fluid mixed with bile. Cystic duct was found to be natural following Callot dissection but the cystic artery could not be isolated as a separate structure. After ligating the cystic duct with 2/0 silk suture 2 times, the cystic duct was cut by placing the clamp on the duct near the Hartmann pouch and cholecystectomy was completed. The cholecystectomy specimen was completely solid-like formed (Figure 1). The postoperative recovery period was uneventful and on blood tests the on postoperative second day, leukocyte: 9700/mm^3, AST: 15U/L, ALT: 21U/L, CRP: 6.2 mg/dl, and total bilirubin: 0.9 mg/dl.

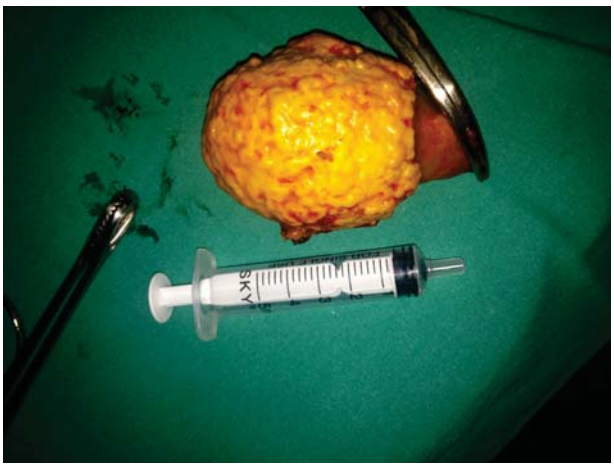

Figure 1. *Porcelain gallbladder*

On the second day, oral soft diet was started and he was discharged on the third day of his operation. No problems were found at the postoperative follow-ups on seven and twenty-first days. Pathological examination of the surgical specimen was reported as PGB and no signs of malignancy were observed.

DISCUSSION

The etiology of PGB has not yet been fully elucidated. The PGB, which the entire gallbladder wall is calcified, was first described by Fabré in 1831 (1). Khan et al found the incidence of PGB to be 1.1% (4). It is frequently observed between 3^{rd}-7^{th} decades of age and in obese women. Female/male ratio is 5/1 (5). Although the pathogenesis of this disease is not clearly understood, it is thought that it occurs due to dystrophic calcification, calcium metabolism disorders or gallbladder ischemia that follows the inflammation of gallbladder. Because of the widespread calcification, the gallbladder is rigid (6).

The relationship between PGB and gallbladder cancer was first described by Kazmierski et al. in 1951 (7). Etala et al. also reported that gallbladder cancer was observed in 16 (26.5%) of 26 patients with PGB (8). Machado reported that the incidence of gallbladder cancer was found to be 6.5% in PGB in the review of articles about PGB published between 1959 and 2016. Machado also found a decrease in the incidence of PGB-related carcinoma in the 70-year period, and argued strongly that this was related to developments in environmental factors and radio-diagnostic technology (9).

Patients present with right upper quadrant pain or a hard mass in the right upper quadrant. However, the disease is mostly asymptomatic and it is diagnosed when calcification is detected in abdominal imaging performed for another reason(10). Our patient presented with right upper quadrant pain.

Abdominal x-ray is helpful in diagnosis, but nowadays ultrasound and computed tomography are the radiological techniques used for diagnosis. In ultrasonography, the disease should be differentiated from emphysematous cholecystitis. Computed tomography is helpful in differential diagnosis (11). In our case, computed tomography was used for diagnosis.

Literature suggests that prophylactic cholecystectomy should be performed in asymptomatic cases with PGB (9). In a study performed by Chen et al, Cholecystectomy was performed to 102 of the 192 PGB cases between 2008 and 2013, and 90 patients without cholecystectomy after 3.5 years of follow-up had no gallbladder cancer (12). Although the laparoscopic approach is the recommended surgical method, but open surgical approach can be preferred because of the surgical technical difficulties due to the stone-like gallbladder and the high probability of conversion to open surgery (1).

CONCLUSION

PGB is an extremely rare disease of the biliary tract and is associated with a high incidence of gallbladder cancer. To our knowledge, the literature suggests prophylactic cholecystectomy even in asymptomatic cases. However, it is noteworthy that the in recent years the conservative approach and follow-up protocol have been used, instead of the surgical approach. We think that there exists a strong need for prospective studies examining the large case groups related to the treatment of this disease, whose etiology is still not fully resolved.

Funding

There is no funding related to this article.

Ethical Approval Statement

For this type of study, formal consent is not required.

Informed Consent Statement

Does not apply.

Abbrevations

AST — Aspartate aminotransferase
ALT — Alanine aminotransferase
CRP — C- reactive protein

DECLARATION OF INTEREST

The authors declare that there are no conflicts of interest.

Sažetak

PORCELANSKA ŽUČNA KESA: PRIKAZ SLUČAJA

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Porcelanska žučna kesa je izuzetno redak oblik hroničnog zapaljenja žučne kese. Prethodne studije navode da je incidenca pojave karcinoma žučne kese čak i do 60% u pacijenata koji imaju porcelansku žučnu kesu, ali najnovije studije navode da se zapravo ispostavilo da je incidenca oko 6%. S toga se hirurška intervencija ne savetuje svakom pacijentu. Iako je metoda izbora laparoskopska hirurgija, u literaturi se preporučuje otvorena hirurgija zbog višeg stepena pojave komplikacija, kao i tehničkih poteškoća prilikom laparoskopskog pristupa.

Ključne reči: porcelan, žučna kesa, holecistitis, holecistektomija, kalcifikacija.

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Case reports

PHANTOM TUMOR OF THE LUNG IN PATIENT WITH PNEUMONIA

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Abstract: **Introduction:** Localized interlobar effusions in congestive heart failure (phantom or vanishing lung tumor/s) are infrequent, but widely recognized entities.

Case report: A 80-years-old woman affected by progressive dyspnea over the previous three months, with productive cough. She was treated hypertension and had a pace maker implanted due to bradycardia. Chest X ray has shown right side pneumonia with high positive inflammatory markers. After resolution of pneumonia, phantom tumor of the lung was revealed, which disappear with intensive loop diuretics.

Conclusions: The diagnosis of the phantom tumor ought to be pondered as a possibility in any patient with congestive heart failure and lung mass. The patient at hand featured no prior history of congestive heart failure, hence indicating that phantom tumor may occur in non-chronic heart failure patients. Albeid the reliable diagnosis of the phantom tumor through the utilization of imaging modalities in patients without congestive heart failure can be rather challenging, such possibility must be considered in a patient with a lung mass in the major fissure of the lungs. Due to accelerated expansion of the geriatric population and subsequent spread of the congestive heart failure, a rise in the incidence of vanishing tumors of the lung may be anticipated.

Key words: congestive heart failure, loop diuretics, vanishing tumor.

INTRODUCTION

Phantom or vanishing tumor is a common term for a localized transudative interlobar pleural fluid collection in congestive heart failure, predominantly on right side and in male population (1). Such term stems from its frequent resemblance to a tumor on the Chest X ray and due to its being prone to disappear following the proper management of heart failure (1). Localized interlobar effusions are relatively infrequent, yet hold enough significance to merit recognition.

CASE REPORT

A 80-years-old woman affected by progressive dyspnea over the previous three months, with producti-

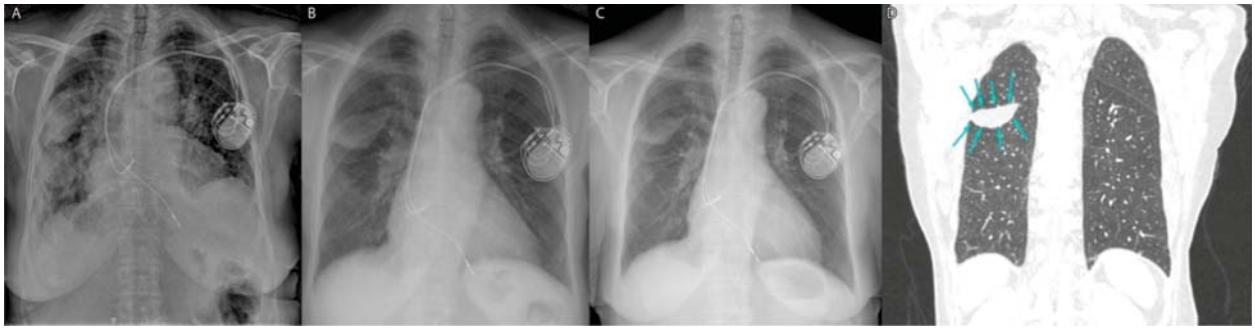

Figure 1. A. *Chest radiograph showing rounded two 4× 3 cm opacity in middle and lower right lung and pace maker in left lung;* ***B.*** *a homogeneous triangle of shadow in the middle pulmonary field on the right lung;* ***C.*** *homogeneous shadow-effusion in little incisura;* ***D.*** *verified effusion in the lung incisura on CT*

ve cough. She was treated hypertension and had a pace maker implanted due to bradycardia. Physical examination revealed cracles on the right lung. Chest x ray confirmed right sided massive pneumonia, which indicated extremely careful access, since serious comorbidity which sometimes could be unpredicted (2, 3). Laboratory findings have shown high values of marker of acute phase of inflammation /SE, CRP, LE, Ne/. Triple antibiotics therapy was introduced according to guidelines /ceftriakson, ciprofloxacin and metronidazole in full doses (4). Chest X ray showed two rounded 4×3 cm (tumor-like) opacity in the middle and lower zone of the right lung (Figure 1(A)). On the third day of hospitalization, she was complaining about irregular heartbeats, ECG showed atrial fibrillation with chamber response of 140/min. Amiodarone, ACE inhibitors, digoxin, loop diuretics and beta blockers were included (1). Echocardiography: ejection fraction around 65–70%. The patient was introduced to intensive IV loop diuretic therapy (1). After second and fifth day, chest X ray was performed (Figure 1 (B), Figure 1 (C)).). In order to confirm the presence of fluid in little incisura, computer tomography (CT) reaffirmed phantom tumor of the lung (Figure 1 (D)).

