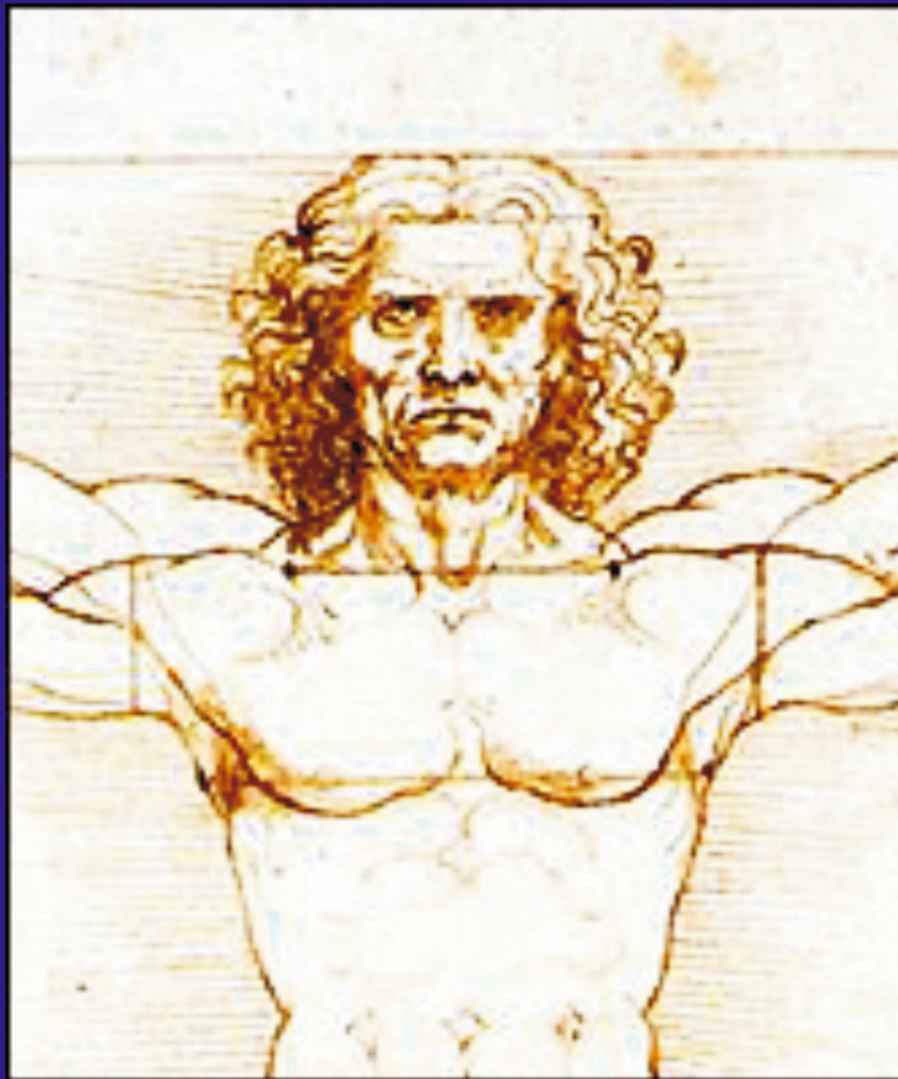


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Avdo Ćeranić

ATRIAL FIBRILLATION AND GAMMA GLUTAMYL TRANSFERASE; OF-PUMP VERSUS ON-PUMP CORONARY ARTERY BYPASS SURGERY

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Abstract: Introduction: Atrial fibrillation (AF) which can be seen as a complication of the open heart surgery, may cause serious problems on post operative period. The exact pathophysiology of AF is unknown but it is thought that factors such as oxidative stress might cause AF. **Material and methods:** We retrospectively surveyed the serum gamma glutamyl transferase (GGT) levels which is accepted as a mediator of oxidative stress, for the Post Operative Atrial Fibrillation (POAF) that occur after of-pump versus on-pump Coronary Artery Bypass Graft (CABG) surgery. Our study included 183 cases (101 male, 72 female; median age 63 ± 4.3 years) of which CABG was performed. **Results:** Echocardiography, routine blood tests, electrocardiography (ECG), test for the serum GGT levels were performed in preoperative and postoperative period to all participants. AF developed in 34 patients (35 %) in Group I and 19 patients (20 %) in Group II. There were no significant differences between two groups (of-pump versus on-pump) in terms of gender, cardiovascular risk factors and the severity of the coronary artery disease. In patients who has developed AF in postoperative period had significantly higher serum GGT levels. **Conclusion:** This study has shown that serum GGT levels were found to be significantly higher in patients whom AF has developed after on-pump CABG surgery.

Keywords: Coronary artery bypass graft, Serum gamma glutamyl transferase, atrial fibrillation.

INTRODUCTION

Atrial fibrillation (AF) is the most common pathologic arrhythmia among clinical arrhythmias and can be seen in coronary artery disease, hypertension, mitral valve diseases and hyperthyroidism. AF can also be seen idiopathically. Recently, in addition to these risk

factors, obesity, metabolic syndrome, chronic alcoholism and atherosclerosis have been reported as other etiological factors of AF (1). Oxidative stress is thought to be an important physiopathological mechanism in the development of POAF since antioxidant agents such as ascorbic acid is found to be important in the prevention of the development of POAF (2, 3). Serum gamma glutamyl transferase (GGT) enzyme is important in the homeostasis of the glutathione which is responsible for the protection of the cells from the free oxygen radicals. GGT is related with hepatobiliary diseases and alcohol consumption. There are studies in which the use of the serum concentrations of GGT as a marker for increased oxidative stress (4). It has also been postulated that increased serum GGT levels and cardiovascular diseases and the metabolic syndrome are closely related (5, 6). Because of these facts we investigated the relationship of serum GGT which is a marker for increased oxidative stress with POAF.

MATERIALS AND METHODS

Our study included 183 cases of which CABG was performed in Gaziantep Dr. Ersin Arslan Education and Research Hospital between 2012 and 2017. Patients who had chronic liver disease, preoperative AF, wide left atrium (> 5 cm) and patients who had indications for emergency CABG were excluded from this study. Echocardiography, routine blood tests, electrocardiography (ECG), test for the serum GGT levels were performed in preoperative and postoperative period to all participants.

Biochemical analysis

A venous blood specimen (5 mL) was collected at 6:00 a.m. to 7:00 a.m. Serum was separated by centri-

fugation at $1500 \times g$ for 15 min. All laboratory analysis were performed at the department of central bio chemistry labarotry. Serum GGT levels were measured spectrophotometrically with the Beckman DXC800 automatic biochemical analyzer (USA). Reference range for GGT was 7-49 U/L.

Surgical Technic

Off-pump and On-pump CABG procedures were performed through a median sternotomy approach. Oc-topus and Starfish (Medtronic, USA) was used to stabilize the target coronary vessel in all off-pump CABG cases . Revascularization in on-pump CABG was performed by standard surgical technique with moderate systemic hyperthermia ($30-32^{\circ}\text{C}$). Conduits for both off-pump and on-pump CABG included the internal

mammary artery or saphenous veins, or a combination of the two. All patients were continuously monitored in the intensive care unit (ICU) postoperatively. A 12-lead ECG recording was performed to confirm the AF episodes. POAF was defined as the characteristic arrhythmia lasting for more than 5 minutes. POAF was treated by amiodarone and replacement of potassium and magnesium. Patients were periodically examined in our outpatient clinics especially who had POAF. All continuous variables were presented as mean $\pm$ SD. Student t-test was used for analysis of continuous variables and Chi-squared test was used.

RESULTS

183 cases were divided into two groups; Group I included the patients (n: 96) who had on-pump CABG,

Table 1. Demographic data

VARIABLES	ON-PUMP (n: 96)	OFF-PUMP (n: 87)	significance
Age	56 ± 2.3	54 ± 2.3	N.S.
Sex	f: 46 (48%) m: 50 (52%)	f: 41 (47%) m: 46 (53%)	N.S.
Positive Familiy History	63 (65%)	53 (60%)	N.S.
Smoking	66 (68%)	61 /70%)	N.S.
Hypertension (BP > 139/89 mmHg)	46 (48%)	41 (47%)	N.S.
Carotid Artery Disease	13 (13%)	11 (12%)	N.S.
Peripheric Artery Disease	21 (21%)	17 (19%)	N.S.
Angina Pectoris	54 (56%)	43 (49%)	N.S.
Myocardial Infarction	25 (26%)	22 (25%)	N.S.
COPD	26 (27%)	23 (26%)	N.S.

COPD: Choronic Obstructive Pulmonary Disease, f: female, m: male

Table 2. Preoperative biochemical markers

VARIABLES	ON-PUMP (n: 96)	OFF-PUMP (n: 87)	significance
WBC ($3.5-10 \times 10^6/\text{L}$)	5.600	6.100	
Hg (11.5-16.5 g/dl)	10.7	10.3	
Hct (%)	32	30	
Platelet ($100-400 \times 10^6/\text{L}$)	221.000	213.000	
Cr (0.7-1,3 mg/dl)	1,0	1,1	
BUN (6-20 mg/dl)	12,7	13,3	
Glucose (< 200 mg/dl)	107	111	
AST (0-37 U/L)	19	23	
ALT (0-41 U/L)	16	13	
LDH (210-425 U/L)	337	411	
GGT(10-	36	31	

WBC: White Blood Cell, Hg: Hemoglobin, Hct: Hemotocrit, Cr: Creatinine, BUN: Blood Urea Nitrogene, AST: Aspartate Transferrase, ALT: Alanine Transferase, LDH: Lactic De Hydrogenase, GGT: Gama Glytamil Transferase.

Table 3. Postoperative biochemical markers

VARIABLES	ON-PUMP (n: 96)	OFF-PUMP (n: 87)	significance
WBC (3.5-10 x 10 ⁶ /L)	12.300	7.100	
Hg (11.5-16.5 g/dl)	8,7	9,8	
Hct (%)	26	28	
Platelet (100-400 x 10 ⁶ /L)	143.000	227.000	
Cr (0.7-1.3 mg/dl)	1,3	0,8	
BUN (6-20 mg/dl)	33	17	
Glucose (< 200 mg/dl)	156	124	
AST (0-37 U/L)	53	18	
ALT (0-41 U/L)	119	26	
LDH (210-425 U/L)	1048	768	
GGT	89	33	

WBC: White Blood Cell, Hg: Hemoglobin, Hct: Hemotocrit, Cr: Creatinine, BUN: Blood Urea Nitrogene, AST: Aspartate Transferease, ALT: Alanine Transferase, LDH: Lactic De Hydrogenase, GGT: Gama Glytamyl Transferase.

Table 4. Operative and postoperative data

VARIABLES	ON-PUMP (n: 96)	OFF-PUMP (n: 87)	significance
Mean Number Of Diseased Coronary Artery	2.3	2.1	
Mean Number of Revascularized Coronary Artery	2.1	2.0	
Preoperative EF	46%	48%	
Postoperative EF (3 Months Later)	43%	49%	
Postoperative AF	34 (35 %)	19 (20 %)	
Postoperative AF (3 Month later)	11 (11 %)	7 (8 %)	
3 months later GGT	74	36	

EF: Ejection Fraction, AF: Atrial Fibrillation, GGT: Gama Glutamyl Transferase

Group II included the patients (n: 87) who had of-pump CABG. There were statistically no significant difference between two groups in terms of demographic data and preoperative clinical conditions (Table 1, 2). AF developed in 34 patients (35 %) in Group I and 19 patients (20 %) in Group II. Also despite the anti AF therapy 3 months later AF persisted in 11 patients (11 %) in Group I and in 7 patients (8 %) in Group II. No significant differences between two groups were found in terms of pre-operative blood tests. No significant differences between two groups were found in terms of post-operative blood tests except for the AST and the GGT. AST in Group I was 23.44±12.89 mg/dl and in Group II 38.48 ± 51.89 mg/dl. GGT which is considered to be a marker for increased oxidative stress was found to be significantly different; in Group I: 47.57 ± 29.44, in Group II: 35.13 ± 18.77, (p < 0.05).

DISCUSSION

POAF is the mostly encountered arrhythmic complication of CABG which is estimated to 5-30 % (7A).