DISCUSSION

The presented case experienced an acute exacerbation of congestive heart failure masked with pneumonia. After successful treatment of pneumonia, control chest X ray discovered characteristic posteroanterior radiographic phantom lung tumor, right-sided, well delineated pulmonary mass with smooth margins. The established presence of fluid in the large pleural cavity makes for the easiest diagnosis of phantom tumor. With adequate rapid resolution of the pneumonia and simple method of chest X ray pseudotumor of the lung was revealed and successfully managed with loop diuretics after patient felt relief. The diagnosis of phantom tumor is facilitated when there is evidence of fluid in the large pleural cavity. The localization of phantom tumor is not necessarily in the horizontal fissure to the right; it can also be less often located to the left, or nearer to the mediastinum (5, 6). The radiological appearance of the phantom tumor may vary, in relation to the volume of septated liquid and its location (6, 7). It usually shows as a homogenous spherical or elliptical opacity at the horizontal fissures, with clearly marked boundaries (6). Lateral chest X-ray could be significant for the enhanced localization of the lesion. Following the procedure of intravenous infusion of potent diuretics, radiological resolution can be observed in less than 24 hours. Injury recurrence may appear in the cases of subsequent cardiac decompensations.

In several patient's chest X rays revealed intermittent appearance of the similar tumor-like shadows in the same region of the right lobe during an acute exacerbation of congestive heart failure confirming that phantom tumors can recur during episodes of cardiac decompensation (Figure D) (6, 7, 8).

CONCLUSION

This case confirms efficacy of the conservative medical treatment (loop diuretics) of the localized interlobar effusion in congestive heart failure. The possibility of phantom lung tumor should be considered and excluded in any patient presenting with congestive heart failure and an apparent lung mass on a Chest X ray. Finally, it is necessary to highlight the importance of recognizing this condition in order to avoid needless, costly and potentially harmful errors in diagnosis and treatment.

DECLARATION OF INTEREST

The authors declare that there are no conflicts of interest.

Sažetak

FANTOM TUMOR PLUĆA KOD PACIJENATA SA PNEUMONIJOM

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Uvod: Lokalizovani interlobarni izlivi kod kongestivnog srčanog zastoja (fantomski ili nestajući tumori pluća) su retki, ali široko priznati entiteti.

Prikaz slučaja: 80-godišnja žena sa progresivnom dispnejom tokom prethodna tri meseca, sa produktivnim kašljem. Lečena od hipertenzije, a implanti-

ran joj je i pejsmejker zbog bradikardije. RTG snimak grudnog koša pokazao je pneumoniju sa desne strane sa visokim inflamatornim markerima. Nakon izlečenja upale pluća, otkriven je fantom tumor pluća koji nestaje nakon intenzivne terapije diureticima.

Zaključak: Dijagnozu fantomskog tumora treba razmotriti kao mogućnost kod svakog pacijenta sa kongestivnim zastojem srca i evidentiranom masom u plućima. Prikazani pacijent ranije nije imao znake kongestivnog zastoja srca, što ukazuje na to da se fantomski tumor može pojaviti kod bolesnika bez hroničnog kongestivnog popuštanja srca. Iako pouzdana dijagnostika fantomskog tumora upotrebom raznih vidova radiološke dijagnostike kod pacijenata bez kongestivnog zastoja srca može biti prilično izazovna, takva mogućnost se mora uzeti u obzir kod pacijenta sa masom u plućima u velikoj incizuri pluća. Zbog porasta broja gerijatrijske populacije i kasnijeg javljanja kongestivnog popuštanja srca, može se očekivati porast učestalosti fantom tumora pluća.

Ključne reči: kongestivno popuštanje srca, diuretici petlje, fantom tumori.

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Case reports

LIP PITS ABSCESS: ISOLATED CONGENITAL MIDLINE UPPER LIP SINUS

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Abstract: Congenital midline upper lip sinuses or fistulas are exceptionally uncommon condition following abnormal fusion of embryologic structures. Here, we report a case of congenital upper lip sinus type I presented as upper vestibular fold abscess in a seven year old boy.

Key words: Congenital, midline sinus, upper lip, vestibular abscess.

INTRODUCTION

Congenital midline lip fistulas or sinuses are infrequent malformations. The anomalies are typically found in Van der Woude syndrome, characterized by a pair of lower-lip dimples in relation with cleft palate. The incidence of the congenital lower lip fistula is considered to be 0.001% whereas upper lip sinuses are even more unusual, and they usually present as a dimpling into a blind sinus, that breaches the orbicularis oris muscle ending under neath the mucosal surface of the lip, without communication with the oral cavity (1, 2). Median fistula of the upper lip may be accompanied with other congenital midline abnormalities, such as nasal dermoid cyst, median cleft, sinus of the labial frenulum, midline sinus of the dorsum of the nose, double frenulum or hypertelorism, suggesting a collective embryological developmental fault of midline malformations (3).

CASE REPORT

A7-year-old boy presented to have a midline pit in the upper-lip philtrum since birth. He had recurrent bulge around the frenulum of the upper lip with clear fluid discharge through external orifice of upper lip. There were no other related congenital anomalies and none of his family members had similar symptoms, lip pits, cleft lips or cleft palates. He was treated by paediatric surgical team with a course of antibiotics but to no avail when the swelling recurred multiple times. He was then referred to our department with features of an abscess and pus discharge coming out from the sinus. Clinical examination revealed an upper lip sinus located on the midline of the philtrum just below the base of columella with a small pit of 1.0 mm in diameter (Figure 1). Over the frenulum portion of upper lip vestibule, there was a fluctuant swelling with very thin erythematous mucosal surface (Figure 2). There were no abnormalities noted elsewhere in the body. He was started with antibiotic and posted for surgical exploration and drainage of the abscess. Intraoperatively, a small transverse incision was made over the upper vestibular swelling to drain the pus and a metal probe was inserted into the opening on the cutaneous surface of the up-

Figure 1. *Small pit in the midline of philtrum just below the base of columella*

Figure 2. *The upper vestibular fold swelling existed on either side of frenulum*

Figure 3. *Communication between the sinus with abscess cavity as shown by the metal probe*

per lip which was found to becomm unicated with the intraoral swelling (Figure 3). Then the entire sinus tract was excised completely, leaving a small ellipse of skin around the defect and the inner surface area was curetted. Layered closure of the skin done while the intraoral wound was packed with saline soaked ribbon gauze dressing for secondary wound healing. Histopathological examination of the specimen showed a tubular structure measuring 7 mm in length and 5 mm in diameter. Cut section shows present of lumen in the centre of the tubular structure. Microscopically, the sinus tract lined by stratified squamous epithelium with underlying stroma show mild lymphocytes and plasma cell infiltrate. The tissue from intraoral mucosa show typical features of an abscess. At one week postoperatively the wound healed well.

DISCUSSION

Congenital upper lip sinuses are so rare and have only been sporadically reported in journals with no consensus on the definitive treatment of choice (2). To date, only several cases of upper lip sinus and fistulas have been reported worldwide with only 31 individual cases comprise of 13 cases of type I with female predilection, 9 cases of type II and 9 cases of type III. Among the 13 cases of type I upper lip sinus, only 1 was a male similar to our case which made it up to only 2 cases have been reported so far over the globe (4). While the mechanisms of the development of congenital upper lip sinuses are still partially understood, there are three leading theories behind their aetiologies; 1) the invagination theory suggests that upper lip sinuses are a result from a failed ectodermal invagination of the nasal placodes during the fronto nasal process development, 2) the merging theory which states that the sinus is due to abnormalities in the normal mesodermal integration development, and 3) the fusion theory proposes an incomplete integration between the fronto nasal and maxillary processes (1). Because this condition is uncommon, much of our understanding is based on details of individual case reports. In 2011 Aoki et al developed a classification system for upper lip sinuses; (a) type I: midline sinus with no associated anomalies; (b) type II: midline sinus with additional anomalies; and (c) type III: the lateral sinus with or without associated anomalies (5).

A high index of suspicion is important in identifying this rare condition especially when patients present with periodic upper lip swelling and discharge. Repeated infections occurred in 25% of the reported cases. A comprehensive history and examination should be conducted, to look properly for congenital pits on the lips and accompanying congenital abnormalities. Van der Woude syndrome is known to be associated with cleft lips, palate and lower lip pits; however, upper lip sinuses are not known to be linked with any specific mode of genetic inheritance (1).

Our case represent type I of midline upper lip sinus, without other accompanying anomalies and the patient's family history also did not reveal any similar conditions, which suggests that the abnormality may be spontaneous rather than inherited and was a rarest of

all forms of classification. Without awareness and concern for underlying sinus, one can never formulate the complete diagnosis and therefore addressing adequately any secondary condition of it e.g. intraoral abscess. Management comprises of complete surgical excision via an intraoral or extra oral approach; whereas incomplete excision leads to recurrences and ultimately cosmetic deformities. Some centres injected 0.5% methylene blue through the opening of fistula to ensure complete excision of the tract and served as indicator of incorrect plane of dissection (3, 5, 6). Different centre may treat the abscess separately whereby the abscess is drained first before an excision of the tract is carried out (5). In this case, the drainage and curettage of the abscess with excision of the sinus tract were done simultaneously to reduce anaesthetic risk to paediatric patient as well as to minimize any psychological trauma to the patient. Nevertheless, longer follow up need to be carried out in order to monitor any recurrence and complication.

In conclusion, recurrent vestibular abscess is one of the complication/sequelae of midline sinus. Complete removal is recommended to render patient free of the disease without recurrence.

DECLARATION OF INTEREST

The authors declare that there are no conflicts of interest.

Sažetak

APSCES NA USNAMA: IZOLOVANI KONGENITALNI SINUS SREDNJE LINIJE GORNJE USNE

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Kongenitalni sinusi ili fistule srednje linije gornje usne su izuzetno retka stanja, koja prate abnormalno spajanje embrioloških struktura. U ovom radu izložićemo prikaz slučaja kongenitalnog sinusa gornje usne tip I, koji se prezentuje kao apsces vestibularnog nabora gornje usne kod sedmogodišnjeg dečaka.

Ključne reči: kongenitalno, sinus srednje linije, gornja usna, vestibularni apsces.