If AF is untreated it is one of the leading cause of post-operative morbidity and mortality (7). It usually is seen on 2nd or 3th postoperative day (8). There are many studies of-pump CABG lowers the incidence of POAF(9,10), but also there are authors on the contrary (11, 12). In our study POAF is seen with significantly higher incidence in on-pump CABG compared to of-pump CABG. This is the main postulate of this study. There are multifactorial mechanisms are questioned for POAF. It could be of either slow atrial conduction nature or dispersion of atrial refractoriness (13). Especially Archobold stated that; a combination of prolonged signal-averaged P-wave duration (SAPD), advanced age, and male sex identifies patients at high risk for development of POAF (13). AF is accepted to be reentrant in origin, so sustained AF requires that the depolarizing wave fronts continuously encounter excitable tissue, a circumstance favored by slow atrial conduction and a short atrial refractory period (14). It has been found that atrial myositic calcium load and electrophysiological remodelling of the atrial tissue is fo-

und to be responsible for the development of POAF (15). Plasma peroxidase levels were found to be increased after aortic cross clamping, in patients whom CABG operation was performed (7, 16). POAF can develop in an environment in which there is increased oxidative but there isn't enough anti oxidants present. Violi reports on experimental and clinical studies exploring the role of Reactive oxygen species (ROS) in eliciting the occurrence or recurrence of AF and the potential efficacy of a treatment by antioxidant vitamins (17). Stanger states that Ischemia-reperfusion has been reported to be associated with augmented oxidative stress in the course of surgery, which might be causally involved in the onset of atrial fibrillation (AF), the most common arrhythmia after cardiac surgery. So he hypothesized that supplementation of antioxidants and n-3 polyunsaturated fatty acids (n-3 PUFAs) might lower the incidence of AF following coronary artery bypass graft (CABG) surgery. And finally he concludes that the administration of vitamins attenuates post-operative oxidative stress in the course of CABG surgery (18). GGT is the enzyme for the separation of gamma glutamyl from glutathione which itself is an important antioxidant. Because of the close relationship between serum GGT levels and inflammation and atherosclerosis (8) the development of POAF which occurs in a similar fashion is found to be significantly related with the serum GGT levels as well. GGT as an enzyme that is derived from the liver is postulated to have an independent relationship between postoperative AF (19). The mean age is found to be significantly higher in Group I in which postoperative AF occurred ($p < 0.05$) and thus the age group in this study is considered to be appropriate. Postoperative AF is found to be more

often in the second and third postoperative days and serum GGT levels are found to be increased in the first postoperative day. This might affect the statistical analysis but since history of MI was among the exclusion criteria elevated levels of serum GGT may be an independent risk factor for AF.

CONCLUSION

The leading etiological factors for the development of postoperative AF are inflammation and oxidative stress. Thus it is imperative to perform the tests for inflammatory markers and the markers of oxidative stress in the preoperative period in order to develop preventive treatment protocols for such complications of CABG operation.

Abbreviations

AF — Atrial fibrillation
GGT — gamma glutamyl transferase
POAF — Post Operative Atrial Fibrillation
CABG — Coronary Artery Bypass Graft
ECG — electrocardiography
ROS — Reactive oxygen species

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

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Sažetak

ATRIJALNA FIBRILACIJA I GAMA GLUTAMIL TRANSFERAZA; AORTOPULMONALNO PREMOŠĆAVANJE SA I BEZ UPOTREBE PUMPE ZA VANTELESNU CIRKULACIJU

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Uvod: Atrijalna fibrilacija (AF), koja se može javiti kao komplikacija operacija na otvorenom srcu, može izazvati ozbiljne probleme u postoperativnom periodu. Tačna patofiziologija AF je nepoznata. Smatra se da faktori kao što je oksidativni stres mogu izazvati AF.

Materijal i metode: Retrospektivno smo ispitali nivo serumske gama glutamil transferaze (GGT), kao medijatora oksidativnog stresa, kod postoperativne atrijalne fibrilacije (POAF) koja se javila posle aortokoronarnog premošćavanja (CABG) uz pomoć i bez

upotrebe pumpe za vantelesnu cirkulaciju. Naša studija je uključila 183 slučaja (101 muškarac, 72 žene; prosečne starosti 63 ± 4.3 godine) kod kojih je izvedeno aortokoronarno premošćavanje.

Zaključak: Ova studija je pokazala da je značajno viši nivo serumske GGT nađen kod atrijalne fibrilacije nakon aortokoronarnog premošćavanja sa upotrebom pumpe za vantelesnu cirkulaciju.

Cljučne reči: aortokoronarno premošćavanje, serumska gama glutamil transferaza, atrijalna fibrilacija.

REFERENCES

1. Prystowsky EN, Padanilam BJ, Fogel RI. Treatment of Atrial Fibrillation. *JAMA*. 2015; 314(3): 278-88.
2. Orenes-PiZero E, Montoro-García S, Banerjee A, Valdés M, Lip GY, Marín F. Pre and post-operative treatments for prevention of atrial fibrillation after cardiac surgery. *Mini Rev Med Chem*. 2012; 12(13): 1419-31.
3. Pavlos P, Olga A, Elefterios C, Fotini A, Charilaos K, Karaikos T et al. The role of ascorbic acid in the prevention of atrial fibrillation after elective on-pump myocardial revascularization surgery: a single-center experience-pilot study *Interact Cardiovasc Thorac Surg*. 2011; 12(2): 121-4.
4. Bulusu S, Sharma M. What does serum γ -glutamyl transferase (GGT) tell us as a cardiometabolic risk marker? *Ann Clin Biochem*. 2016; 53(Pt 3): 312-32.
5. Cho HS, Lee SW, Kim ES, Mo EY, Shin JY, Moon SD, et al. Clinical significance of serum bilirubin and gamma-glutamyl transferase levels on coronary atherosclerosis assessed by multidetector computed tomography. *Nutr Metab Cardiovasc Dis*. 2015; 25(7): 677-85.
6. Wei D, Chen T, Li J, Gao Y, Ren Y, Zhang X, et al. Association of Serum Gamma-Glutamyl Transferase and Ferritin with the Metabolic Syndrome. *J Diabetes Res*. 2015; 2015: 741731. doi: 10.1155/2015/741731. Epub 2015 Jun 21.
7. Mao Z, Zhong X, Yin J, Zhao Z, Hu X, Hackett ML. Predictors associated with stroke after coronary artery bypass grafting: A systematic review. *J Neurol Sci*. 2015; 357(1-2): 1-7.
8. Zakkar M, Ascione R, James AF, Angelini GD, Suleiman MS. Inflammation, oxidative stress and postoperative atrial fibrillation in cardiac surgery. *Pharmacol Ther*. 2015; 154: 13-20.
9. Abo-Salem E, Lockwood D, Boersma L, Deneke T, Pison L, Paone RF, et al. Surgical Treatment of Atrial Fibrillation. *J Cardiovasc Electrophysiol*. 2015; 26(9): 1027-37.
10. Patel S, Wang S, Pauliks L, Chang D, Clark JB, Kunselman AR, et al. Evaluation of a novel pulsatile extracorporeal life support system synchronized to the cardiac cycle: effect of rhythm changes on hemodynamic performance. *Artif Organs*. 2015; 39(1): 67-76.
11. Benedetto U, Ng C, Frati G, Biondi-Zoccai G, Vitulli P, Zeinab M, et al. Miniaturized extracorporeal circulation versus off-pump coronary artery bypass grafting: a meta-analysis of randomized controlled trials. *Int J Surg*. 2015; 14: 96-104.
12. Pecha S, Schäfer T, Subbotina I, Ahmadzade T, Reichen-spurner H, Wagner FM. Rhythm outcome predictors after concomitant surgical ablation for atrial fibrillation: a 9-year, single-center experience. *J Thorac Cardiovasc Surg*. 2014; 148(2): 428-33.
13. Sezai A, Nakata K, Iida M, Yoshitake I, Wakui S, Osaka S, et al. A Study on the occurrence and prevention of perioperative stroke after coronary artery bypass grafting. *Ann Thorac Cardiovasc Surg*. 2015; 21(3): 275-81.
14. Bouchot O, Guenancia C, Kahli A, Pujos C, Malapert G, Vergely C et al. Low circulating levels of growth differentiation factor-15 before coronary artery bypass surgery may predict postoperative atrial fibrillation. *J Cardiothorac Vasc Anesth*. 2015; 29(5): 1131-9.
15. El-Chami MF, Binongo JN, Levy M, Merchant FM, Halkos M, Thourani V et al. Effect of surgical atrial fibrillation ablation at the time of cardiac surgery on risk of postoperative pacemaker implantation. *Am J Cardiol*. 2015; 116(1): 88-91.
16. Li T, Sun ZL, Xie QY. Meta-analysis identifies serum C-reactive protein as an indicator of atrial fibrillation risk after coronary artery bypass graft. *Am J Ther*. 2016; 23(6): e1586-e1596. doi: 10.1097/MJT.0000000000000255.
17. Violi F, Pastori D, Pignatelli P, Loffredo L. Antioxidants for prevention of atrial fibrillation: a potentially useful future therapeutic approach? A review of the literature and meta-analysis. *Europace*. 2014; 16(8): 1107-16.
18. Stanger O, Aigner I, Schimetta W, Wonisch W. Antioxidant Supplementation Attenuates Oxidative Stress in Patients Undergoing Coronary Artery Bypass Graft Surgery. *Tohoku J. Exp. Med*. 2014; 232(2): 145-54.
19. Ndrepepa G, Xhepa E, Collieran R, Braun S, Cassese S, Fusaro M et al. Gamma-glutamyl transferase and atrial fibrillation in patients with coronary artery disease. *Clin Chim Acta*. 2017; 465: 17-21.

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INVESTIGATING THE FACTORS THAT AFFECT THE FREQUENCY OF VISITS DUE TO CORNEAL FOREIGN BODIES

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Abstract: Introduction: The purpose of this study is to show whether or not there is a relationship between number of visits in shipyard workers who visit clinics with complaints of foreign bodies in their cornea and parameters of working hours, duration of working in years, time of working without a break and age.

Methods: All patients who visited the Emergency Service of the Ahi Evran University Research and Training Hospital between 1 March 2018 and 31 March 2019 with complaints of corneal foreign bodies were examined based on their number of visits in the last one year, daily hours of work, duration of working in years, time of working without a break and age. While corneal foreign body traumas for up to 3 times in the last one year were included in one group, those that were experienced for 4 times or more frequently were included in the other group.

Results: 140 male patients were included in the study. While 67 of the participants were included in the group of patients with corneal foreign body traumas for up to 3 times in the past year, 73 were included in the group of patients with corneal foreign body traumas for 4 times or more frequently in the past year. There was a statistically significant relationship between experiencing corneal foreign body traumas for 4 times or more frequently per year and more daily working hours, longer times of working without a break, short working period and younger age (p -value: < 0.001).

Conclusion: Corneal foreign bodies are eye injuries that may lead to loss of sight or reduced sight and are associated with loss of labor and increased treatment costs. In our study, among the patients who came up with complaints of corneal foreign body traumas for 4 times or more per year, the risk factors was observed to consist of long daily working hours, long time of working without a break, shortness of the time of starting work and early age.

Keywords: Cornea, foreign body, frequency of application.

INTRODUCTION

Corneal foreign bodies constitute the most frequently encountered group of ocular traumas after corneal abrasions. Corneal foreign body traumas are preventable eye traumas, and they are frequently associated with metallic foreign body trauma (1). Corneal foreign body traumas are frequently accompanied by symptoms of pain (2). Encountering reduction in sharpness of sight is not prevalent, but issues such as corneal scar formation, infectious keratitis and rarely endophthalmitis may lead to reductions in sharpness of sight (1, 2). While most corneal foreign bodies are superficial and benign in nature, they are associated with severe ocular problems in contrast to this. In addition to creating an economic burden by causing loss of labor by from a few hours up to a few days, corneal foreign bodies are one of the leading causes of monocular blindness in industry workers (1, 3).

While the etiology of corneal foreign body injuries varies, the most frequently encountered example is the combination of lack of protective glasses and high-risk jobs (4). These high-risk jobs involve activities such as grinding, forging, drilling and welding. In addition to these widespread causes, unexpected causes such as exposure of the eye to debris during activities like driving or walking may also result in corneal foreign bodies.

Self-medication and removal of the foreign body by the person are common practices associated with lack of an ophthalmologist at the workplace. Treating corneal foreign bodies with over-the-counter drugs and trying to remove them with the help of various apparatuses may lead to severe ocular complications. It is def-

initely possible to prevent corneal foreign body accidents and potentially severe outcomes. Wearing suitable protective glasses prevents approximately two thirds of these accidents (3).

The objective of this study is to show whether or not there is a relationship between being included in the groups of visits of up to 3 times and 4 times or more due to corneal foreign body traumas and parameters of working hours, duration of working in years, time of working without a break and age.

MATERIAL AND METHODS

The study was planned in compliance with the Patient Rights Directive and ethical rules by considering the principles of the Declaration of Helsinki. It is a cross-sectional and observational study. Each case that was included in the study provided written consent stating that they voluntarily participated in the study.

Among the cases who visited the polyclinic between the dates of 1 March 2018 and 31 March 2019, 280 eyes of 140 male patients who had corneal foreign bodies and were working at a shipyard were included in the study. After receiving detailed anamnesis from the cases, anterior segment and fundus examinations were performed. Information was received from all cases on frequency of visiting due to corneal foreign bodies in the last year, daily working hours, working without a break, years of work and age.

While corneal foreign body traumas for up to 3 times in the last one year were included in one group, those that were experienced for 4 times or more frequently were included in the other group. The two groups were examined based on daily working hours, working without a break, years of work and age. The data were statistically analyzed by using SPSS (Statistical Package for the Social Sciences) for Windows 17.0. Mann-Whitney U test was used to determine the relationships between parameters. The results were interpreted in a 95% confidence interval and on a significance level of $p < 0.05$.

RESULTS

While 134 eyes of 67 participants were included in the group of patients with corneal foreign body tra-

mas for up to 3 times in the past year, 146 eyes of 73 were included in the group of patients with corneal foreign body traumas for 4 times or more frequently in the past year.