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Case reports

THE OXYBUTYNIN ABUSE IN ADOLESCENT CASE

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Abstract: Oxybutynin is one of the most commonly prescribed drugs in overactive bladder treatment. Because of its lipophilic structure, it crosses the blood-brain barrier and causes cognitive side effects in the central nervous system. Abuse of the drug is due to its hallucinogenic effect. In terms of substance use disorder, adolescents are one of the groups at risk. In addition to well-known addictive substances, drugs which have sedative, anticholinergic-antimuscarinic, stimulant properties and prescribed for any treatment also can be abused in adolescents with substance abuse. In this article, it is aimed to raise awareness of physicians and health workers about oxybutynin abuse because of the pharmacodynamic characteristics of the drug and its effects on the central nervous system. The health professionals should therefore prescribe this drug with more attention and follow-up those patients.

Key words: oxybutynin, adolescent, addiction, abuse.

INTRODUCTION

Oxybutynin chloride is one of the most commonly prescribed drugs for the treatment of overactive bladder. It also is indicated in patients with detrusor instability related to neurogenic bladder. It has been studied in and approved for patients over 5 years of age (1). In practice, the minimum therapeutic dose is 5 mg/day and the maximum dose is 20 mg/day. Besides its antimuscarinic effects, oxybutynin has direct anesthetic and smooth muscle relaxant effects (2). Side effects are mainly constipation and dry mouth. There are also side effects in the central nervous system since it is a lipophilic agent so that it can cross the blood-brain barrier. As a result of the studies; concentration problems, decreased alertness and deterioration in decision-making abilities were found in patients with oral oxybutynin use (3). Overdose of the drug may cause anorexia, insomnia, agitation, delusions, hallucinations, confusion, and delirium (4). Abuse of the drug is due to its hallucinogenic effect. It causes an increase in neurotransmitters such as dopamine, GABA and serotonin in the synaptic cleft due to anticholinergic effect. This situation leads to aggravationof addiction behavior (5). In terms of substance abuse, adolescents are one of the groups at risk. When the age of onset for substance abuse is evaluated, it is seen that it usually arises in adolescence (6). There are many risk factors that affect substance use in adolescents. The most investigated factors are; age, gender, personality traits, genetic and environmental characteristics. The most prominent one of these factors is to have friends with substance addiction (7). In addition to well-known addictive substances, drugs which have sedative, anticholinergic-antimuscarinic, stimulant properties and prescribed forany treatment also can be abused in adolescents with substance abuse. In this article, we aimed to discuss a case with oxybutynin abuse.

CASE REPORT

A. A 17year-old male patient who was taking care at the child support institute was brought to our clinic because of substance abuse and excessive irritability. It was learned that his parents had adivorce 6 years ago, the custody was given to the father and he had started living with his father. After the second marriage of his father, he started going away from home, when he had a first encounter with this substance. It was learned that he had robbed for the purpose of accessing the substance and was later handed over to the institution by the police. He told that he started to smoke at the age of 10. He was smoking 1 pack/day and later he used cannabis and alcohol. He also said that he used alcohol and cannabis 4-5 times a week, and usually was consuming both of them together. On a day when he couldn't find cannabis and alcohol about 6 months ago, he said that

he was given a pill by his friend and continued using it because he felt good afterwards.We learned that he bought 5 to 10 (25-50 mg) pills per dayat the pharmacy, and the amount of sleep and appetite decreased when he took them. It was learned that drugs took 5-10 times a day sometimes 2-3 times a day. He also stated increased energy with drugs.The institute officer stated that the pills were brought to the institute by the patient. When he was not able to find any pill, his irritability increased and he forced the staff to prescribe it to him. When he couldn't find any pill he escaped from the institute to apply to the hospital.

As the patient had no family, his developmental history was not taken. Educational history revealed that he completed 5th gradeand gave up school in sixth grade. He told that he learned reading and writing on time but never liked to study, he was generally an unsuccessful student. He said he was bored in class and could not listen to the teacher. He was very active child, he had broken his arm twice and had sustained minor injuries several times.

In the psychiatric evaluation; general appearance was cachectic, consistent with low socioeconomic level, self-care was inadequate. Large and small superficial cuts in the arms which were made for self-destruction were observed. It was learned that the cuts were after substance use. He had a dysphoric mood and his affect was compatible with his mood. Frustration tolerance was low, irritability and anger bursts were observed. It was determined that the rate and the amount of speech were normal.Overthinking about substances, especially oxybutynin was detected in thought content. Concentration problems, hyperactivity and impulsivity were also determined. Visual hallucinations were remarkable only when he took oxybutynin.

DSM-IV-based screening and evaluation scale for attention-deficit and disruptive behavioral disorders filled by the patient was consistent with attention deficit hyperactivity disorder (ADHD) and conduct disorder. BAPI (addiction profile index-adolescent application form) was found to be compatible with substance use disorder and impaired functionality.

As a result of psychiatric evaluation and scales, ADHD,conduct disorder, substance use disorder and oxybutynin abuse were detected in our patient. Since the patient refused to be followed up in the inpatient service and the service was semi-closed, the patient was followed as an outpatient because of the risk of escape. Motivational interview was used. Sertraline (50 mg/day) and risperidone (2 mg/day) were initiated to treat substance use disorder and to reduce craving. Atomoxetine was planned for ADHD. In the evaluation of the patient on the second week after he was discharged from the hospital; it was observed that the irritability decreased, he used the medications regularly and no side effects were described. It was learned that the substance and oxybutynin craving were still present but less disturbing. Atomoxetine 25 mg/day was added to the treatment of the patient and then he was called for control.

DISCUSSION AND CONCLUSION

In adolescence, in addition to the physical changes, there are many psychological changes. Identity acquisition is one of the most important achievements of this period and this situation may turn into anidentity confusion in some individuals. These individuals who are in the process of identity formation are at great risk for substance use. Our patient is at a risky period in terms of substance use. At the same time, the chaotic family structure and divorced parents have made our patient prone to substance use. In many studies, it has been shown that the prevalence of smoking, alcohol and substance use are higher in adolescent individuals with inadequate family functioning and problematic family structure (6, 7).

Children and adolescents with ADHD have a higher rate of alcohol, tobacco and illicit substance use than children and adolescents without ADHD (8). In the same study, smoking, cannabis and alcohol use were found 2.5 times higher in ADHD patients. In addition to untreated ADHD, conduct disorder also increases the risk of substance use. The same situation is valid for substance use disorder. The prevalence of ADHD and conduct disorder have been found to be 66% and 35%, respectively, in a study in which patients with substance use disorder have been evaluated (9). Our patient had previously no proper treatment for his diagnose of ADHD and conduct disorder. Starting to smoke at an early age in our case supports the fact that tobacco is the transition substance. Early smoking increases the risk of substance use for later periods (10). In our case, smoking was followed with the use of cannabis and alcohol.

Oxybutynin abuse can be seen in adolescents, although it is not a common condition. In the two case reports about abuse of this drug in adolescence, the drug dose was similar to our case. After drug use, auditory-visual hallucinations and euphoria have been reported. Tremor, increase of anxiety and sweating have been reported as withdrawal symptoms of the drug (11, 12). Other case reports related to drug abuse belong to adult age group. Two cases of alcohol and substance use disorder were found to have an abuse of oxybutynin. The drug dose of one of these cases was 100 tablets (500 mg) and this is the highest dose we encountered in the literature. Depression, irritability, in-

somnia and sweating have been reported as withdrawal symptoms (13).

In another case report in the literature, it has been reported that the case who had no substance use before had used oxybutynin in military service. Similar to our case, the subject started oxybutynin with peer effect. It has been reported that it started to be re-used due to fatigue, anger, irritability, carelessness, speech difficulties, introversion symptoms after the discontinuation of the drug use and increased the dose (4). In another case report, it was reported that 60-70 tablets (300-350 mg) oxybutynin was used and psychotic findings were observed similar to our case (14). Psychotic symptoms with low doses of 10-15 mg have been reported in two cases without the abuse of oxybutynin. One of these cases was 7 years old and he used it by mistake. The other patient was 21 years old and he was taking medication with the diagnosis of enuresis nocturna (15). On the other hand, psychotic findings have been not found to occur in another two case reports; although one of the patients with oxybutynin abuse at the prison consumed the drug with a dose of 150 mg/day and the other had 400 mg/day(16).

Oxybutynin is a drug which may cause dependence and differs from other psychotropic agents that we encounter in practice with this property. It has been taken by prescription since March 2017 in Turkey. However, it can be easily prescribed. Individuals with substance use disorder can easily become addicted to the drug. Therefore, the use of anticholinergic drugs should be carefully considered in risky groups and should be prescribed with caution. In this case report, it is aimed to report that oxybutynin is a drug that can be abused and adolescents are at high risk for the abuse of this drug.

Abbreviations

GABA — Gamma-aminobutyric acid

DSM-IV — Diagnostic and Statistical Manual of Mental Disorders 4th. edition

ADHD — Attention-Deficit/Hyperactivity Disorder

BAPI — Addiction profile index-adolescent application form

DECLARATION OF INTEREST

The authors declare that there are no conflicts of interest.

Licensing

Sažetak

ZLOUPOTREBA OKSIBUTINA U SLUČAJU ADOLESCENATA

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Oksibutinin je jedan od najčešće propisivanih lekova u lečenju hiperaktivne mokraćne bešike. Zbog svoje lipofilne strukture, lako prolazi kroz krvno-moždanu barijeru i izaziva brojne neželjene efekte u centralnom nervnom sistemu, koji se pre svega odnose na poremećaje kognicije. Zloupotreba ovog leka može dovesti i do halucinogenih efekata. Odnoseći se na zloupotrebu supstance, može se reći da su adolescenti grupa koja je najviše pod rizikom od zloupotrebe ovog leka. Dobro su poznati sastavni delovi ovog leka, koji izazivaju zavisnost, kao i supstance koje imaju sedativno, antiholinergičko-antimuksarinsko dejstvo, kao i one koje imaju stimulativne karakteristike i koje su propisivane u svrhe lečenja drugih simptoma i bolesti, a koje adolescenti mogu koristiti i zloupotrebljavati. Cilj ove studije bio je da se proširi svest doktorima medicine i zdravstvenim radnicima u vezi sa zloupotrebom oksibutinina, pre svega zbog njegovih farmakodinamskih karakteristika i efekata na centralni nervni sistem. Zdravstveni radnici i profesionalci, s toga, moraju da propisuju lek pažljivije i da prate ove pacijente.

Ključne reči: oksibutinin, adolescenti, zavisnost, zloupotreba.

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Letter to editor

ACCESSORY THYROID GLAND OF THE LATERAL NECK

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A 34-year-old Turkish woman presented with a left-sided cervical accessory thyroid gland. Her B-Mode thyroid ultrasonography exhibited an accessory thyroid parenchyma adjacent to the inferolateral border of left lobe of the thyroid gland (Figure 1a). Fine-needle aspiration (FNA) cytology (FNAC) is a frequently used primary diagnostic procedure worldwide due to its preciseness, easiness, non-invasiveness, possessing very little complications and low cost (1, 2). The thyroid gland ectopia and accessory thyroid tissue are two patterns of the abnormal thyroid gland migration. Ectopic thyroid gland is a rare phenomenon and described as a functioning thyroid tissue in an aberrant area along the embryological descending line of the thyroid gland. Its most common form is known as lingual thyroid, accounting for 90 %. Aproximately 70 % of patients will exposed to the hormonal status of subclinical hypothyroidism (3). These phenomenon may later undergo a malignant transformation (4). An accessory thyroid gland is determined as a permanence of the thyroidal parenchyma anywhere from the base of the tongue to the thyroid isthmus, with the majority of the functional thyroid in its normal pretracheal area. The incidence of accessory thyroid gland is unknown (3). Of 58 cadavers just one (1/58) was detected as the accessory thyroid gland on the thyroid cartilage by Braun et al (3). Radkowski et al (5) performed thyroid ultrasonography on 230 cases of the throglossal duct cyst and detected four cases (4/230) with the accessory thyroid tissue and three (3/230) with the ectopic thyroid gland. Therefore, they propunded the possibility of their equality in the incidence. The accessory thyroid glands are classified into five groups, based on their anatomical location: (1) cranial, (2) caudal, (3) lateral, (4) ventral, and (5) dorsal glands. They usually are founded along the former course of the thyroglossal duct and emigrate laterally (6). Pyramidal lobes, superior accessory thyroids, retrotracheal, inferior/lateral extensions or extrusions are involved in the reasons of the recurrent thyroid diseases as the anomalies of the gland. Richards et al (3) asserted both thyroid gland ectopia and accessory thyroid tissue being vulnerable to the same potential diseases as a normally-situated thyroid gland. An accessory thyroid gland do not lead to clinical complication except in cases of the pathologic conditions such as goitre, malignancy, and the others. A thyroid FNA were planned,

Figure 1a. *The photograph of B-Mode ultrasonography, exhibiting a left-sided accessory thyroid parenchyma and its location*

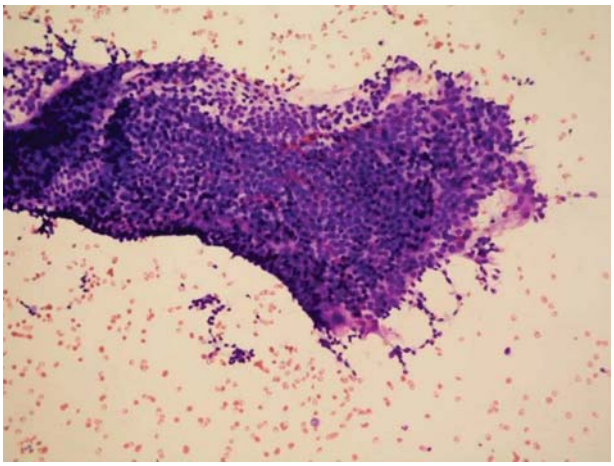

Figure 1b. *The photomicrograph, exhibiting a huge cellular cluster, composed of the thyrocytes in a benign nature (Haematoxylin and Eosin, Original magnification, 100x)*

performed and its cytopathologic evaluation with Haematoxylin and Eosin revealed a huge cellular cluster including the benign thyrocytes (Figure 1b). Therefore, a clinical follow-up was suggested for the present case, after a benign FNAC. Conclusively, education, training, and cognition of the thyroid embryology and anatomy and its associated variations and anomalies are very much essential for these kinds of the cases and it will lead to increasing the level of awareness.

Abbreviations

FNA — Fine-needle aspiration
FNAC — Fine-needle aspiration cytology

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Review article

THE INFLUENCE OF CHRONIC STRESS ON HEALTH AND COPING MECHANISMS

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Abstract: Stress represents a negative life experience, closely followed by physiological, cognitive, emotional, and behavioral changes that focus on changing the event or adapting to its effects. Any situation or occurrence that requires adaptation can be experienced as a stress, even positive situations and circumstances may be stressful, whether they come from the outside world, or the sources of stress is internal. While acute stress does not necessarily have a negative effect, if it lasts for a long time, or is frequently repeated, it becomes chronic, and can cause various serious disorders. During chronic stress, there is an exhaustion of the body's capacity for an adequate reaction, which can lead to long-lasting immunological dysfunction, which significantly impairs health and quality of life. According to the WHO (2017), stress is one of the causes of even 60% known diseases, and in a number of mental disorders a direct connection with stress has been reported: in acute stress reactions, "posttraumatic stress disorder", adjustment disorders and other reactions to severe stress. In addition, in all categories of mental disorders (ICD-10), the stressful situation or event plays a significant role in occurrence of the symptoms. A particular category of stress-related disorders are psychosomatic disorders. These are functional disorders in which there is no pathoanatomic substrate. In contrast to these, psychosomatic diseases are the type of illness in which there are structural changes of tissues and organs, the etiology of which is based on chronic stress, in addition to a number of other factors (Adamović, 1983) and which occur when there is a biological predisposition. The paper presents the mechanism of development of these diseases and some of the ways of coping with stress. According to the DSM-V, psychosomatic diseases are divided into skin diseases, gastrointestinal diseases, respiratory diseases, heart and blood vessel diseases, disorders of endocrine glands, rheumatoid diseases, gynecological diseases and others. In order to overcome stress and preserve health, psychological strategies for coping with stress play an important role. Multiple strategies are used, which include various stress control techniques: relaxation techniques, meditation methods, and assertive training, biofeedback and stress inoculation techniques. Successful mastering of coping stressful situations, constructive problem solving in life crisis, relaxation techniques and contributions to better adaptation to unexpected changes in life are of key importance for both mental and physical health.

Key words: stress, psychosomatic diseases, coping stress strategies.

INTRODUCTION

Nowadays, the concept of stress has been adopted, both in professional circles and among layman and is used to explain many phenomena in everyday life (1, 2, 3). To what extent does stress represents a medical problem, indicates WHO (World Health Organization) report, which proclaimed 20th century as "the century of collective and individual stresses in epidemic proportions and various forms, unseen so far in the history of the human race." Thus, over the past century, stress became a critical factor in maintaining health and the cause of psychosomatic diseases.

Stress represents a negative life experience, closely followed by physiological, cognitive, emotional, and behavioral changes that focus on changing the event or adapting to its effects. Stress is indeed the result of a subjective assessment of a particular person who lacks ca-

pacity to adapt to the newly emerging situation. Every situation or event that requires adaptation can be experienced as stress (3, 4, 5). This implicates that stress can represent not only negative, but also positive situations and circumstances: marriage, relocation, starting school etc. In addition to the "external", there are "internal" stressors, such as illness, perfectionism, unrealistic expectations, and so on. If it lasts for a long time, or is repeated frequently, acute stress becomes chronic, which is the cause of a whole range of disorders (2, 3).

There are various definitions of stress, however, one of the most frequently quoted is the one by Lazarus (1950): "A subjective assessment of the events includes the assessment of the degree of demand and the support that is available in the process of coping with problems". Stressors impersonate external or internal events that cause stress, whereby it is crucial to appraise whether an event is stressful for a particular person or not. This subjective assessment of stressful events leads to changes in psychological functioning, in physiology and in the experience of the entire process which is actually a stress reaction.

Epictetus, Greek philosopher (50-138) stated: "People are not upset by the event itself, but by their own perception of a certain event."

Universal stressors are disasters (earthquakes, floods, wars), traumas (exceptional unpleasant individual experiences like rape or torture), and crises-expected unpleasant life events which represent normal experience, and in most people cause similar reactions. In addition to these high-intensity stressors, there are also chronic low-stress intensity stressors such as unsatisfactory marriage, burnout or poor relationships in the working environment. Nevertheless, in addition to the fact that there are universal stresses, we must bear in mind that the experience of stress is purely individual, having said that, some situations will be experienced by one as stressful, while other will have quite different experience. Reactions are depending on the individual assessment, as well as the capacity of a person to coup with it. When stress exceeds the ability to adapt, it distorts the quality of life and leads to physical or mental disorders. Nowadays, in contemporary literature, the prevailing assumption is that the overcoming of stress represents a mediator of stress. This implicates that stress and various disorders are not directly related to stress itself, but that stress is a factor that triggers prevailing behavior which affect the outcome (3).

Short-term or "acute" stress does not necessarily have negative consequences. This kind of stress is also called "eustress" and it can encourage person to progress and to achieve success. In the state of "eustress", one is conscious, with sharpened attention and perception, with shortened reaction time, (e.g. exam, job interview, etc.). Distress, however, means that there is no way to overcome the stressful situation, which makes individuals helpless and significantly jeopardizes our sense of well-being (3).

Acute stress occurs within a few minutes as a response to a strong stressor, causing a defensive reaction which causes the individual to experience the feeling of physical and psychological fatigue. Some individuals during the acute stress may experience muscle paralysis ("paralyzed from fear"), while other experience- "fight-or-flight response". In the first phase, organism prepares for action and the adrenal cortex is activated through the sympathetic nervous system leading to an increase blood levels of adrenaline and noradrenaline. As a result of this, heart rate increases as well as blood pressure, glycaemia rises and the sweat glands are stimulated. Frequent urination, vomiting, or diarrhea may also be associated symptoms (1, 4, 5).

In the second phase, which occurs several minutes later, hypothalamic-pituitary-adrenal axis is activated which leads to hypercortisolaemia. This axis has the opposite effect on the organism from the sympathetic-adrenal-medullary axis. It ensures preservation of the body and energy and it also engages in passive behavior and avoidance (1, 4, 6, 7).