For the group of patients with corneal foreign body traumas for up to 3 times in the past year, the daily working time was 513.25 ± 36.4 minutes (min.), time of working without a break was 253.2 ± 19.5 min., working duration was 78.6 ± 15.4 months, and the mean age was 41.2 ± 14.7 years, while, for the group of patients with corneal foreign body traumas for 4 times or more frequently in the past year, the daily working time was 618.1 ± 40.6 min., time of working without a break was 300.7 ± 26.8 min., working duration was 60.2 ± 10.5 months, and the mean age was 26.1 ± 10.5 years (Table 1).

When the relationships between parameters were examined by Mann-Whitney U Test, a significant relationship was found between visiting 4 times or more per year due to corneal foreign bodies and more daily working hours, long times of working without a break, short working period and younger (p -value: < 0.001).

DISCUSSION AND CONCLUSION

Although they are accepted as small ocular traumas, foreign bodies are associated with significant ocular morbidity. They are economically significant as they usually lead to loss of labor by affecting young men at working ages (5, 6, 7). The patients who were included in our study were male workers of a shipyard, and while the mean age in one group was 26.1 ± 10.5 years, the mean age in the other group was 41.2 ± 14.7 years. These mean ages were similar to those reported by previous studies (8-11). Nevertheless, the finding that the mean age in the group with 4 or more corneal foreign body complaints per year was significantly lower showed that the frequency of corneal foreign body trauma increased among the younger participants.

Serinken et al. studied work-related eye injuries and found that the frequency of eye trauma increased as ages got younger and work experience got shorter (11). Gobba et al. found the frequency of ocular trauma in young patients to be two times higher than older patients (12). As a result of their study on port workers,

Table 1. Factors that affect frequency of corneal foreign body visitation frequency

	Corneal foreign body trauma for up to 3 times (n : 67)	Corneal foreign body trauma for 4 times or more (n : 73)	P-value*
Daily working time (min.)	513.25 ± 36.4	618.1 ± 40.6	< 0.001
Working without a break (min.)	253.2 ± 19.5	300.7 ± 26.8	< 0.001
Duration of work (months)	78.6 ± 15.4	60.2 ± 10.5	< 0.001
Age	41.2 ± 14.7	26.1 ± 10.5	< 0.001

Cesar-Vaz et al. determined that usage of protective glasses would reduce symptoms related to ocular trauma (13). We also found that young age, lack of sufficient work experience, long working hours and working without a break are risk factors for the frequency of corneal foreign body traumas.

The standard method for treating corneal foreign bodies involves removal of the foreign body, covering up the eye, antibiotic drops and drops containing non-steroid analgesics (14, 15, 16). Krogsgaard et al. argued that patient cooperation is better with ointments rather than drops, and oral non-steroid analgesic tablets should be added to the treatment (17). There are also studies suggesting that, in treatment of corneal foreign bodies, although covering up the eye is conventionally recommended, it is not useful (18, 19). It was reported that some cases require corneal debridement.

Consequently, we have determined with this study that recurring corneal foreign body traumas rather af-

fect young men, those with less work experience, those with long daily working hours and those who work for a long time without a break. At this point, it is important for employers and employees to collaborate to determine a working plan towards preventing the negative effects of corneal foreign body traumas.

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Sažetak

ISPITIVANJE FAKTORA KOJI UTIČU NA UČESTALOST POSETA ZBOG POVREDA SA PRISUSTVOM STRANOG TELA U ROŽNJAČI

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Uvod: Cilj ove studije je bio da pokaže da li postoji povezanost broja poseta klinici od strane radnika brodogradilišta zbog sumnji na strano telo u rožnjači i parametara kao što su broj radnih sati, godine radnog staža, period na poslu bez pauze i broj godina.

Metode: Svi pacijenti koji su posetili urgentnu službu Ahi Evran University Research and Training Hospital, u periodu od 1. marta 2018. do 31. marta 2019. zbog sumnji na strano telo u rožnjači, su bili ispitivani u skladu sa brojem poseta tokom prethodnih godina dana, broju radnih sati tokom dana, godinama radnog staža, perioda na poslu bez pauze i broj godina. Dok su povrede sa prisustvom stranog tela u rožnjači do tri puta u protekloj godini svrstane u jednu grupu, oni sa 4 ili više puta tokom protekle godine su svrstani u drugu grupu.

Rezultati: 140 muških pacijenata je uključeno u studiju. Dok je 67 ispitanika bilo svrstano u grupu paci-

jenata sa povredom sa prisustvom stranog tela u rožnjači do tri puta tokom prethodne godine, 73 je bilo u grupi sa povredom sa prisustvom stranog tela u rožnjači 4 ili više puta u protekloj godini. Postoji statistički značajna povezanost između povreda sa prisustvom stranog tela u rožnjači 4 ili više puta godišnje i većeg broja radnih sati u danu, dužeg perioda rada bez pauze, kraćeg radnog iskustva i manjeg broja godina (p-value: < 0.001).

Zaključak: Povrede sa prisustvom stranog tela u rožnjači mogu dovesti do gubitka ili oštećenja vida i povezane su sa gubitkom radne sposobnosti i povećanjem troškova lečenja. U našoj studiji, među pacijentima koji su se javili Klinici 4 ili više puta tokom protekle godine, primećeno je da faktori rizika predstavljaju veći broj radnih sati u danu, duži period rada bez pauze, kraće radno iskustvo i manji broj godina.

Ključne reči: Rožnjača, strano telo, učestalost.

REFERENCES

1. Macedo Filho ET, Lago A, Duarte K, Liang SJ, Lima AL, Freitas Dd. Superficial corneal foreign body: laboratory and epidemiologic aspects. *Arq Bras Oftalmol.* 2005; 68(6): 821-3.
2. Alexander MM, MacLeod JD, Hall NF, Elkington AR. More than meets the eye: a study of the time lost from work by

patients who incurred injuries from corneal foreign bodies. *Br J Ophthalmol.* 1991; 75(12): 740-2.

3. Gumus K, Karakucuk S, Mirza E. Corneal injury from a metallic foreign body: an occupational hazard. *Eye Contact Lens.* 2007; 33(5): 259-60.

4. Calli U, Bulut MN, Ayyildiz T, Kandemir B, Ozerturk Y. The inquiry of applications in corneal foreign body patients and

questioning safety goggles use. *New journal of medicine*. 2015; 32: 132-4.

5. Nicaeus T, Erb C, Rohrbach M, Thiel HJ. An analysis of 148 outpatient treated occupational accidents. *Klin Monbl Augenheilkd*. 1996; 209(4): A7-11.

6. Ergin A, Ç2nar P, Ba} O, Alt2n A, Ergin P. Acil servisten göz acili olarak göz klini—ine sevk edilen hastalar2n özellikleri. *Bidder T2p Bilimleri Dergisi*. 2011; 3: 6-9.

7. Akdur O, Ozkan S, Erkilic K, Durukan P, Duman A, Ikizceli I. Acil servise göz travması nedeniyle başvuran olgular2n değerlendirilmesi. *Akademik Acil Tıp Dergisi*. 2009; 8: 47-50.

8. Ramakrishnan T, Constantinou M, Jhanji V, Vajpayee RB. Corneal metallic foreign body injuries due to suboptimal ocular protection. *Arch Environ Occup Health*. 2012; 67(1): 48-50.

9. Hussain A, Shaukat Q, Mahmood, N. Metallic corneal foreign body; a preventable work related cause of ocular morbidity. *Professional Med J*. 2019; 26(4): 688-91.

10. Uzun I, Gul A. Yüzeyel korneal yabancı cisimlerde tedaviye kadar geçen süre ile ilişkili faktörlerin değerlendirilmesi. *Cumhuriyet Medical Journal*. 2013; 35(2): 239-43.

11. Serinken M, Turkcuier I, Cetin EN, Yilmaz A, Elicabuk H, Karcioğlu O. Causes and characteristics of work-related eye injuries in western Turkey. *Indian J ophthalmol*. 2013; 61(9): 497-501.

12. Gobba F, Dall'Olio E, Modenese A, De Maria M, Campi L, Cavallini G. Work-related eye injuries: A relevant health problem. Main epidemiological data from a highly-industrialized area of Northern Italy. *Int J Environ Res Public Health*. 2017; 14(6): 604.

13. Cezar-Vaz MR, Xavier DM, Bonow CA, Mello MCVAD. Ocular manifestations in port workers: prevalence and associated factors. *Acta Paul Enferm*. 2019; 32(1): 72-8.

14. Goyal R, Shankar J, Fone DL, Hughes DS. Randomised controlled trial of ketorolac in the management of corneal abrasions. *Acta Ophthalmol Scand*. 2001; 79(2): 177-9.

15. Kaiser PK, Pineda R. 2nd. A study of topical nonsteroidal anti-inflammatory drops and no pressure patching in the treatment of corneal abrasions. *Corneal Abrasion Patching Study Group. Ophthalmology*. 1997; 104(8): 1353-9.

16. Patterson J, Fetzter D, Krall J, Wright E, Heller M. Eye patch treatment for the pain of corneal abrasion. *South Med J*. 1996; 89(2): 227-9.

17. Krogsgaard MR, Danborg L, Jensen P, Kristensen MO. Complaints following treatment of common acute eye diseases. *Ugeskr Laeger*. 1990; 152(19): 1365-8.

18. Wilson SA, Last A. Management of corneal abrasions. *Am Fam Physician*. 2004; 70(1): 123-8.

19. Le Sage N, Verreault R, Rochette L. Efficacy of eye patching for traumatic corneal abrasions: a controlled clinical trial. *Ann Emerg Med*. 2001; 38(2): 129-34.

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QUALITY OF IMPRESSIONS USING TWO DIFFERENT BRANDS OF POLYVINYL SILOXANE IMPRESSION MATERIALS

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Abstract: Background: This study was to evaluate the impression quality and clinical success of 2 Polyvinyl siloxane (PVS) impression materials by using dual-viscosity 1-step impression technique and the putty-wash two-step impression technique.

Methods: In this study, Variotime (Heraeus, Hanau, Germany) and a novel silicone Spirias (Imicryl, Konya, Turkey) were selected as PVS impression materials. A total of 40 samples were divided into groups according to the impression technique. Three possible categories were established to rate the impression quality. The impression was examined using a laboratory microscope (Opmi Pico, Zeiss) and lenses with 2X to 6X magnification for the presence or absence of bubbles or voids and the complete reproduction of the preparation finish line. A spreadsheet (Excel v2016; Microsoft Corp) was used for processing statistical data. Results of the analysis were calculated as mean and frequency.

Results: In the impressions taken with Variotime, the percentage of the successful impression is 95% (Criteria I - II). Only one impression was found unacceptable (criteria III). In impressions with Spirias, the percentage of successful impressions is 100% (Criteria I - II). No-impression was found unacceptable (criterion III).

Conclusion: The quality of impressions of both brands Polyvinyl siloxane impression materials revealed a high rate (97.5%) For more precise results, many new studies were needed on different Polyvinyl siloxane impression materials.

Keywords: polyvinyl siloxane, additional silicone, quality of impression.

INTRODUCTION

Impressions made to replicate the condition of teeth and surrounding tissues are a main part of prosthetic dentistry. The purpose of acceptable impressions is to provide exact information for indirect restorations

(1). Although a successful dental prosthesis depends on many factors associated with the dentist, material, and patient, the impression is the most critical step (2).

Making the impression is a critical clinical step to accurately record the three-dimensional intraoral relationships among teeth and surrounding structures (1). Laboratory errors that lead to incompatibility in indirect restorations are most often the result of inaccuracies that occur during the impressions (1, 2, 3). Many factors, such as the experience and skill of clinicians, proper material handling, the choice of impression materials, technique, working time, and the patient's compliance, affect the acceptability of the impression (3).

Polyvinyl siloxane impression material (PVS), also called addition silicone impression material, which has been used for many years, is one of the most commonly used impression materials for indirect denture restorations today. This material has many advantages, such as low polymerization shrinkage, virtually ideal dimensional stability and durability, good detail reproduction, non-toxic or non-allergic behavior, adequate tear resistance, and quick elastic recovery.

Its stability makes it possible to pour the molds up to several days after they have been removed from the mouth. PVS is the best choice among elastic impression materials if there is likely to be a delay in pouring the molds. Innovations in PVS impression materials aim to enhance precision and limit some clinical handicaps, such as bubbles, voids, tears, and pulls (4). On the other hand, PVS is inherently hydrophobic; because of its hydrophobic behavior, PVS applications are limited to dry conditions. A new formulation of "hydrophilic" PVS has been produced that can better penetrate moist dental surfaces (5).

PVS impression materials can be used in several techniques in accordance with the manufacturer's recommendations (6), taking into account their viscosi-

es: the dual-viscosity one-step impression technique, the single-viscosity monophasic impression technique, and the putty-wash two-step impression technique (3).

The aim of this study was to evaluate the impression quality and clinical success of two PVS impression materials by using the dual-viscosity one-step impression technique and the putty-wash two-step impression technique. The null hypothesis of this study was that there would be no difference between PVS impression materials and techniques.