However, over chronic stress, we notice exhaustion of the body's capacity for adequate fight- or-flight response, and chronic hypersecretion of glucocorticoids leads to volume reduction in the hippocampus and hypothalamus (6, 7, 8). In the same time, chronic stress, according to modern knowledge, leads to long-lasting immunological dysfunction, which at the end disturbs health and quality of life (8).

During chronic stress, the high level of cortisol is prolonged, which leads to a reduced immune response and functional disorder of normal immune response (there is an increased risk for autoimmune disorders due to the production of pro-inflammatory substances responsible for the emergence of chronic inflammatory diseases) and they also increase the risk of developing some of the autoimmune diseases such as lupus, rheumatoid arthritis, fibromyalgia, etc.).

In 2017. WHO stated that for 60% of known diseases one of the causes is stress (7, 8). Much less surprising is the fact that many mental disorders are caused by stress, where we can trace direct association such as in the acute stress reaction, posttraumatic stress disorder, adjustment disorders, and other reactions to severe stress. In addition, in all categories of mental disorders (ICD-10), the stressful situation or event plays a significant role in occurrence of the symptoms.

PSYCHOSOMATIC DISORDERS

It was already known in ancient times that exposure to long-lasting stress, as well as various emotional

states, could lead to physical illness. Socrates (470-300 BC) stated during the treatment of numerous bodily diseases that the body cannot be cured if "the soul is not healed". He also believed that any problem that patient has and is unsolvable to him can cross into the physical sphere and become bodily disease. The term "psychosomatic" was first used in 18th century by Hainroth, who cited numerous physical disorders that he connected with the influence of strong emotions. G. Groddeck (1866-1934), who advocated for the holistic treatment of every physically ill patient, is regarded as a pioneer of psychosomatic medicine. In the beginning of the 20th century, interest in psychosomatic disorders was growing, and in scientific circles there was an increasing number of publications citing chronic stress as a possible cause of many bodily illnesses. In the basis of psychosomatic diseases, somatization is actually a mechanism by which emotional content is transformed into the body sphere, and the pathological substrate occurs when the flow of anxiety through the body becomes dominant in the "emptying of an excess of anxiety." This leads to the manifestation of psychosomatic disorders or psychosomatic diseases (8, 9, 10).

Psychosomatic disorders are functional disorders caused by stress, and without a pathoanatomic basis, while in psychosomatic diseases there are structural disorders of organ and organic systems and chronic stress in addition to a number of other etiological factors, plays a crucial role (8).

A link that connects chronic stress with physical illnesses is certainly a neuroendocrine and immune system, but so far pathophysiological mechanisms are not clear enough.

Franz Alexander, (1891-1964) described the "big 7" diseases in whose genesis, stress plays a key role. These are: arterial hypertension, gastroduodenal ulcer, ulcerative colitis, hyperthyroidism, asthma, chronic poli-rheumatism and neuro-dermatitis. His interpretation was that the etiology of these diseases were most commonly unpleasant emotions but when there was a biological predisposition. Emotions responsible for the onset of the psychosomatic disease are most often suppressed aggression and jealousy that are caused by psychological trauma in childhood. In doing so, psychosomatic symptoms are a form of stress release in the absence of a more convenient way.

The latest classification of the American Psychiatric Association (DSM-5, 2013) classifies psychosomatic diseases as follows:

1. Dermatological diseases (acne, urticaria, neurodermitis, angioneurotic edema)

2. Digestive system diseases (ulcer, constipation, irritable bowelsyndrome, Crohn's disease)

3. Respiratory system diseases (asthma, tuberculosis)

4. Heart and blood vessels (hypertension, angina pectoris, arrhythmias)

5. Endocrine disorders (diabetes, hyperinsulinism, and hyperthyroidism)

6. Rheumatic diseases (chronic back pain, lumbar syndrome, polyurheumatism)

7. Gynecological diseases (dysmenorrhea, spontaneous abortion)

8. Other (obesity, overeating, migraines, tumors)

It is evident that the number of psychosomatic diseases is on the rise, and therefore it is necessary for therapeutic purposes to include psychotherapeutic interventions in all the above disorders.

COPING STRESS STRATEGIES

Coping stress strategies involve the activation of external and internal capacities in the fight against stress which means reduction of the "threat" to the personality, changing of what is possible and acceptance of the occasions that overcome personal or human possibilities (11, 12, 13).

Successful coping strategies aim to maintain a positive self-image, preserve emotional stability and maintain stable social relationships.

According to Lazarus and Folkman (1950), strategies for overcoming stress involve direct external actions directed towards solving problems or escaping from problems, as well as intrapsychic actions aimed at mitigating emotional consequences (redefining, activating defense mechanisms).

Successful strategies for coping stress include:

1. Confronted overcoming which represents active approach to dealing with the source of stress, an assertive "attack" on the problem with maintenance of the internal locus of control.

2. Mastery planning- orientation toward the problem and solution, but with the preliminary elaboration of tactics and searching for additional information for a better understanding of the situation.

3. Seeking social support from the environment, which means that the aid is actively sought or expected, as well as obtaining emotional support or additional information from other people.

4. Establishing self-control, which implies distancing of problems and being calm or "cool headed." It is advisable that in some situations postponing reactions and problem solving are much better than to succumb to impulsive behavior.

5. Finding positive meanings and suppressing the negative consequences of stressful situations that cannot be avoided.

In overcoming stress psychologists use multiple strategies, which include various stress control techniques such as: relaxation methods, meditation, assertive training, biofeedback, stress inoculation techniques, and others.

AUTOGENIC TRAINING

The creator of this relaxation technique is a German neuropsychiatrist and psychotherapist Johannes Hainrich Schulz. Schulz, and later his associate Lute, presented autogenic training to the scientific public as a technique of psychophysical relaxation back in 1932.

The mechanism behind the exercise of autogenic training is activation of the so-called relaxed response, which is opposite to the "fight-or-flight" mechanism. Regular practice of this technique leads to the re-establishment of homeostasis, which is impaired by long-lasting stress. Autogenic training has positive effects both on physiological and psychological functions (14, 15).

The technique of autogenic training is structured as a system of six standard exercises during which the patient, with the help of auto suggestive verbal formulas, releases himself in a state of relaxation. Results are normalizing breathing, regulating blood pressure, improving the quality of sleep, mood stabilizing, reducing anxiety and improving concentration and most cognitive functions.

ASSERTIVE TRAINING

Assertive training is training in communication skills and self-confidence. By mastering this technique, people acquire social and communication skills that enable them to openly communicate their wishes or feelings to others, and thus achieve their goals.

The effects of applied assertive training are manifested in the reduction of anxiety, stress, shyness, ability to manage emotions and develop greater sensitivity for other people, and finally self-esteem strengthening.

BIOFEEDBACK

This technique implies the strengthening of control over one's own psychophysiological functions, with the help of functions feedback that person receives through modern technology. The client learns to recognize physiological responses and to change them (similar to learning to ride a bicycle or playing a piano).

By adopting biofeedback technique clients learn about their own psychophysiological patterns of stress response and how to control them. Skilled arts become automatic and the person use them independently from the therapist after training.

Biofeedback effects are expressed in improving circulation, rhythm of breathing, normalizing blood pressure, reducing muscle tension, improving concentration and achieving relaxation (16).

STRESS INOCULATION THERAPY

The creator of this technique is Meinchenbaum (1977), and the name itself could be translated as "stress immunization". During the application of this technique, a therapist teaches the client to recognize his emotions and situations that trigger a certain (irrational) thinking, which is the generator of negative emotions. The next step in this technique is learning new and more effective ways to deal with stressful situations. The client and therapist are exercising together new patterns of thinking and behavior in real life situations that previously represented a trigger for stress responses.

CONCLUSION

Stress is a disease of the modern way of life. Nowadays, man is facing more and more demands in every walk of life. The alienation, which occurs with technological advances, grows bigger and bigger and it gives rise to loneliness which the plaque of modern man. The sources of stress are numerous, both external and internal. Methods of dealing with stressful situations, constructive resolution of problems in crisis situations, relaxation techniques, as well as better adaptation to unexpected changes in life are of key importance for both mental and physical health. Since stress situations often cannot be completely avoided, it is useful to look at them as a source of new experiences, challenges and possible progress.

DECLARATION OF INTEREST

The authors declare that there are no conflicts of interest.

Sažetak

UTICAJ HRONIČNOG STRESA NA ZDRAVLJE I MEHANIZMI PREVAZILAŽENJA STRESA

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Stres predstavlja negativno životno iskustvo, praćeno fiziološkim, kognitivnim, emocionalnim i bihejvioralnim promenama, koje su usmerene na izmenu događaja ili na prilagođavanje njegovim efektima. Svaku situaciju ili događaj, koji zahteva prilagođavanje, možemo doživeti kao stres, tako da stresogeno mogu delovati i pozitivne situacije i okolnosti, bilo da dolaze spolja, ili se radi u unutrašnjim izvorima stresa. Dok akutan stres ne mora imati negativne posledice, ukoliko on traje dugo, ili se učestalo ponavlja, prelazi u hronični, koji može biti uzrok čitavog niza poremećaja. Tokom hroničnog stresa dolazi do iscrpljivanja kapaciteta organizma za adekvatnu reakciju, što može da dovede do dugotrajne imunološke disfunkcije, koja remeti zdravlje i kvalitet života. Prema SZO (2017), čak kod 60% poznatih obolenja kao jedan od uzročnika navodi se stres, a kod brojnih mentalnih poremećaja je otkrivena direktna povezanost sa stresom: kod akutne reakcije na stres, „posttraumatskog stresnog poremećaja“, poremećaja prilagođavanja i drugih reakcija na težak stres. Pored toga, kod svih kategorija mentalnih poremećaja (MKB-10), stresna situacija ili događaj imaju značajnu ulogu u ispoljavanju simptoma. Posebnu kategoriju poremećaja izazvanih stresom predstavljaju psihosomatski poremećaji. Radi se o funkcionalnim poremećajima kod kojih ne postoji patoanatomski supstrat. Za razliku od njih, psihosomatske bolesti su svrsta obolenja kod kojih postoje strukturni poremećaji organa ili organskih sistema, u čijoj etiologiji, pored niza drugih činilaca, hronični stres ima presudnu ulogu (Adamović, 1983) i koje nastaju kada za to postoji biološka predispozicija. U radu je objašnjen mehanizam nastanka ovih bolesti i načina prevazilaženja stresa koji se smatra njihvim glavnim okidačem. Prema DSM-V psihosomatska obolenja se dele na kožne bolesti, bolesti probavnog sistema, bolesti respiratornih organa, bolesti srca i krvnih sudova, bolesti žlezda sa unutrašnjim lučenjem, reumatske bolesti, ginekološke bolesti i ostalo. U cilju prevazilaženja stresa i očuvanja zdravlja, značajnu ulogu imaju psihološke strategije.