MATERIAL AND METHODS

A standard maxillary dentulous acrylic model (Integra, Ankara, Turkey) was selected as the master model. Tooth 26 was prepared with the preparation finish line located in the epigingival position. In this study, Variotime (Heraeus, Hanau, Germany) and a novel silicone, Spirias (Imicryl, Konya, Turkey), were selected as PVS impression materials. The viscosity of the new PVS brand Type 3 Extra Light Body Spirias (rheometer, at shear stress of 100 Pa) is 10 PaS. Sharp fin test and Consistency test results are 16 mm and 42-45mm respectively (ISO 4823 Consistency test).

A total of 40 samples were divided into groups according to the impression technique and pouring time. Grup I is "Variotime putty and light body / one-step technique" and Grup II is "Spirias putty and extra light

body / two-step technique". Spirias produces an extra light body, and the company's recommendation is to perform a two-stage impression. Variotime, which we frequently use in our routine clinical practices, suggests a single-stage impression (5). We planned our work by considering the manufacturers' suggestions.

Stock trays were used for impressions of all groups. For standardization of impression loading, a square metal plate weighing 1.5 Kg was placed on the impression trays.

Three possible categories were established to rate the impression quality (Figure 1):

a. Perfect impressions, with an absence of voids or bubbles and perfect reproduction of the preparation finish line, were rated Criteria I.

b. Minimal defects in the impression up to 2 mm in diameter not involving the preparation finish line that could be corrected by the technician on the casts were considered acceptable and rated Criteria II.

c. If impressions showed bigger voids or bubbles (more than 2 mm in diameter) or defects involving the preparation finish line, they were categorized as unacceptable and rated Criteria III.

The impression was examined using a laboratory microscope (Opmi Pico, Zeiss) and lenses with 2X to 6X magnification for the presence or absence of bubbles or voids and the complete reproduction of the preparation finish line.

Table 1. The distribution of impression quality for Variotime and Spirias (No. and %)

	criteria I*	criteria II**	criteria III**	total
Group I	18 (%90)	1 (%5)	1 (%5)	20 (%100)
Group II	19 (%95)	1 (%5)	0 (%0)	20 (%100)
total	37 (%92.5)	2 (%5)	1 (%2.5)	40 (%100)

*Criteria I. Perfect impressions, no voids or bubbles

**Criteria II. Acceptable impressions, minimal defects in the impression (less than 2 mm in diameter) or not involving the preparation finish line

***Criteria III. Unacceptable impressions, big voids or bubbles (more than 2 mm in diameter) or defects involving the preparation finish line

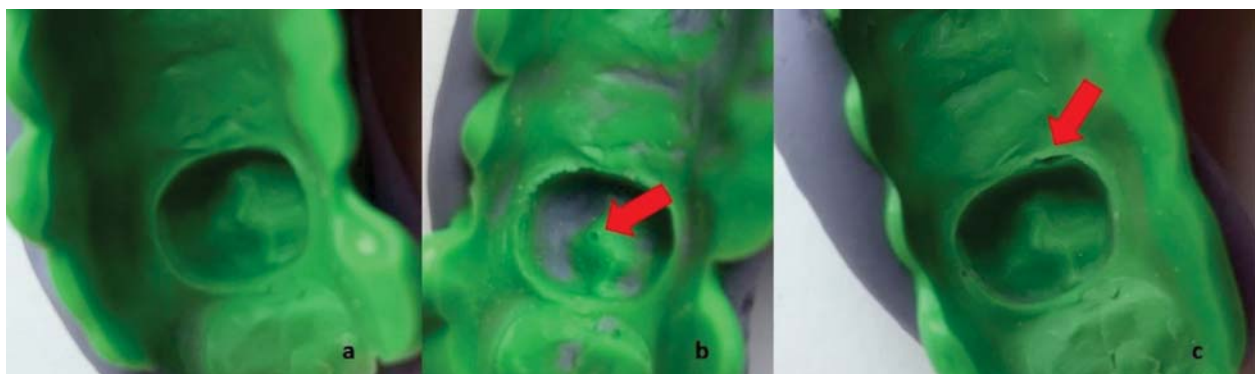


Figure 1. Three categories were established to rate the quality of the final impressions: (a) Criteria I: perfect impression, with no voids or bubbles; (b) Criteria II: acceptable impression, minimal voids or bubbles not involving the preparation finish line; (c) Criteria III: unacceptable impression, with large voids and bubbles

A spreadsheet (Excel v2016; Microsoft Corp) was used for processing statistical data. Results of the analysis were calculated as mean and frequency.

RESULTS

Table 1 shows the number and percentages of PVS impressions according to three impression quality criteria. In the impressions taken with Variotime, the percentage of successful impressions was 95% (criteria I–II). Only one impression was found unacceptable (criterion III). In impressions with Spirias, the percentage of successful impressions was 100% (criteria I–II). No impression was found unacceptable (criterion III). An acceptable percentage for all PVS impression materials is 97.5%.

DISCUSSION

The aim of this in-vitro study was to evaluate the quality of impressions made with PVS materials (Variotime, Spirias), as determined by the presence or absence of bubbles or voids and the complete reproduction of the preparation finish line.

One reason for insufficient impressions is that the air bubbles between the impression material and the tooth are trapped. This may be due to the accidental shut-down of air when applying a light body material with the syringe, especially if the syringe tip is raised during the procedure. The clinician's experience and manual skill are responsible for the quality of these results. In this study, the preparations and impressions were carried out by experienced clinicians, with an overall success rate of 92.50%.

The ideal impression material should have high dimensional stability, which is critical for the correct replication of intraoral structures. PVS has been used as an impression material for many years and has gained popularity due to its excellent accuracy and dimensional stability (7). Pereira et al. found that the dimensional stability of the additive silicone did not change significantly (linear size changes did not exceed 1%), even 96 hours after measurement (8). These results are consistent with previous researchers' work (9).

In addition, the physical properties of the impression material will affect success. The PVS material used in this study offers good wettability and flow behavior in dental tissue. In general, some rules must be followed to process PVS materials. One thing to note is that rubber gloves or rubber dams are not used (10).

According to the literature, the one-step technique with PVS leads to very accurate impressions (11). The one-step technique is quite simple, cost-effective, and less time-consuming; it also protects the impression material. However, this technique has several disadvantages. First, there is no stack control. With this technique, more bubbles are produced and included in the set impression. In this study, a double stage Spirias impression showed better results than a single stage Variotime impression. However, both techniques and both brands showed close results.

CONCLUSION

Two significant conclusions were reached in this study:

1. Although the values of the Spirias sample were slightly better than the values of Variotime, the impression quality and clinical success of both PVS impression materials revealed a high rate (97.5%)
2. For more precise results, many new studies are needed on different PVS impression materials and different techniques.

Abbreviations

PVS — polyvinyl siloxane

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Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

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Sažetak

KVALITET ZUBNOG OTISKA DVA RAZLIČITA BRENDA POLIVINIL SILOKSAN IMPRESIONIH MATERIJALA

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Uvod: Ova studija je ispitala kvalitet zubnog otiska i klinički uspeh dva polivinil siloksan (PVS) im-

presiona materijala koristeći dvostruko viskoznu monofaznu tehniku otiska i putty-wash bifaznu tehniku.

Metode: U ovoj studiji, *Variotime* (Heraeus, Hanau, Nemačka) i inovativni *Spirias* (Imicryl, Konya, Turska) su izabrani kao PVS materijali. Ukupno 40 uzoraka je podeljeno u dve grupe prema tehnici otiska. Određene su tri moguće kategorije za merenje kvaliteta otiska. Utisci su ispitivani pomoću laboratorijskih mikroskopa (*Opmi Pico*, *Zeiss*) i sočivima sa uvećanjem od 2X do 6X za detektovanje prisustva mehurića ili praznina i kompletne reprodukcije završnih linija. Tabela (*Excel v2016*; *Microsoft Corp*) je korišćena za statističku obradu podataka. Rezultat analize su računati kao prosečne vrednosti i učestalosti.

Rezultati: Kod otisaka uzetih sa *Variotime* materijalom, procenat uspešnosti je 95% (Kriterijumi I - II). Samo jedan otisak je bio u potpunosti neprihvatljiv (Kriterijum III). Kod otisaka uzetih *Spirias* materijalom, procenat uspešnosti je 100% (Kriterijumi I - II). Nije nađen nijedan neprihvatljiv otisak (Kriterijum III).

Zaključak: Pokazana je visoka stopa uspešnosti kvaliteta otisaka oba brenda PVS impresionih materijala (97.5%). Za preciznije rezultate, mnoge nove studije su potrebne na različitim PVS impresionim materijalima.

Ključne reči: polivinil siloksan, dodatni silikon, kvalitet zubnog otiska.

REFERENCES

1. Dogan S, Schwedhelm ER, Heindl H, Mancl L, Rai-grodski AJ. Clinical efficacy of polyvinyl siloxane impression materials using the one-step two-viscosity impression technique. *J Prosthet Dent*. 2015; 114(2): 217–22.
2. Garg S, Kumar S, Jain S, Aggarwal R, Choudhary S, Reddy NK. Comparison of dimensional accuracy of stone models fabricated by three different impression techniques using two brands of polyvinyl siloxane impression materials. *J Contemp Dent Pract*. 2019; 20(8): 928–34.
3. Levartovsky S, Zalis M, Pilo R, Harel N, Ganor Y, Brosh T. The effect of one-step vs. two-step impression techniques on long-term accuracy and dimensional stability when the finish line is within the gingival sulcular area. *J Prosthodont*. 2014; 23(2): 124–33.
4. Leao MP, Pinto CP, Sponchiado AP, Ornaghi BP. Dimensional stability of a novel polyvinyl siloxane impression technique. *Brazilian J Oral Sci*. 2014; 13(2): 118–23.
5. Basapogu S, Pilla A, Pathipaka S. Dimensional accuracy of hydrophilic and hydrophobic VPS impression materials using different impression techniques - an invitro study. *J Clin Diagn Res*. 2016; 10(2): 56-9.
6. Kit HT. Impression Technique Guide. :33–4. Available from: http://www.brainserver.net/uploads/og/ContentImages/HealthProImages/Dental_Offers/Heraeus_Offers/36398_Variotime_StepGuide_EE.pdf
7. Ghahremanloo A, Seifi M, Ghanbarzade J, Abrisham SM, Javan RA. Effect of polyvinyl siloxane viscosity on accuracy of dental implant impressions. *J Dent (Tehran)*. 2017; 14(1): 40-7.
8. Pereira JR, Murata KY, do Valle AL, Ghizoni JS, Shira-tori FK. Linear dimensional changes in plaster die models using different elastomeric materials. *Braz Oral Res*. 2010; 24(3): 336–41.
9. Ahmed M, Chakmakchi M. An in vitro study to evaluate the accuracy of addition silicone and polyether impression materials after different pouring time. *Al-Rafidain Dent J*. 2016; 16(1): 10–8.
10. Hiremath V, Vinayakumar G, Ragher M, Rayannavar S, Bembalagi M, Ashwini BL. An evaluation of the effect of various gloves on polymerization inhibition of elastomeric impression materials: an in vitro study. *J Pharm Bioallied Sci*. 2017; 9(1): 132-7.
11. Franco EB, da Cunha LF, Herrera FS, Benetti AR. Accuracy of single-step versus 2-step double-mix impression technique. *ISRN Dent*. 2011; 2011: 341546. doi: 10.5402/2011/341546

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COMPARISON OF CARDIAC MAGNETIC RESONANCE AND CARDIAC ULTRASOUND IMAGING FINDINGS IN CONGENITAL AND ACQUIRED HEART DISEASES

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Abstract: Objective: Nowadays, non-invasive methods are emerging in the evaluation of cardiovascular diseases. The aim of this study was to determine the diagnostic performance of cardiac magnetic resonance (CMR) imaging and cardiac ultrasound imaging (Echo) in cardiac patients diagnosed with Echo previously.

Methods: In total of 32 various cardiac patients with Echo findings including congenital and acquired heart pathologies who applied to our clinic were included in the study. The distribution of cardiac pathologies including valve dysfunctions, right and left ventricular wall lesions and movement disorders, atrioventricular hypertrophy, septal defect, pericardial effusion-mass, additional congenital or acquired vascular pathologies and additional thoracic pathology, age and gender correlations were determined. The CMR and Echo findings were compared statistically.

Results: It was found that 12 (37.5%) of the individuals were female, 20 (62.5%) were male, aged between 6 and 80 years with an average age of 29.9 years. The cardiac parameters were positive in 27 (84.4%) patients according to Echo and were positive in 22 (68.8%) patients according to CMR. There was no statistically significant correlation between CMR and Echo for cardiac pathology detection rates ($p > 0.05$). However, only 18 out of 22 patients who were positive on CMR were positive on Echo. CMR was superior in detecting congenital cardiac pathologies.

Conclusion: Echo has a diagnostic advantage and in general, CMR and Echo findings overlap in cases with valve dysfunctions, ventricular wall motion disorders, and hypertrophy, whereas we found that Echo findings were insufficient for diagnosis of congenital heart pathologies.

Key words: cardiac magnetic resonance, echocardiography, heart diseases, comparison.

INTRODUCTION

Heart diseases are among the most common pathologies worldwide and responsible for 31% of all deaths in the world (1). In our country they are also among the leading causes of mortality and morbidity, and according to Turkish Statistical Institute 2010 data, the most common early causes of death are cardiovascular diseases in both sexes (2). Cardiac diseases are four times more common in males than in females and are more frequent in 50-60 year old females and 60-70 year old males (3).

In the evaluation of heart diseases, non-invasive methods are now at the forefront. Cardiac ultrasound imaging (Echo) is the most important method used during follow-up of cardiovascular patients and is a safe and reliable imaging technique for patients. With Echo, proximal aortic wall thickness, diameters, aorta valve structure and their functions can be assessed in detail, while mitral valve pathology, myocardium systolic and diastolic functions can be assessed with both 2D and M-mod, continuous wave and pulsed wave Doppler ultrasound. Thanks to its different usage modalities, Echo is a guide for surgical complications, morphologic variations, rejection, and allograft vasculopathy (4).

In recent years, studies about cardiac magnetic resonance (CMR) imaging have gained speed because they show tissue features. Various studies are continuing to reduce unnecessary biopsies and coronary angiographies, and for diagnosis of complications and rejection at early stages. CMR has been used increasingly for the evaluation of myocardial diseases (5).

CMR was used non-invasively to evaluate coronary artery disease, to evaluate cardiac ischemia and determine prevalence, measure ventricular function, contractile reserve, and image luminal narrowing of the arteries (6, 7, 8). It also has an important place in congenital heart diseases. Besides the anatomical imaging of the heart's compartments, it can also show atrioventricular morphological evaluation and structural features can be demonstrated. In summary, CMR imaging is useful to distinguish normal and pathological myocardial tissue. The reason for preference is that it does not involve ionizing radiation and is less costly.

The aim of this study is to identify supporting or opposing findings of cases with cardiac pathology proven by Echo and compare with a non-invasive method, CMR which provides additional findings about neighboring anatomic structures, in light of magnetic resonance technology.

MATERIAL AND METHODS

A total of 32 various cardiac patients with Echo findings including congenital and acquired heart pathologies who applied to our clinic were included in the study. Among the patient groups, cardiac pathologies, valve dysfunctions (aortic, pulmonary, mitral and tricuspid valves), both right and left ventricular wall lesions (noncompaction, trabeculation, UHL/ARVD anomalies) and movement disorders (hypokinesia, movement, acquired), atrioventricular hypertrophy, septal defect, pericardial effusion-mass, additional congenital or acquired vascular pathologies (acquired such as congenital aortic and pulmonary arterial embolisms, strictures and aneurysmal dilatations such as aortic coarctation, dextra malposition, giant eustachian valve) distributions, findings, age and gender correlations with thoracic pathology were included.

The CMR test was performed using a phase sequential coil in a 1.5 T MR device (Siemens, Magnetom Avanto Syngo, Erlangen, Germany). Cine gradient echo T2A long axis, TSE T1A and fat-suppressed T2A short and long axis sequences (2 and 4 chamber images), identification of standard cardiac morphology (wall lesions especially ARVD, wall movements, valve lesions, large vessel lesions and congenital anomalies), mediastinal and thoracic pathologies were implemented. In spin-echo sequence routine cardiac examination, TR appropriate to R-R' interval in ECG, TE: 30 ms, section thickness=8 mm, Matrix: 224 x 224, FOV = 300 X 400 mm; parameters for cine-cardiac MR examination TR/TE, 3.4/1.5, flip angle (FA) = 45°; sectional thickness = 8 mm, matrix = 224 x 224, FOV = 35 cm were applied. Patients with myocarditis and cardiomyopathies and myocardial involvement had imaging

taken 10-20 minutes after intravascular (IV) extracellular contrast agent injection (0.1-0.2 mmol/kg) with late contrast IR images in multiplanar sections. Late contrast imaging used TR/TE, 4.8/1.3, flip angle (FA) 20°, receiver band width $\pm$ 31.25 kHz, FOV = 35 cm, cross section thickness 8 mm, cross sectional area 2 mm and matrix 256 x 160 parameters. Echocardiographic images were obtained in the standard parasternal long and short axis and apical 4 chamber and 2 chamber views utilizing digital Vivid 7 ultrasound equipment with a combined tissue imaging 2.5 – 4.0 MHz transducer (GE, Milwaukee, WI). At least 3 cardiac cycles were captured at the left ventricular (LV) base, mid papillary muscle level, and apex for wall motion assessment. No intravenous echocardiographic contrast agent was used.

Statistical analysis

Chi-square and Fisher's Exact Chi-Square tests were used to compare descriptive statistics (mean, standard deviation, frequency), as well as qualitative data when evaluating study data. McNemar test and diagnostic screening tests were used for CMR and Echo evaluations of cardiac pathologies; significance was evaluated as $p < 0.05$.

RESULTS

The ages of the 32 patients included in the study ranged from 6 to 80 years with a mean age of 29.93 ± 19.80 , with 12 (37.5%) women and 20 (62.5%) men.

From cardiac parameters, Echo was positive in 27 (84.4%) cases and CMR was positive in 22 (68.8%) cases (Tables 1 and 2). Congenital cardiac pathologies were detected in six cases. In 15 (46.9%) of the cases, valve dysfunction was present. On the right, 4 (12.5%) of the cases had abnormal ventricular wall motion or structural abnormality. On the left, 9 (28.1%) of the cases with abnormal ventricular wall motion or structural abnormality diagnosed by CMR. Fourteen of the cases had atrial-ventricular hypertrophy (43.8%), and 5 (15.6%) of the cases had additional vascular abnormality and nonspecific wall tumors.

There was no statistically significant correlation between cardiac pathology rates on CMR and Echo ($p > 0.05$) (Table 1). With the Echo method, 84.4% of the

Table 1. Distribution of cardiac pathologies according to imaging method

Cardiac pathology	Positive n (%)	Negative n (%)
Echo	27 (84.4)	5 (15.6)
CMR	22 (68.8)	10 (31.2)

Table 2. Relationship between CMR and Echo in cardiac pathology

	Cardiac pathology CMR		<i>P</i> *
	Positive	Negative	
	n (%)	n (%)	
Cardiac pathology Echo			
Positive	18 (56.3)	9 (28.1)	0.267
Negative	4 (12.5)	1 (3.1)	

*McNemar test.

cases received positive diagnosis and with cardiac MR 68.8% of the cases received positive diagnosis. Of the 22 patients positively diagnosed with CMR, only 18 had the same positive diagnosis in Echo; whereas the other cases were negative in Echo. The sensitivity of CMR was 81.8% and specificity was determined as 10%. The positive predictive value was 66.67% and the negative predictive value was 20%. Of the 27 patients who had pathology detected on Echo, only 18 had pathological diagnosis on CMR. Two cases of ventricular septal defect (VSD), one case of left ventricular hypertrophy and one case of tricuspid insufficiency, a total of four, were positive on CMR unlike Echo findings which were all negative (Figure 1). In contrast with the two imaging methods, it was found that Echo findings were inadequate in cases of congenital heart disease, while CMR and Echo findings overlapped in cases with valve dysfunctions, ventricular wall motion disorders and hypertrophy in general.

There was no statistically significant difference between cardiac pathologies according to gender with

Echo findings and CMR findings ($p > 0.05$). There was no statistically significant difference between the findings of valve dysfunction according to gender ($p > 0.05$). For similar structural features of ventricular wall motion on the right and left according to gender, atrial ventricular hypertrophy, additional vascular abnormalities and non-specific wall tumors, septal defect and additional thoracic pathology findings were not statistically significant ($p > 0.05$).

When both imaging methods were evaluated in terms of age in cardiac pathologies, there was no statistically significant difference between the Echo and CMR findings with age ($p > 0.05$) (Table 3). Similarly, there was no statistically significant difference between the findings of valve dysfunction according to age distribution ($p > 0.05$) (Table 4).

DISCUSSION

Cardiac MRI is now an important diagnostic imaging method for detecting congenital and acquired cardiac pathologies. CMR provides more findings incar-

Table 3: Evaluation of cardiac pathologies by age

	Age			<i>p</i> *
	< 15	16-40	> 40	
	n (%)	n (%)	n (%)	
Cardiac pathology Echo	9 (81.8)	9 (75)	9 (100)	0.283
Cardiac pathology CMR	7 (63.6)	8 (66.7)	7 (77.8)	

* Chi square test

Table 4. Evaluation of valve dysfunctions by age

	Age			<i>p</i> *
	< 15 year (n = 11)	16-40 year (n = 12)	> 40 year (n = 9)	
	n (%)	n (%)	n (%)	
Valve Dysfunction	3 (27.3)	6 (50)	6 (66.7)	0.206
TI	3 (27.3)	5 (41.7)	2 (22.2)	0.598
AI	1 (9.1)	1 (8.3)	1 (11.1)	0.976
MI	2 (18.2)	2 (16.7)	4 (44.4)	0.282
AS	0	0	1 (11.1)	0.267

* Chi square test (TI: Tricuspid Insufficiency, AI: Aortic Insufficiency, MY: Mitral Insufficiency, AS: Aortic Stenosis)

diac diseases compared to other methods like echo, scintigraphy or angiography in just a single examination. For evaluation of congenital heart diseases, it ensures important benefits in providing cardiac anomaly imaging and additional information.

MRI shows the anatomical health of the compartment of the heart and evaluates the atrium and ventricle morphologically. In our study, 14 cases of atrial and/or ventricular hypertrophy were present. In addition to showing hypertrophy on MRI, due to real-time and high-resolution imaging of the affected valve functions in cine imaging, progress is being made to obtain important information that will lead to diagnosis and treatment.

Subendocardial perfusion defects, as is well known in acute myocardial ischemia, are the first findings followed by transmural perfusion defects and wall motion disorders. Electrocardiographic changes and angina are relatively late developing findings (9). Cardiac MRI has an important benefit in detecting infarcts. Especially, choosing late contrast sequences provides great benefits on this subject. In studies performed by De Roos et al. late contrast enhancement in the infarct area was confirmed before and after administration of i.v.0.1 mmol/kg Gd DTPA2 to 17 days after myocardial infarction. Images are acquired 30 minutes after injection to reveal late involvement (10).

One of the most common clinical methods for detecting perfusion abnormalities is myocardial perfusion single photon emission computed tomography (SPECT). An important advantage of this method is its validity with a large number of multicenter studies. However, it has the disadvantage of having low temporal and spatial resolution, attenuation artifacts and ionizing radiation. Concomitant contrast-enhanced MR angiography provides better diagnostic imaging of myocardial ischemia (11, 12).

Another limited imaging method for myocardial blood flow is positron emission tomography (PET). It has some disadvantages like low resolution of subendocardial tissue, difficult to access due to cost and involving ionizing radiation. In addition, the analysis of images is quite time-consuming and complicated. However, evaluation of subendocardial perfusion is much better with cardiac MRI with high temporal and spatial resolution (13). MRI can also be used to visualize complications such as aneurysm formation due to ischemic heart diseases, valvular regurgitation and pericardial effusion. There is a high risk of thrombus formation in these areas, especially due to slowing blood flow in transmural infarcts and aneurysmal areas developing after infarction. Detection of thrombi between the left ventricular apex and endocardial trabeculations may not be easy with transthoracic echocardiography. Throm-

bi can be easily visualized and distinguished from slow blood flow with contrast and cine MR images (14). In one case we could not distinguish thrombus or mass with Echo, then we performed cardiac MRI to image the location, and displacement during the cycle and non-enhancing internal structure and easily demonstrated the thrombi. Unlike mass-thrombus diagnosed with Echo, a giant eustachian valve which is hard to distinguish was diagnosed with CMR in one case. In total, six cases had congenital cardiac pathology; in three of them we detected the diagnostic addition and in the other three, one with Uhl abnormality and two with septal defects, we detected the diagnostic superiority of MRI compared to Echo.

Conventional coronary angiography is still considered the gold standard imaging method for the coronary arteries. However, CMR angiography is preferred to conventional coronary angiography because of the risk of radiation exposure during operation, being an invasive procedure and complications (15).

In hypertrophic cardiomyopathy cases, the main diagnosis is made by echocardiography. However, CMR provides higher spatial resolution, can easily detect the localization and the damage of the myocardial abnormality (16).

The limits of our study are the inclusion of a certain number of patients with a wide heart disease spectrum. We think that more specific findings and specific pathologies may be obtained if performed with more study groups.

The CMR technique has the capability of presenting a wide range of information in a single study in contrast with echocardiography, scintigraphy and angiography, which are commonly used in the assessment of cardiac pathologies.

CONCLUSION

Echo has diagnostic advantage and in general, CMR and Echo findings overlap in cases with valve dysfunctions, ventricular wall motion disorders, and hypertrophy, whereas we found that Echo findings were insufficient for diagnosis of congenital heart pathologies. We believe that in the near future we will eliminate many of the methods used for cardiac pathologies with technological developments that resolve the limitations of the procedure.