Ključne reči: stres, psihosomatske bolesti, strategija suočavanja sa stresom.

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Review article

PULMONARY THROMBOEMBOLISM AND ROLE OF FACTOR V LEIDEN IN ITS DEVELOPMENT - REVIEW OF LITERATURE

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Abstract: Pulmonary embolism (PE) and deep vein thrombosis (DVT) are associated with considerable morbidity and mortality, and for as much as twenty-five percent of PE patients the primary clinical appearance is unexpected death. Diagnosis of PE is based on clinical suspicious at first, but sometimes its diagnostics can be extremely difficult. Newly increased interest in an inherited thrombophilic states has been provoked by the discovery of several common inherited abnormalities, i.e. the prothrombin (PT) gene G20210A, Factor V Leiden (FVL) mutation (Arg506Gln), hyperhomocystenemia and homocysteiuria, Wein-Penzing defect, Sticky Platelet Syndrome (SPS), Quebec platelet disorder (QPD) and Sickle Cell Disease (SCD). PE incidence rates increase in recent years. The only explanation at this moment is increased awareness of PE, especially after any kind of surgery, immobile state or unexplained shorthness of breath.

Key words: Inherited thrombophilic states, venous thromboembolism, pulmonary embolism.

INTRODUCTION

Venous thromboembolic disorders (VTE) are serious disorders with high morbidity and mortality rates. Many genetic and acquired risk factors were identified to cause VTE (1).

Thrombophilia is the term given to abnormal blood coagulation condition leading to hypercoagulability status. People with hypercoagulability are at risk of developing thrombosis, especially venous thromboembolic disorders (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE is a significant cause of morbidity and mortality in many countries with an annual incidence of 1/1000 (2, 3). Many genetic and acquired risk factors for the development of VTE were identified. In fact, the WHO expert group (1996) defined thrombophilia as a tendency to develop VTE that may be genetically determined, acquired or both (4). Genetic factors include activated protein C resistance (APC-R) associated with Factor V, Prothrombin G20210A mutation associated with high levels of prothrombin, genetic deficiencies of proteins C, S and antithrombin, and others. Acquired risk factors include lupus anticoagulants, pregnancy,the use of contraceptives, major surgeries, cancer, inflammations, and others. This review article focuses on the epidemiology of APC-R/FVL as the most common risk factor for PE in 20-40% patients (5).

HEMOSTASIS

Normal human hemostasis is a balanced system which, on one hand, prevents excessive bleeding from any injured site, while on the other hand maintains blood circulation inside intact blood vessels by inhibiting intravascular coagulation. A healthy hemostatic process involves proteins called the plasma clotting factors (enzymes). These enzymes circulate in the blood in an inactive form, and get activated in case of vessel injury. In summary, when a blood vessel is injured, the coagulation cascade is initiated by the release of tissue factor (thromboplastin) and the exposure of intravascular collagen, which activates clotting factors VII and XII, respectively. These clotting factors activate other clotting factors in a stepwise procedure ending

up with the formation of a fibrin clot. A fibrin clot, in association with platelets, form a plug that blocks the injured blood vessel, preventing bleeding and allowing for wound healing. After healing, the fibrin clot is dissolved by the enzyme plasmin in a process called fibrinolysis. The whole process is under careful supervision by three main proteins that circulate normally in the blood; namely protein C (and its active form activated protein C; APC), protein S (PS) and antithrombin (AT). These so-called "natural anticoagulants" monitor the processes of coagulation and fibrinolysis in order to prevent excessive clotting.Abnormalities in clotting factors may lead to bleeding problems (hemophilia), while abnormalities in the natural anticoagulants may lead to hypercoagulability and thrombosis, with certain exceptions in both (5-8).

APC-R/FVL

Factor V Leiden (rs6025) is a variant (mutated form) of human factor V (one of several substances that helps blood clot), which causes an increase in blood clotting (hypercoagulability). With this mutation, protein C, an anticoagulant protein (which normally inhibits the pro-clotting activity of factor V), is not able to bind normally to Factor V, leading to a hypercoagulable state, i.e., an increased tendency for the patient to form abnormal and potentially harmful blood clots. Factor V Leiden is the most common hereditary hypercoagulability disorder amongst ethnic Europeans. It is named after the Dutch city Leiden, where it was first identified in 1994 by Prof R. Bertina under the direction of (and in the laboratory of) Prof P. Reitsma (7, 8, 9).

Together, protein C and S deficiencies and antithrombin III comprise between 5 percent and 10 percent of all DVT cases. Factor V Leiden is responsible for many more, between 20 percent and 40 percent. Normally, APC should inactivate clotting Factor V (FV) and therefore slow down the coagulation process. About 3 percent of the general population has this gene alteration, also called a mutation. Dahlbäck and al. called this phenomenon "APC resistance", and they originally though this could be due a deficiency in a yet unknown protein that co-helps APC in inactivating FV (5). It is about a missense point mutation in the FV gene and nucleotide replacement. Because of the amino acid change in FVL, APC can no longer inactivate FV efficiently, but FV retains its coagulation capabilities and therefore carriers of FVL develop hypercoagulability which may clinically manifest as VTE episodes. Later studies showed that people with FVL were at higher risk of developing VTE (10-fold in heterozygous carriers and 30 to 140-fold in homozygous carriers) (9, 10, 11). Additionally most homozygotes for FVL were reported to get at least one VTE event in their life time (12, 13). This explains the great clinical and scientific consideration this mutation had appealed and the hundreds of studies conducted on its prevalence and risk for developing VTE in almost every part of the world.

Interesting thing is that clinical symptoms in patients with the factor V Leiden mutation are variable. Some patients could never experience thrombosis, whereas other patients suffer recurrent and severe thrombotic events. Because of this marked variance, lifelong anticoagulation may not be necessary for all individuals with factor V Leiden mutation. Lifelong anticoagulation should be reserved for patients who experience two or more thrombotic events or a single life-threatening thrombosis (14).

DISTRIBUTION PF THE COAGULATION FACTOR V

Distribution of the coagulation factor VR506Q (FV Leiden) mutation, which is known to be a cause of VTE, is often seen in Caucasians, whereas the mutation has not been reported in other population, in fact the prevalence was almost zero in other ethnic groups (15, 16). Therefore, its development is of historicalsignificance. A group of scientists got a perception that FVL has occurred once in the past time in one European Caucasian person. Anthropology proposes that Caucasoid populations who settled in Europe were diverted from Mongoloid populations (who moved to East Asia) around 32 thousands of years ago; therefore FVL should have appeared sometime earlier than 32,000 years ago (17-20). It was suggested that the mutation occurred in Europe first, and then spread to other parts of the world. The rarity of FVL in the French and Spanish Basque populations, which are thought to be the oldest ethnic groups in Europe of Paleolithic origin, has also suggested FVL to occur outside Europe first (21, 22). Lucotte et al proposed that FVL expanded in Europe during the Neolithic period, from a probable Anatolian center of origin in Turkey, which has occurred around 10,000 years ago (23). This may explain the highest prevalence of FVL in East Mediterranean countries, and that the prevalence decreases when radiating away from this region towards Europe or other parts of the world. Still, more genetic and molecular studies may be needed to detect certain genetic loci or markers that may help in following the movement of carriers of FVL in the Mediterranean region to definitely determine the exact location where FVL might have occurred first.

CONCLUSION

DVT has been focused on and recognized by medical professionals and by general citizens. In medical professionals, mechanical compressions, malignant di-

seases, lower limb operations, sedentary postures for long periods and central vein catheters cause VTEs, and DVT often results in fatal pulmonary thromboembolism, which is unacceptable in the modern diagnostic and medical treatment. We cannot fight against hereditary factors, but if one is to have lung thromboembolism, it is necessary to have hematological testing.

Abbreviations

PE — Pulmonary embolism
DVT — deep vein thrombosis
PT — prothrombin
FVL — Factor V Leiden
SPS — Sticky Platelet Syndrome
QPD — Quebec platelet disorder
SCD — Sickle Cell Disease
VTE — Venous thromboembolic disorders
APC-R — activated protein C resistance

DECLARATION OF INTEREST

The authors declare that there are no conflicts of interest.

Licensing

Sažetak

PLUĆNA TROMBOEMBOLIJA I ULOGA FAKTORA V LEIDEN U NJENOM NASTANKU — PREGLED LITERATURE

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Plućna embolija (PE) i duboka venska tromboza (DVT) su povezani sa značajnim stepenom mortaliteta i morbiditeta, a za 25% PE pacijenata prvi klinički znak je neočekivana smrt. Dijagnoza PE zasnovana je na kliničkoj sumnji u prvom koraku, ali ponekad je i određivanje same dijagnostike izuzetno otežano. U poslednje vreme dosta pažnje se posvećuje urođenim stanjima trombofilije, koja su bila najviše izazvana otkrićem nekoliko čestih naslednih abnormalnosti, npr gen za protrombin (PT) G20210A, mutacija za faktor V Leiden (FVL) /Arg506Gln), hiperhomocisteinemija i homocistinurija, Wein-Penzing defekt, Sindrom lepljivih Trombocita (SPS), poremećaj trombocita – Kvebek (QPD) i anemija srpastih ćelija (SCD). Incidencija PE beleži značaj porast u poslednjih par godina. Jedno od mogućih rešenja je proširena svest o pojavi PE, posebno nakon bilo kakvih oblika hirurgije, stanja nepokretnosti i neobjašnjivog gubitka daha.

Ključne reči: nasledna trombofilna stanja, venska tromboembolija, plućna embolija.