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Sažetak**UPOREĐIVANJE NALAZA MAGNETNE REZONANCE I ULTRAZVUKA SRCA KOD KONGENITALNIH I STEČENIH SRČANIH BOLESTI**Serinsoz Serdar,¹ Akturk Remzi,² Bayramoglu Sibel³¹ Istanbul Safa Private Hospital, Istanbul, Turkey² Istanbul Gelisim University, Istanbul Turkey³ Istanbul Sultan Abdulhamid Han Training and Research Hospital

Uvod: U današnje vreme, za evaluaciju kardiovaskularnih oboljenja, prednost se daje neinvazivnim metodama. Cilj ove studije bio je da se ispita dijagnostički učinak magnetne rezonance srca i ultrazvuka srca kod pacijenata koji boluju od srčanih bolesti, a kod kojih je prethodno utvrđena dijagnoza pomoću ultrazvuka srca.

Metod: Ukupno 32 pacijenta sa različitim bolestima srca, koje su potvrđene ultrazvučnim nalazima, a koja su uključivala kongenitalnu i stečenu srčanu patologiju, bila su uključena u ovu studiju. Distribucija kardioloških oboljenja uključivala je valvularnu disfunkciju, lezije zidova i poremećaje pokreta leve i desne komore, atrioventrikularnu hipertrofiju, septalni defekt, perikardijalnu efuziju, dodatna kongenitalna i stečena vaskularna oboljenja, kao i dodatnu torakalnu patologiju, a ispitivani su i uzrast i pol. Nalazi magnetne rezonance srca i ultrazvučni nalazi srca, su upoređivani statistički.

Rezultati: Utvrđeno je da 12 (37,5%) ispitanika je bilo ženskog, a 20 (62,5%) muškog pola, starosti od

6 do 80 godina, sa srednjom vrednosti od 29,9 godina. Kardijalni parametri bili su pozitivni kod 27 pacijenata (84,4%) prema nalazima ultrazvuka srca i pozitivni kod 22 pacijenta (68,8%), prema nalazima magnetne rezonance. Nije utvrđena statistička značajnost između MR i ultrazvučnog nalaza srčane patologije ($p > 0,05$). Međutim, samo 18 od 22 pacijenta koji su bili pozitivni na MR, su imali pozitivan nalaz na ultrazvučnom pregledu. Magnetna rezonanca srca se pokazala kao superiornija u dijagnostici kongenitalnih srčanih patologija.

Zaključak: Ultrazvučna dijagnostika srca ima prednosti u odnosu na MR uopšteno govoreći, nalazi ultrazvučnog pregleda srca i MR srca se preklapaju kod slučajeva sa valvularnom disfunkcijom, poremećajem pokreta zidova srčanih komora, hipertrofije, dok je nađeno da su ultrazvučni nalazi nedovoljni za dijagnozu kongenitalnih bolesti srca.

Cljučne reči: magnetna rezonanca srca, ehokardiografija, srčane bolesti, upoređivanje.

REFERENCES

1. Global action plan for the prevention and control of NCDs 2013-2020..Geneva, World Health Organization. https://www.who.int/nmh/events/ncd_action_plan/en/
2. Sahan C, Sozmen K, Doganay S, Unal B. Türkiye'de kalp ve damar hastalıkları sikliklarındaki değişimin değerlendirilmesi. *Türk J Public Health*. 2015; 13(1): 62-80.
3. Onat A, Karakoyun S, Akbas T, Karadeniz OF, Karadeniz Y, Cakir H et al. Turkish Adult Risk Factor survey 2014: Overall mortality and coronary disease incidence in Turkey's geographic regions. *Türk Kardiyol Dern Arş - Arch Turk Soc Cardiol*. 2015; 43(4): 326-32.
4. Sade LE, Muderrisoglu IH. Kalp nakil hastalarının gürültüleme ile değerlendirilmesi. *Türkiye Klinikleri Kalp Damar Cerrahisi-Ozel Konular*. 2018; 10(2): 102-8.
5. Yalin K, Guler TE, Sanli S. Cardiac magnetic resonance imaging experience of a newly established cardiology center. *Kocaeli Med J*. 2018; 7(1): 2-6.
6. Dursun M, Yilmaz S, Yilmaz E, Yilmaz R, Onur I, Oflaz H et al. The utility of cardiac MRI in diagnosis of infective endocarditis: preliminary results. *Diagn Interv Radiol*. 2015; 21(1): 28-33.
7. Danad I, Szymonifka J, Twisk JWR, Norgaard BL, Zarins CK, Knaapen P et al. Diagnostic performance of cardiac imaging

methods to diagnose ischaemia-causing coronary artery disease when directly compared with fractional flow reserve as a reference standard: a meta-analysis. *Eur Heart J*. 2017; 38 (13): 991-8.

8. Sachdeva S, Song X, Dham N, Heath DM, DeBiasi RL. Analysis of clinical parameters and cardiac magnetic resonance imaging as predictors of outcome in pediatric myocarditis. *Am J Cardiol*. 2015; 115 (4): 499-504.
9. Hamirani YS, Kramer CM. Cardiac MRI assessment of myocardial perfusion. *Future Cardiol*. 2014; 10(3): 349 58.
10. Rajiah P, Desai MY, Kwon D, Flamm SD. MR imaging of myocardial infarction. *RadioGraphics*. 2013; 33(5): 1383-412.
11. Salata BM, Singh P. Role of cardiac PET in clinical practice. *Curr Treat Options Cardiovasc Med*. 2017; 19(12): 93.
12. Rahman H, Ryan M, Lumley M, Modi B, McConkey H, Ellis H et al. Coronary microvascular dysfunction is associated with myocardial ischemia and abnormal coronary perfusion during exercise. *Circulation*. 2019; 140(22): 1805 16.
13. Schwitler J, Wacker CM, Wilke N, Al Saadi N, Sauer E, Huettler K et al. MR-IMPACT II: Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary artery disease Trial: perfusion-cardiac magnetic resonance vs. single-photon emission computed tomography for the detection of coronary artery disease: a comparative multicentre, multivendor trial. *Eur Heart J*. 2013; 34(10): 775 81.

14. Di Leo G, Fisci E, Secchi F, Ali M, Ambrogio F, Sconfienza LM et al. Diagnostic accuracy of magnetic resonance angiography for detection of coronary artery disease: a systematic review and meta-analysis. *Eur Radiol.* 2016; 26(10): 3706-18.

15. Neglia D, Rovai D, Caselli C, Pietila M, Teresinska A, Aguade-Bruix S et al. Detection of significant coronary artery

disease by noninvasive anatomical and functional imaging. *Circ Cardiovasc Imaging.* 2015; 8(3): e002179.

16. Hoey E, Ellassaly M, Ganeshan A, Watkin RW, Simpson H. The role of magnetic resonance imaging in hypertrophic cardiomyopathy. *Quant Imaging Med Surg.* 2014; 4(5): 397–406.

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DOES PREOPERATIVE TIBIAL TUBEROSITY – TROCHLEAR GROOVE DISTANCE EFFECT ON POSTOPERATIVE PATELLAR INSTABILITY IN THE PATIENTS WITH KNEE ARTHROPLASTY DUE TO MEDIUM-ADVANCED KNEE OSTEOARTHRITIS?

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Abstract: Objectives: Determining tibial tubercle-trochlear groove distance range as measured before the operation in the patients to whom total knee prosthesis will be applied due to mid to advanced level of osteoarthritic and seeing the post-operative variations in tibial tubercle-trochlear groove distance and evaluating whether it has any impact on the patellofemoral instability that might develop after the operation. 46 knees planned to be applied total knee prosthesis due to mid-advanced level of osteoarthritic were examined.

Methods: In the preoperative and postoperative magnetic resonance images MRI routinely taken, tibial tubercle-trochlear groove distance was measured. Later it was examined whether there was correlation between these preoperative and postoperative tibial tubercle-trochlear groove measurements and the data recorded before operation.

Results: Preoperative tibial tubercle-trochlear groove distance was found to be 8.83 ± 3.54 , postoperative tibial tubercle-trochlear groove distance was found to be 8.30 ± 3.89 and preoperative-postoperative tibial tubercle-trochlear groove variation was found to be 0.52 ± 3.64 ($p = 0.337$). In the patients whose alignment was 10 degrees or less, Pre-Op tibial tubercle-trochlear groove distance was measured as 8.74 ± 3.18 and in the patients whose alignment was more than 10 degrees, it was measured as 8.89 ± 3.83 ($p = 0.888$). In the patients whose alignment was 10 degrees or less, Post-Op tibial tubercle-trochlear groove distance was measured as 8.00 ± 2.85 and in the patients whose alignment was

more than 10 degrees, it was measured as 8.52 ± 4.52 ($p = 0.661$). In the patients whose alignment was 10 degrees or less, tibial tubercle-trochlear groove distance variation was measured as 0.74 ± 3.25 and in the patients whose alignment was more than 10 degrees, it was measured as 0.37 ± 3.95 ($p = 0.741$).

Cocclusion: As a result, although tibial tubercle-trochlear groove distance was observed with a great variation in the osteoarthritic knees at stage 3-4, it was nonetheless measured within normal limits and Post-Op variation was not meaningful. Since this is the first study in the literature on the measurement of tibial tubercle-trochlear groove distance in the total knee prosthesis applications, we hope that it would shed some light on similar studies to be conducted in the future.

Key words: Knee biomechanics, Tibial tubercle, Trochlear groove, Total knee arthroplasty, Patellar instability.

INTRODUCTION

Osteoarthritic (OA) was defined by the American College of Rheumatology (ACR) as the heterogeneous group of disorders causing symptoms in the joint due to the degenerated structure of the joint cartilage and resulting in alterations in the bones nearby the joint (1). It is mostly seen in the knee joint (2). Knee joint arthrosis is a pathology commonly observed in 10% of the population older than 55 years. Advanced stage of osteoarthritic causes severe restrictions in the functions of the knee joint along with strong pain. A treatment option is total knee arthro-

plasty (TKA) and it is known as a final solution in eliminating the pain felt by the patient, helping him/her to regain his/her normal bodily functions. Number of total knee prosthesis (TKP) applied is increasing in parallel to prolonged lifetimes and increased rate of obesity. In the period 2010-2014, total 283.400 primary TKP was applied in Turkey and it was determined that these figures increased every year (3). Reason of approximately 12% of the revisions was found to be patellofemoral disorders.

Anterior knee pain felt after TKA is one of the most important problems observed in 20% of the patients (4, 5). Recent studies made on cadaver, along with biomechanical research showed that main reason of the anterior knee pain and patellar alignment problems was the misalignment of femoral and tibial component (6, 7). Factors causing patellofemoral instability are excessive femoral anteversion, genu valgum, genu recurvatum, joint hyperlaxity, patella alta, high Q angle, patellar dysplasia, trochlear dysplasia, high tibial tubercle-trochlear groove (TT-TG) distance (8, 9, 10). Acute or chronic patella subluxation, repeated patella dislocation and chronic patella dislocation are all known as patellofemoral joint instabilities (9).

However; there are some patients in whom exact reason of this instability cannot be explained (5, 6, 11). Patellofemoral motion is statically and dynamically affected by many factors. While static factors include rotation of femoral and tibial component, size of patellar implant, trochlear groove shape of the femoral implant and soft tissue balance, dynamic factors depend on the effect of the quadriceps muscle during the motion of the knee joint and on its size and TT-TG distance is one the static indicators affecting the patellofemoral motion (12, 13).

In many studies assessing the TT-TG distance, it was said that values considered as normal might change (14, 15). When TT-TG distance is > 15 mm, it is considered abnormal and when it is > 20 mm, it is considered pathologic (16). TT-TG distance has been observed as pathologic in the patients suffering from patella dislocation and anterior knee pain (17). However; there is no final consensus on the TT-TG distance variation in the osteoarthritic knees. In addition to certain studies confirming that no difference was measured in TT-TG distances between the osteoarthritic knees and normal knees, there is research in which these measurements resulted in great variations, bringing a strong need for the preoperative measurement of TT-TG distance in order to achieve better results (13, 14).

This study aims to determine the TT-TG distance range measured in the patients preoperative and see the postoperative variation in TT-TG distance in order to evaluate whether this variation has any effect on the patellofemoral instability that might potentially developed in the patient and on the knee functions.

METHODS

46 TKA applications performed in our clinic with different surgeons in the period (November 2017-November 2018) were prospectively examined. Male and female patients aged 50-85 with mid-advanced level of knee osteoarthritic were included into the study group. Patients on whom TKA was performed after a diagnosis of rheumatoid arthritis, patients on whom revision TKA was performed, patients who had sequencing operation before around the knee, patients operated before due to patellofemoral instability and patients with valgus knee were not included into the study. 46 knees of total 39 patients were included into the study. The average age of the patients was 66.89 ± 7.49 and 41 patients were female, while 5 was male. 25 of these 46 knees (54,3%) was right knee and 21 (45,7%) was left knee. Bilateral TKA was performed on 7 patients.

In all patients included into the study, the knee was opened with median parapatellar arthrotomy and patellar surface was not replaced in any of the patients. All of the implants used in the operations had posterior stabilized design and prosthesis of different brands were used. While femoral rotation alignment was made on some patients using space balancing technique, surgery was performed on some other patients using measured resection technique. Operations were performed on the patients in a single center by different surgeons. Preoperative physical examination findings, sequence, joint range of motion (JRM), Knee Society Score (KSS) knee and function points, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score, length, weight, additional diseases and knee osteoarthritis level according to radiographic staging of Kellgren-Lawrence (18) were recorded.

After detailed anamnesis and physical examination of the patients in the preoperative phase, radiographic and laboratory examinations were performed. As radiographic examination, compared two-directional knee graphics and knee MRI images were taken by applying load on the foot. With the knee radiographies, sequence measurement and osteoarthritis staging was performed, while TT-TG distance was measured on the MRI images taken with a MR device branded GE Healthcare, model 1.5 Tesla Signa. Measurement of TT-TG distance was made on axial sections as described by Wittstein and friends (19). Measurements were performed by 2 experienced orthopaedics surgeons. In order to evaluate this distance, midpoint of the site where patellar tendon grips the tuberosity tibia was marked and later deepest point of the cartilaginous part of the trochlear groove was marked. By taking as a reference posterior femoral condylar line, a perpendicular line was drawn between the both two marked points and the ref-

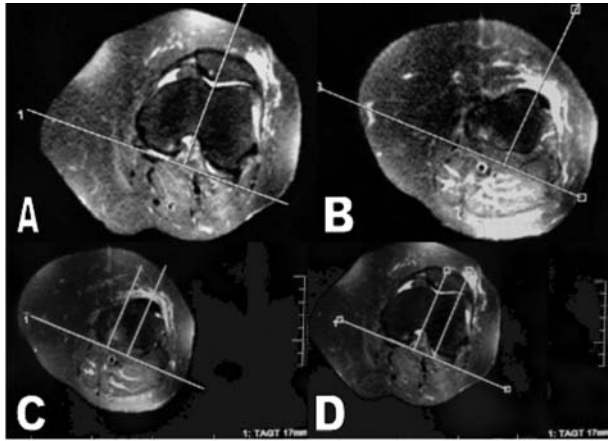


Figure 1. Pre-op MR Assessment: A. Perpendicular drawn from the deepest part of the trochlear groove by taking as a reference posterior condylar axis B. Perpendicular drawn from the midpoint of the part where patellar tendon grips TT to the posterior condylar axis C. Image of the distance between two perpendiculars (11 mm) in the TT section, D. Image of the distance between two perpendiculars (11 mm) in the trochlear groove section

erence line. Then the distance between these two perpendicular lines was measured in order to determine TO-TG distance (Figures 1 and 2). Postoperative knee MRI was repeated in all patients. In order to avoid prevention of measurement because of the metal artifact, a postoperative MRI imaging was performed in MAVRIC sequence by using GE Healthcare branded 1.5 Tesla Signa model MRI device and TT-TG distance was measured and recorded with the same technique used in preoperative phase. The patients were evaluated in the postoperative 6th month and their joint range of motion, WOMAC knee and function scores and KSS scores were recorded.

Later all data were analyzed by using SPSS 20.0 package program. Descriptive statistics were expressed

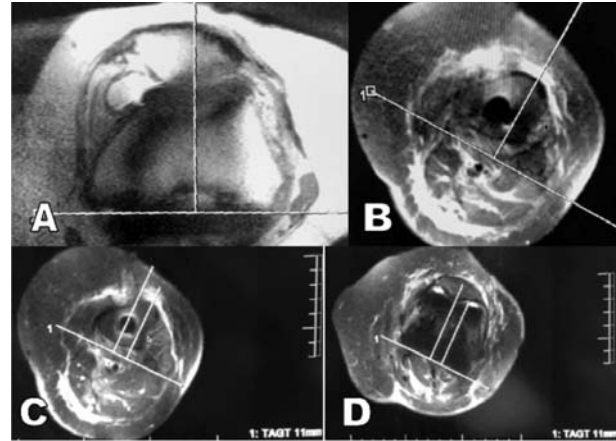


Figure 2. Post-op MR Assessment: A. Perpendicular drawn from the deepest part of the trochlear groove by taking as a reference posterior condylar axis B. Perpendicular drawn from the midpoint of the part where patellar tendon grips TT to the posterior condylar axis C. Image of the distance between two perpendiculars (17 mm) in the TT section D. Image of the distance between two perpendiculars (17 mm) in the trochlear groove section

as $\pm$ standard deviation (SD), median (minimum-maximum value), n and %. Compatibility of numerical variants to the normal distribution was examined using coefficients of skewness. Preoperative and postoperative TT-TG distances were compared in the dependent groups by using T-test. For the analyses involving two variables; T-test, Mann-Whitney U test, unilateral ANOVA (post hoc LSD), chi-square test and Pearson correlation analysis were used in the independent groups. P value $< 0,05$ was considered as statistically meaningful.

RESULTS

Main conclusion criterion in this research was TT-TG distance. TT-TG distance was measured preoperatively and postoperatively and difference in between

Table 1. Examined Variables

			%95 GA			%95 GA			
	Ave.	SD	Anterior	Posterior	Ave.	Anterior	Posterior	Min.	Max.
Length (cm)	158.87	5.81	157.14	160.60	160.00	160.00	165.00	150.00	170.00
Weight (kg)	81.76	13.58	77.73	85.79	80.00	80.00	90.00	60.00	115.00
BMI	32.44	5.61	30.77	34.10	31.25	31.23	33.30	25.71	48.89
Pre-op TT-TG (mm)	8.83	3.54	7.78	9.88	8.00	7.00	10.00	2.00	18.00
Post-op TT-TG (mm)	8.30	3.89	7.15	9.46	8.00	7.00	10.00	,00	18.00
Pre-op and post-op TT-TG difference (mm)	0.52	3.64	-0.56	1.60	0.00	0.00	2.00	-8.00	9.00
Pre-op flexion angle	100.67	15.90	95.89	105.44	95.00	90.00	100.00	80.00	135.00
Pre-op extension angle	-2.67	4.47	-4.01	-1.32	0.00	0.00	0.00	-15.00	,00
Pre-op KSS knee scoring	38-64	18.01	33.23	44.06	35.00	32.00	45.00	-2.00	84.00
Pre-op KSS keen function scoring	42.00	25.41	34.36	49.64	45.00	45.00	60.00	0.00	95.00
Pre-op WOMAC score	66.87	17.69	61.56	72.18	65.62	61.45	71.87	4.16	93.75
Alignment	12.09	4.88	10.64	13.53	11.00	10.00	13.00	2.00	30.00

(**BMI**: Body Mass Index **Pre-op**: Preoperative **TT-TG**: Tibial Tubercle-Trochlear Groove. **Post-op**: Postoperative **WOMAC**: Western Ontario and McMaster Universities Osteoarthritis. Index **KSS**: Knee Society Score Ave: Average)

en was compared. Data relating to 46 knees of 39 patients were analyzed. Bilateral TKA was performed on 7 patients. In this study, 34 patients were female and 5 patients were male and average age was calculated as 66.48 ± 7.49 . 25 knees included into the study were operated from the right side (54.3%) and 21 knees were operated from the left side (45.7%). Osteoarthritis stage of twelve patients (26.1%) was Kellgren-Lawrence (KL) stage 3, while it was stage 4 in 34 patients (73.9%). Descriptive statistics relating to the numerical variables examined are shown in Table 1. Other variables examined in this study included age (year), operated side (right-left), length (cm) and weight (kg) and body mass index (BMI). In addition, preoperative and postoperative flexion and extension angle, KSS knee scoring, KSS function scoring, WOMAC score, osteoarthritis stage and sequence were recorded (Table 2).

No meaningful difference was determined in terms of pre-op and post-op TT-TG difference between the TT-TG values of female and male patients and operative interventions from the right and left side of the knee ($p = 0.808$).

No meaningful difference was determined in terms of pre-op TT-TG distance, post-op TT-TG distance and pre-op and post-op TT-TG difference according to the specific osteoarthritis stage. TT-TG distance was reduced by 1.21 mm in average in the patients with stage 3 osteoarthritis as compared to the stage 4 patients but it was not found statistically meaningful ($p = 0.328$).

While varus alignment of 19 patients was 10 degrees and less, it was more than 10 degrees in 27 patients. According to the varus alignment grouping, the difference between Pre-op TT-TG ($p: 0.888$), Post-op TT-TG ($p: 0.661$) and Pre-op and Post-op TT-TG ($p: 0.741$) differences was not statistically meaningful.

When pre-op TT-TG distances are classified as < 10 mm, 11-15 mm and > 15 mm, a meaningful difference was determined between the groups in terms of Post-op TT-TG (meaningful on the limit), Pre-op and Post-op TT-TG difference ($p: 0.013$) and Pre-op flexion angle (0.009) (Table 2).

When Pre-op TT-TG distances are grouped, although there was no meaningful difference between the groups in terms of length, a meaningful difference was determined in terms of weight ($p: 0.016$) and BMI ($p: 0.004$).

Upon an examination of the correlations between the variables, a statistically meaningful correlation was seen in the Pre-op TT-TG distance with the Post-op TT-TG distance and Pre-op and Post-op TT-TG distance difference (Table 3).

The difference between the Pre-op and Post-op TT-TG distance measurements was 0.52 ± 3.64 mm and this difference was not found statistically meaningful ($t = 0.971$; $p = 0.337$). A linear regression model was created to examine the independent factors affecting the Pre-op and Post-op TT-TG difference. In the model into which BMI, Pre-op TT-TG, Pre-op flexion angle, Pre-op extension angle, Pre-op KSS knee scoring, Pre-op KSS knee function, Pre-op WOMAC and alignment was integrated, only Pre-op TT-TG values were determined to be independent indicator ($p = 0.024$).

Upon comparison of post-op flexion, post-op extension, post-op KSS knee score, post-op KSS knee function and post-op WOMAC scores according to pre-op TGS-TG distance categories by using unilateral ANOVA test, a meaningful difference was determined between the groups in terms of post-op extension angle ($p = 0.02$). When Pre-op TT-TG distance increases, post-op extension angle decreases.

Table 2. Comparison of various scores according to the pre-op TT-TG distance categories

Pre-op TT-TG								
	< 10 mm		11-15 mm		> 15 mm		H*	P
	Ave.	SD	Ave.	SD	Ave.	SD		
Post-op TT-TG (mm)	7.20	3.59	10.43	3.92	10.00	1.41	5.961	0.051
Pre-op and Post-op TT-TG diff. (mm)	-0.50	3.15	1.71	3.47	7.50	2.12	8.625	0.013
Pre-op flexion angle	98.10	13.98	108.93	16.78	80.00	0.00	9.492	0.009
Pre-op extension angle	-1.72	3.60	-4.29	5.50	-5.00	7.07	3.196	0.202
Pre-op KSS knee scoring	40.00	16.36	37.43	22.22	27.50	6.36	1.983	0.371
Pre-op KSS knee function	45.17	23.39	37.86	29.33	25.00	28.28	2.012	0.366
Pre-op WOMAC score	65.58	15.05	69.49	23.67	67.18	0.74	1.708	0.426
Alignment	11.90	4.40	12.50	6.21	12.00	1.41	0.184	0.912

(Pre-op: Preoperative, TT-TG: Tibial Tubercle-Trochlear Groove, Post-op: Postoperative, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, KSS: Knee Society Score.)

Table 3. Correlation analysis between studied variables

		1	2	3	4	5	6	7	8	9
0-BMI	R	0.348	0.250	0.071	0.274	-0.105	-0.101	-0.203	0.191	0.020
	P	0.018	0.094	0.640	0.068	0.494	0.508	0.181	0.208	0.897
1-Pre-op TT-TG (mm)	R		0.521	0.414	0.000	-0.222	-0.163	-0.208	0.090	0.033
	P		< 0.001	0.004	0.998	0.142	0.284	0.171	0.558	0.827
2-Post-op TT-TG (mm)	R			-0.561	0.043	0.108	0.095	0.176	-0.337	0.139
	P			< 0.001	0.780	0.481	0.536	0.248	0.023	0.356
3-Pre-op and AS TT-TG difference (cm)	R				-0.047	-0.344	-0.270	-0.404	0.461	-0.116
	P				0.758	0.021	0.073	0.006	0.001	0.441
4-Pre-op flexion angle	R					-0.182	0.325	-0.041	0.065	-0.021
	P					0.231	0.029	0.788	0.671	0.893
5-Pre-op extension angle	R						0.128	0.203	-0.228	0.023
	P						0.403	0.181	0.132	0.878
6-Pre-op KSS knee scoring	R							0.546	-0.515	-0.518
	P							< 0,001	< 0,001	<0,001
7-Pre-op KSS knee scoring	R								-0.785	0.072
	P								< 0,001	0.636
8-Pre-op WOMAC	R									-0.148
	P									0.333
9-Sequence	R									
	P									

1-Pre-op TT-TG (mm); 2-Post-op TT-TG (mm); 3-Pre-op ve Post-op TT- TG difference (mm); 4-Pre-op flexionangle; 5-Post-op extension angle; 6-Pre-op KSS knee scoring; 7-Pre-op KSS knee function, 8-Pre-op WOMAC; 9-Sequence (BMI: Body Mass Index, **Pre-op:** Before surgery, **TT-TG:** tibial tubercle-trochlear groove, **Post-op:** After surgery, **WOMAC:** Western Ontario and McMaster Universities Osteoarthritis Index, **KSS:** Knee Society Score.)