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Special Awards and Grants: ***AESBH Award, Technical Exhibition***

Abstract Submission Deadline: **15th of April 2019**
Early Registration Deadline: **15th of June 2019**

Registration and abstract submission on **www.aesbh.org**

1st CONGRESS OF THE Association of Endoscopic Surgeons of Bosnia & Herzegovina

6th-8th September 2019. Congress Center of Hotel Holiday, Sarajevo, Bosna&Hercegovina

Dear Colleagues,

The First Congress of Endoscopic Surgeons in Bosnia and Herzegovina is to be held soon in Sarajevo. Thanks to the beauty of Sarajevo and the pleasant atmosphere of the Holiday Hotel, we expect that the selected topics from the realm of endoscopic surgery and the speakers from Bosnia and Herzegovina, the region and other parts of Europe will attract the attention of doctors who work in abdominal, thoracic or paediatric surgery, urologists, neuro-surgeons, orthopaedic surgeons, gynaecologists, ear-nose-and-throat specialists, gastroenterologists, and other medical professionals who work in endoscopic surgery. For a surgeon to do his work correctly, it is vital for him to have broad medical knowledge, the necessary equipment and instruments, and also knowledge of techniques and technology. But he also needs the rich experience of his colleagues.

We have the honour and pleasure to invite you on behalf of the Association of Endoscopic Surgeons of Bosnia and Herzegovina (UEHBiH/AESBH) to the First Congress of Endoscopic Surgeons in Bosnia and Herzegovina, which will be held from 6th to 8th September 2019, in Sarajevo.

We are proud of the fact that the Association has been formed on a state level with the aim of further developing and popularizing endoscopic surgery in Bosnia and Herzegovina. The foundation of the Association was prompted by the fact that every country in Europe, as well as our neighbours, Croatia and Serbia, have their own independent Associations of Endoscopic Surgeons, through which they have encouraged the development and progress of this type of surgery.

The Congress will be under the patronage of the European Association of Endoscopic Surgeons (EAES) and its president Prof. J. Bonjer, but it will also gather together the most prominent surgeons who work with laparoscopic surgery in the region: Prof. Dr. Miloš Bjelović, president of the Association of Endoscopic Surgeons of Serbia, Prof. Dr. Igor Stipančić, president of the Association of Endoscopic Surgeons of Croatia, and Prof. Dr. Aleš Tomašić, president of the Association of Endoscopic Surgeons of Slovenia, and others. This will be a good opportunity for experts in this field to exchange experiences, current information and ideas, which will help us all to further develop endoscopic surgery.

We invite you to contribute by your participation to the quality of this Congress, which will be held in our capital, Sarajevo, the leading political, social and cultural centre of Bosnia and Herzegovina, and a prominent cultural centre in the Balkans. The city is well-known for its traditional cultural and religious diversity.

"At whatever time of day and from which ever height you cast your gaze over Sarajevo, you always and unintentionally have the same thought. It is a city, a city that is ageing and dying, but at the same time being born and transformed. Today it is the city of our best aspirations and hopes," were the words of Ivo Andrić, the writer and winner of the Nobel Prize for literature.

We hope that you will be interested and find the time to join us!

Welcome!

The aim of the Congress is to discuss the results of the latest research, present experiences from practice, and open new paths for integrating different approaches and procedures, so the Congress will be an incentive for new achievements in our everyday work, for the benefit of patients in this field. The Vision is to ensure the highest quality services in this country and the region, in order to achieve excellent results in prevention and in the treatment of surgical patients. The Mission is to ensure a contemporary, effective, evidence-based approach to treatment in this profession, with high standards, through maximum engagement and continuous education.

HIGHLIGHTS

Scientific sessions: Clinical, Scientific and Technology sessions

Free paper sessions: Oral, Video and Poster

Special Awards and Grants: AESBH Award, Technical Exhibition

Abstract Submission Deadline: 15 th of April 2019

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Category	By 14.4.2019.	By 15.7. 2019.	From 16.7.2019.
Active participant	50 Euros	75 Euros	125 Euros
Trainee	25 Euros	35 Euros	50 Euros

ASSOCIATION OF ENDOSCOPIC SURGEONS OF B&H

Congress President: Prof. Samir Delibegović

Ibre Pašića bb, 75000 Tuzla, B&H

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UPUTSTVO AUTORIMA

SANAMED je medicinski časopis osnovan 2006. godine. Časopis objavljuje: originalne naučne i stručne članke, prikaze bolesnika, revijske radove, pisma uredniku, članke iz istorije medicine, prikaz objavljenih knjiga i druge medicinske informacije.

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www.sanamed.rs

Prispeli rukopis Uređivački odbor šalje recenzentima radi stručne procene. Ukoliko recenzenti predlože izmene ili dopune, kopija recenzije se dostavlja autoru s molbom da unese tražene izmene u tekst rada ili da argumentovano obrazloži svoje neslaganje s primedbama recenzenta. Konačnu odluku o prihvatanju rada za štampu donosi glavni i odgovorni urednik.

Časopis se štampa na engleskom jeziku, sa kratkim sadržajem prevedenim na srpski jezik.

OPŠTA UPUTSTVA

Tekst rada kucati u programu za obradu teksta *Word*, latinicom, sa dvostrukim proredom, isključivo fontom *Times New Roman* i veličinom slova 12 tačaka (12 pt). Sve margine podesiti na 25 mm, a tekst kucati sa levim poravnanjem i uvlačenjem svakog pasusa za 10 mm, bez deljenja reči (hifenacije).

Rukopis mora biti organizovan na sledeći način: naslovna strana, sažetak na srpskom jeziku, sažetak na engleskom jeziku, ključne reči, uvod, cilj rada, bolesnici i metodi/materijal i metodi, rezultati, diskusija, zaključak, literatura, tabele, legende za slike i slike.

Svaki deo rukopisa (naslovna strana, itd.) mora početi na posebnoj strani. Sve strane moraju biti numerisane po redosledu, počev od naslovne strane. Podaci o korišćenoj literaturi u tekstu označavaju se arapskim brojevima u zagradama, i to onim redosledom kojim se pojavljuju u tekstu.

Obim rukopisa. Celokupni rukopis rada, koji čine naslovna strana, kratak sadržaj, tekst rada, spisak literature, svi prilozi, odnosno potpisi za njih i legenda (tabele, slike, grafikoni, sheme, crteži), naslovna strana i sažetak na engleskom jeziku, mora iznositi za originalni rad, saopštenje, rad iz istorije medicine i pregled literature do 5.000 reči, a za prikaz bolesnika, rad za praksu, edukativni članak do 3.000 reči; radovi za ostale rubrike moraju imati do 1.500 reči.

Provera broja reči u dokumentu može se izvršiti u programu *Word* kroz podmeni *Tools-Word Count* ili *File-Properties-Statistics*.

Sva merenja, izuzev krvnog pritiska, moraju biti izražena u internacionalnim SI jedinicama, a ako je neophodno, i u konvencionalnim jedinicama (u zagradi). Za lekove se moraju koristiti generička imena. Zaštićena imena se mogu dodati u zagradi.

Naslovna strana. Naslovna strana sadrži naslov rada, kratak naslov rada (do 50 slovnih mesta), puna prezimena i imena svih autora, naziv i mesto institucije u kojoj je rad izvršen, zahvalnost za pomoć u izvršenju rada (ako je ima), objašnjenje skraćenica koje su korišćene u tekstu (ako ih je bilo) i u donjem desnom uglu ime i adresu autora sa kojim će se obavljati korespondencija.

Naslov rada treba da bude sažet, ali informativan.

Ako je potrebno, može se dodati i podnaslov.

Kratak naslov treba da sadrži najbitnije informacije iz punog naslova rada, ali ne sme biti duži od 50 slovnih mesta.

Ako je bilo materijalne ili neke druge pomoći u izradi rada, onda se može sažeto izreći zahvalnost osobama ili institucijama koje su tu pomoć pružile.

Treba otkucati listu svih skraćenica upotrebljenih u tekstu. Lista mora biti uređena po abecednom redu pri čemu svaku skraćenicu sledi objašnjenje. Uopšte, skraćenice treba izbegavati, ako nisu neophodne.

U donjem desnom uglu naslovne strane treba otkucati ime i prezime, telefonski broj, broj faksa i tačnu adresu autora sa kojim ce se obavljati korespodencija.

Stranica sa sažetkom. Sažetak mora imati do 350 reči. Treba koncizno da iskaže cilj, rezultate i zaključak rada koji je opisan u rukopisu. Sažetak ne može sadržati skraćenice, fusnote i reference.

Ključne reči. Ispod sažetka treba navesti 3 do 8 ključnih reči koje su potrebne za indeksiranje rada. U

izboru ključnih reči koristiti Medical Subject Headings — MeSH.

Stranica sa sažetkom na engleskom jeziku. Treba da sadrži pun naslov rada na engleskom jeziku, kratak naslov rada na engleskom jeziku, naziv institucije gde je rad urađen na engleskom jeziku, tekst sažetka na engleskom jeziku i ključne reči na engleskom jeziku.

Struktura rada. Svi podnaslovi se pišu velikim slovima i boldovano.

Originalni rad treba da ima sledeće podnaslove: uvod, cilj rada, metod rada, rezultati, diskusija, zaključak, literatura.

Prikaz bolesnika čine: uvod, prikaz bolesnika, diskusija, literatura.

Pregled iz literature čine: uvod, odgovarajući podnaslovi, zaključak, literatura.

Bolesnici i metode/materijal i metode. Treba opisati izbor bolesnika ili eksperimentalnih životinja, uključujući kontrolu. Imena bolesnika i brojeve istorija ne treba koristiti.

Metode rada treba opisati sa dovoljno detalja kako bi drugi istraživači mogli proceniti i ponoviti rad.

Kada se piše o eksperimentima na ljudima, treba priložiti pismenu izjavu u kojoj se tvrdi da su eksperimenti obavljeni u skladu sa moralnim standardima Komiteta za eksperimente na ljudima institucije u kojoj su autori radili, kao i prema uslovima Helsinške deklaracije. Rizične procedure ili hemikalije koje su upotrebljene se moraju opisati do detalja, uključujući sve mere predostrožnosti. Takođe, ako je rađeno na životinjama, treba priložiti izjavu da se sa njima postupalo u skladu sa prihvaćenim standardima.

Treba navesti statističke metode koje su korišćene u obradi rezultata.

Rezultati. Rezultati treba da budu jasni i sažeti, sa minimalnim brojem tabela i slika neophodnih za dobru prezentaciju.

Diskusija. Ne treba činiti obiman pregled literature. Treba diskutovati glavne rezultate u vezi sa rezultatima objavljenim u drugim radovima. Pokušati da se objasne razlike između dobijenih rezultata i rezultata drugih autora. Hipoteze i spekulativne zaključke treba jasno izdvojiti. Diskusija ne treba da bude ponovo iznošenje zaključaka.

Literatura. Reference numerisati rednim arapskim brojevima prema redosledu navođenja u tekstu. Broj referenci ne bi trebalo da bude veći od 30, osim u pregledu literature, u kojem je dozvoljeno da ih bude do 50.

Izbegavati korišćenje apstrakta kao reference, a apstrakte starije od dve godine ne citirati.

Reference se citiraju prema tzv. Vankuverskim pravilima, koja su zasnovana na formatima koja koriste *National Library of Medicine* i *Index Medicus*.

Primeri:

1. **Članak:** (svi autori se navode ako ih je šest i manje, ako ih je više navode se samo prvih šest i dodaje se *"et al."*)

Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg. 2003; 29(2): 650–652.

2. **Knjiga:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Poglavlje ili članak u knjizi:**

Latković Z. Tumori očnih kapaka. U: Litričin O i sar. Tumori oka. 1. izd. Beograd: Zavod za udžbenike i nastavna sredstva, 1998: 18–23.

Tabele. Tabele se označavaju arapskim brojevima po redosledu navođenja u tekstu, sa nazivom tabele iznad.

Slike. Sve ilustracije (fotografije, grafici, crteži) se smatraju slikama i označavaju se arapskim brojevima u tekstu i na legendama, prema redosledu pojavljivanja. Treba koristiti minimalni broj slika koje su zaista neophodne za razumevanje rada. Slova, brojevi i simboli moraju biti jasni, proporcionalni, i dovoljno veliki da se mogu reprodukovati. Pri izboru veličine grafika treba voditi računa da prilikom njihovog smanjivanja na širinu jednog stupca teksta neće doći do gubitka čitljivosti. Legende za slike se moraju dati na posebnim listovima, nikako na samoj slici.

Ako je uveličanje značajno (fotomikrografije) ono treba da bude naznačeno kalibracionom linijom na samoj slici. Dužina kalibracione linije se unosi u legendu slike.

Uz fotografije na kojima se bolesnici mogu prepoznati treba poslati pismenu saglasnost bolesnika da se one objave.

Za slike koje su ranije već objavljivane treba navesti tačan izvor, treba se zahvaliti autoru, i treba priložiti pismeni pristanak nosioca izdavačkog prava da se slike ponovo objave.

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Svi autori radova, imaju obavezu da pre nego što dobiju potvrdu da će rad biti objavljen u Sanamedu, izvrše uplatu za pokriće dela troškova štampe koja za autora rada iznosi 2500 dinara, a za koautore po 1500 dinara, za svaki prihvaćeni rad. Za autora rada iz inostranstva naknada za štampanje iznosi 40 eura (u dinarskoj protivrednosti po kursu na dan uplate), a za koautore 20 eura. Dodatno će biti naplaćena svaka stranica na kojoj se nalaze slike u boji, po ceni od 30 eura; crno bele slike se ne naplaćuju.

Za sva dalja uputstva i informacije kontaktirajte Uredništvo.

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INSTRUCTIONS TO AUTHORS

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Address manuscripts to:
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(for Sanamed)
Ul. Palih boraca 52, 36300 Novi Pazar
Email sanamednp2006@gmail.com
www.sanamed.rs

Arrived manuscript is sent to reviewers for expert assessment by the Editorial Board. If reviewers propose changes or amendments, copies of reviews are submitted to authors with a request to enter the required changes to the text or explain its disagreement with the remarks of the reviewer. The final decision of acceptance for publishing is given by Editor in chief.

The journal is published in English, with the summary translated into Serbian.

GENERAL GUIDELINES

Text of the paper should be typed in a word processing program *Word*, written in Latin, double-spaced, only in *Times New Roman* font size 12 points. All margins should be set at 25 mm, and the text should be typed with the left alignment and paragraph indentations of 10 mm, without dividing the words.

The manuscript should be arranged as following: title page, abstract, key words, introduction, patients and methods/material and methods, results, discussion, conclusion, references, tables, figure legends and figures.

Each manuscript component (title page, etc.) begins on a separate page. All pages are numbered consecutively beginning with the title page.

References in the text are designated with Arabic numerals in parentheses, and the order in which they appear in the text.

Manuscript volume. The complete manuscript, which includes title page, short abstract, text of the article, literature, all figures and permisions for them and legends (tables, images, graphs, diagrams, drawings), title page and abstract in English, can have the length up to 5000 words for original paper, report, paper on the history of medicine and literature overview, while for patient presentation, practice paper, educative article it can be up to 3000 words, and other papers can be up to 1500 words.

The word count check in a document can be done in *Word* processor program in submenu *Tools Word Count* or *File Properties Statistics*.

All measurements, except blood pressure, are reported in the System International (SI) and, if necessary, in conventional units (in parentheses). Generic names are used for drugs. Brand names may be inserted in parentheses.

Title page. The title page contains the title, short title, full names of all the authors, names and full location of the department and institution where work was performed, acknowledgments, abbreviations used, and name of the corresponding author. The title of the article is concise but informative, and it includes animal species if appropriate. A subtitle can be added if necessary.

A short title of less than 50 spaces, for use as a running head, is included.

A brief acknowledgment of grants and other assistance, if any, is included.

A list of abbreviations used in the paper, if any, is included. List abbreviations alphabetically followed by an explanation of what they stand for. In general, the use of abbreviations is discouraged unless they are essential for improving the readabillity of the text.

The name, telephone number, fax number, and exact postal address of the author to whom communications and reprints should be sent, are typed at the lower right corner of the title page.

Abstract page. An abstract of less than 180 words concisely states the objective, findings, and conclusion of the studies described in the manuscript. The abstract does not contain abbreviations, footnotes or references.

Below the abstract, 3 to 8 keywords or short phrases are provided for indexing purposes.

The structure of work. All headings are written in capital letters and bold.

Original work should have the following headings: introduction, aim, methods, results, discussion, conclusion, references.

A case report include: introduction, case report, discussion, references.

Review of the literature include: an introduction, subheadings, conclusion, references.

Patients and methods/Material and methods. The selection of patients or experimental animals, including controls is described. Patients' names and hospital numbers are not used.

Methods are described in sufficient detail to permit evaluation and duplication of the work by other investigators.

When reporting experiments on human subjects, it should be indicated whether the procedures followed were in accordance with ethical standards of the Committee on human experimentation of the institution in which they were done and in accordance with the Declaration of Helsinki. Hazardous procedures or chemicals, if used, are described in detail, including the safety precautions observed. When appropriate, a statement is included verifying that the care of laboratory animals followed the accepted standards.

Statistical methods used, are outlined.

Results. Results are clear and concise, and include a minimum number of tables and figures necessary for proper presentation.

Discussion. An exhaustive review of literature is not necessary. The major findings should be discussed in relation to other published works. Attempts should be made to explain differences between results of the present study and those of the others. The hypothesis and speculative statements should be clearly identified. The discussion section should not be a restatement of results, and new results should not be introduced in the discussion.

References. References are identified in the text by Arabic numerals in parentheses. They are numbered consecutively in the order in which they appear in the text. Number of references should not exceed 30, except in the literature review, which is allowed to be to 50.

Avoid using abstracts as references and abstract older than two years are not cited.

References are cited by the so-called Vancouver rules, which are based on formats that use the National Library of Medicine and Index Medicus. The following are examples:

1. **Article:** (all authors are listed if there are six or fewer, otherwise only the first six are listed followed by *"et al."*)

Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg. 2003; 29(2): 650–652.

2. **Book:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Chapter or article in a book:**

Trier JJ. Celiac sprue. In: Sleisenger MH, Fordtran J5, eds. Gastro-intestinal disease. 4 th ed. Philadelphia: WB Saunders Co, 1989: 1134–52.

Tables. Tables are typed on separate sheets with figure numbers (Arabic) and title above the table and explanatory notes, if any, below the table.

Figures and figure legends. All illustrations (photographs, graphs, diagrams) are to be considered figures, and are numbered consecutively in the text and figure legend in Arabic numerals. The number of figures included is the least required to convey the message of the paper, and no figure duplicates the data presented in the tables or text. Letters, numerals and symbols must be clear, in proportion to each other, and large enough to be readable when reduced for publication. Figures are submitted as near to their printed size as possible. Legends for figures should be given on separate pages.

If magnification is significant (photomicrographs), it is indicated by a calibration bar on the print, not by a magnification factor in the figure legend. The length of the bar is indicated on the figure or in the figure legend.

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Letters to the Editor. Both letters concerning and those not concerning the articles that have been published in SANAMED will be considered for publication. They may contain one table or figure and up to five references.

Cover letter. The letter signed by all authors must be attached with the manuscript. The letter should consist of: the statement that the paper has not been published previously and that it is not submitted for publication to some other journal, the statement that the manuscript has been read and approved by all the authors who fulfill the authorship criteria. Furthermore, authors should attach copies of all permits: for reproduction of previously published materials, for use of illustrations and for publication of information about pub-

licly known persons or naming the people who contributed to the creation of the work.

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All authors of papers, have obligation, before they receive confirmation that the paper will be published in Sanamed, to pay part of expenses of printing, which is 2500 RSD for author, 1500 RSD for co-authors, for each paper.

For paper author from abroad printing fees are 40 Euro (in Dinar equivalent at the exchange rate on the day of payment), and 20 Euro for co-authors. Additionally will be charged each page with pictures in color, costing 30 Euro; black and white pictures will not be charged.

For any further instructions and information, contact Editorial Board.

Note. The paper which does not fulfill the conditions set in this instruction cannot be set to reviewers and will be returned to the authors for amendments and corrections. By following the instructions for writing the papers for Medical Journal, the time needed for the process of publication of papers in the journal will be shortened, which will have positive impact on the quality and regularity of publication of volumes.

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