Upon an examination of the correlation between post-op TT-TG distance categories and post-op extension angle, knee scoring and WOMAC scores, it was determined that post-op WOMAC scores was different between the groups ($p = 0.005$). When Post-op TT-TG distance increases, post-op WOMAC score decreases.

Upon an examination of the correlation between pre-op post-op TT-TG distance difference and post-op extension angle, KSS knee scoring and WOMAC scores, a meaningful correlation was determined in terms of post-op extension angle, post-op KSS knee function and post-op WOMAC scores. While a negative correlation was observed between the Pre-op Post-op TT-TG distance difference and post-op extension angle and post-op KSS knee function, a positive correlation with the post-op WOMAC scores was noticed.

DISCUSSION

Generally in most of the societies, rate of knee and hip osteoarthritis in population older than 65 is approximately 40% and knee osteoarthritis is more common than hip osteoarthritis. In patients with advanced stage of knee osteoarthritis, TKA is a frequently used surgery operation with high success rate and it reduces the pain

and develops the knee function (20). Patellar instability that might develop after TKA is a serious complication disrupting functional results and causing revision surgery (21, 22). Especially anterior knee pain felt during the activities in which excessive load is imposed on the knee joint is an indication of patellar instability (21) Etiology includes surgery techniques applied, position of the components, extensor mechanism imbalance and other reasons and malalignment of the components is the most important reason of patellar instability (21, 22). TT-TG distance is a measurement method preferred to assist the diagnosis and treatment of patellofemoral instability (13). In this study, it was determined that pre-op and post-op variation in the TT-TG distance was not meaningful in the patients with mid- and advanced level of knee osteoarthritis with whom TKA was performed.

In a study performed on 11 cadaver knees, Worden et al (23) 11 compared measurements of TT-TG distance and evaluated their reliability by means of direct graph, computerized tomography (CT) and anatomical dissection. They also evaluated whether the knee flexion and tibia rotation affected the measurement. As a result, it was observed that there was no difference in

the measurement of TT-TG distance by means of CT and by means of anatomical dissection. It was concluded that knee flexion did not affect the measurement of TT-TG distance but tibia internal rotation reduced the measurement while external rotation increased the measurement. In our study, MRI was performed on the patients in neutral tibial rotation and extension position. In a study examining 11 patients, Schoettle et al (24) evaluated reliability of MRI in the measurement of TT-TG distance as compared to the CT. 12 knees of 11 patients were included into the study and in the measurements where bone signs were taken as reference, average TT-TG distance was found to be 14.4 ± 5.4 with CT and 13.9 ± 4.5 with MRI. When cartilaginous structures were taken as reference, results were 15.3 ± 4.1 with CT and 13.5 ± 4.6 with MRI imaging. As a result, it was concluded that in determining the TT-TG distance, measurements made with MRI imaging using bone or cartilaginous structures were reliable and additional CT scanning was not necessary. In our study, TT-TG distance was measured by taking cartilaginous structures as reference in the MRI images with no additional CT scanning performed and Pre-op TT-TG distance was found to be 8.83 ± 3.54 in average whereas Post-op TT-TG distance was found to be 8.30 ± 3.89 in average. In a study involving 100 patients, Pandit et al (15) evaluated normal TT-TG distance values on the MRI images and found 10 ± 1 mm, concluding that MRI imaging was a reliable measurement method.

In a study involving 120 patients, Dornacher et al (25) evaluated the correlation between TT-TG distance and patient's length and knee size. While MR imaging scan was performed on 60 patients due to trochlear displacement, MR imaging scan was performed on the other 60 patients because of a different pathology. TT-TG distance was measured and trochlear displacement was classified as high and low and trans-epicondyle distance was taken into account as the indication of the knee size. It was declared that there was no correlation between the TT-TG distance and knee size or body height but in a study comparing 45 patients aged between 20-14 having patellar instability with 180 patients having no instability complaints and used as control group, Pennock et al. (23) determined that with each 1 cm of increase in the body length, there was a 0.12 mm increase in the TT-TG distance. In our study, we assessed Pre-op TT-TG distances by dividing them into groups of body length, weight and BMI. While body length variable was not found effective on the TT-TG distance, it was seen that an increase in the body weight and BMI caused an increase in the TT-TG distance. However; as the distribution of TT-TG distances was imbalanced, this increase was thought to be related to the high chance factor. In a study performed

by Pandit et al. (15), comparing 100 patients including 53 male and 47 female patients which arthroscopically proved that there was no osteoarthritic change with normal alignment, no correlation was found to exist between the TT-TG distance and sex. And also in our study, when we evaluated the patients by dividing them according to their sex, we observed that there was no correlation between the TT-TG distance and female-male sex.

In a study performed on 962 patients, Hochreiter et al. (13) retrospectively analyzed the TT-TG distance variation in patients with whom pre-op planning was made using approved commercial 3d planning software and on whom TKP was performed. As a consequence, they found a wide range of TT-TG variation in osteoarthritic knees. They also found TT-TG distance to be more pathologic in valgus knees, concluding that with each 2 degrees of increase in the valgus degree, 1 mm increase occurred in the TT-TG distance, while TT-TG distance was not found to be pathological in varus knees even if deformity was more than 10 degrees. Sothey concluded that evaluating TT-TG distance in pre-op planning was important in the application of any individual TKP. And similarly in our study, pre-op measured TT-TG distance showed a wide range of variation and it was seen that TT-TG distance was not affected when the alignment was less or more than 10 degrees. Besides that, in patients with varus alignment, pre-op and post-op TT-TG values were found to be within normal limits. In a study involving 175 cases and comparing pre-op TT-TG distances in patients with stage 3-4 osteoarthritis and patients with no osteoarthritis, Sahin et al. (14) determined that TT-TG distances measured in both groups was less than 20 mm and were also similar. Similarly in our study, in patients with stage 3 and stage 4 osteoarthritis, pre-op and post-op TT-TG distances were found to be less than 20 mm. Our study further showed that pre-op KSS and WOMAC scores were bad in the patients with stage 3-4 osteoarthritis and with a malalignment of more than 10 degrees as compared to the other group of patients. And in the patients with bad post-op KSS and WOMAC scores, there was a correlation with pre-op and post-op TT-TG distance range. In a study involving 85 patients on whom TKP was performed, Otsuki et al. (26) evaluated the correlation between varus malalignment and patellofemoral osteoarthritis. They also checked the pre-op TT-TG distance measurement of the patients and tilt of the patella. They concluded that in patients with varus malalignment, lateral patellofemoral osteoarthritis was specifically developed and there was a strong correlation between the TT-TG distance and patellar tilt. They also declared that patellar tilt and TT-TG distance were critical factors in patellofemoral osteoarthritis. In our

study, pre-op and post-op TT-TG distance was found to be within normal limits in the patients with varus malalignment. Although pre-op and post-op TT-TG distance difference was not found to be statistically meaningful, we saw that TT-TG distance variation got better 2 times more in the patients whose varus alignment was 10 degrees or less as compared to the patients whose varus alignment was more than 10 degrees. It was noticeable that TT-TG distance variation increased with the reduction in varus alignment. In our study, we think that meaningful highness determined in the post-op TT-TG distance variation in the patients having high pre-op TT-TG distance could be related to the rotational changes in the tibial and femoral components in the knee prosthesis application and these changes caused variations in the TT-TG distance.

When pre-op TT-TG distance increases, post-op extension angle decreases. And when post-op TT-TG distance increases, post-op WOMAC score decreases. When pre-op and post-op TT-TG distance difference increases, post-op extension angle and post-op KSS knee function score decrease and post-op WOMAC score increases.

CONCLUSION

This study brings certain advantages and disadvantages. Since data was recorded prudentially in our study, there was no data loss. Although there are many studies in the literature about TT-TG distance, there is no study involving post-op TT-TG distance measurement in the patients on whom TKA was performed, and this factor increases the value of our study. Measurement of TT-TG distance on MRI images will surely have advantages since it will standardize the measurements and avoid additional radiation exposure with the patients. And there are also certain disadvantages as

this technique is quite expensive and difficult to find. Besides that, all patients participating into the study were not operated by the same surgeon using a single type of prosthesis and number of female patients was more than the number of male patients because osteoarthritis is seen more commonly in women. However surplus in the number of female patients did not affect the results of this study because it did not cause any difference between the groups. Lack of patients with neutral or valgus alignment was another factor restricting the evaluation. As a result, although TT-TG distance showed a wide range of variation in stage 3-4 osteoarthritic knees, it was measured within the normal limits and decrease in the post-op TT-TG distance average was not statistically found to be meaningful. Since this is the first study in the literature about TT-TG distance measurement in TKP applications, we hope that it would shed some light to the future studies.

Abbreviations

OA — osteoarthritic

TKA — total knee arthroplasty

TT-TG — tibial tubercle-trochlear groove

JRM — joint range of motion

KSS — Knee Society Score

WOMAC — Western Ontario and McMaster Universities Osteoarthritis Index

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Sažetak

DA LI PREOPERATIVNA TUBEROSITAS TIBIAE - TROHLEARNI ŽLEB DISTANCA UTIČE NA POSTOPERATIVNU PATELARNU NESTABILNOST KOD PACIJENATA SA ARTROPLASTIKOM KOLENA ZBOG SREDNJE UZNAPREDOVALOG OSTEOARTRITISA KOLENA?

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Uvod: Zbog određivanja tibijalni tuberkulum-trohlearni žleb distance preoperativno, kod pacijenata kojima će biti urađena totalna proteza kolena zbog srednjeg

do uznapredovanog oblika osteoartritisa i uvida u postoperativne varijacije tibijalni tuberkulum-trohlearni žleb distance i procene da li je bilo uticaja na patelofemoral-

nu nestabilnost koja bi se mogla razviti nakon operacije, 46 kolena planirana za totalnu protezu zbog srednje do uznapredovalog artritisa, su pregledana.

Metode: U preoperativnim i postoperativnim snimcima magnetske rezonance koja je rutinski rađena, izmerena je tibijalni tuberkulum-trohlearni žleb distanca. Kasnije je ispitano postoji li povezanost između tih preoperativnih i postoperativnih merenja i podataka zabeleženih pre operacije.

Rezultati: Nađeno je da je preoperativna tibijalni tuberkulum-trohlearni žleb distanca bila $8,83 \pm 3,54$, dok je postoperativno iznosila $8,30 \pm 3,89$, uz preoperativno-postoperativnu tibijalni tuberkulum-trohlearni žleb distanca varijaciju od $0,52 \pm 3,64$ ($p = 0,337$). Kod pacijenata kod kojih je poravnanje bilo 10 stepeni ili manje, izmerena je preoperativna tibijalni tuberkulum-trohlearni žleb distanca $8,74 \pm 3,18$, a kod pacijenata čije je poravnanje bilo veće od 10 stepeni, iznosila je $8,89 \pm 3,83$ ($p = 0,888$). Kod pacijenata čiji je poravnanje bio 10

stepeni ili manje, postoperativno je tibijalni tuberkulum-trohlearni žleb distanca iznosila $8,00 \pm 2,85$, a kod pacijenata čije je poravnanje bio veće od 10 stepeni, iznosila je $8,52 \pm 4,52$ ($p = 0,661$). Kod pacijenata čiji je poravnanje bilo 10 stepeni ili manje, varijacija je izražena kao $0,74 \pm 3,25$, a kod onih sa poravnanjem većim od 10 stepeni, iznosila je $0,37 \pm 3,95$ ($p = 0,741$).

Zaključak: Iako je zapažena tibijalni tuberkulum-trohlearni žleb distanca s velikom varijacijom kod osteoartritičnih kolena 3-4 stadijuma, ona je ipak bila u granicama normale i postoperativna varijacija je bila bez značaja. Budući da je ovo prva studija u literaturi o merenju tibijalni tuberkulum-trohlearni žleb distance kod totalne proteze kolena, nadamo se da će imati uticaja na slična istraživanja koja će se provoditi u budućnosti.

Cljučne reči: biomehanika kolena, tibijalni tuberkulum, trohlearni žleb, totalna proteza kolena, patelar-na nestabilnost.

REFERENCES

- Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum.* 1986; 29(8): 1039-49.
- Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part I: Critical appraisal of existing treatment guidelines and systematic review of current research evidence. *Osteoarthritis Cartilage.* 2007; 15(9): 981-1000.
- Ceyhan E, Gursoy S, Akkaya M, Ugurlu M, Koksali I, Bozkurt M. Toward the Turkish National Registry System: a prevalence study of total knee arthroplasty in Turkey. *J Arthroplasty.* 2016; 31(9): 1878-84.
- Rand JA. Extensor mechanism complications after total knee arthroplasty. *Instr Course Lect.* 2005; 54: 241-50.
- Tanikawa H, Tada M, Harato K, Okuma K, Nagura T. Influence of total knee arthroplasty on patellar kinematics and patellofemoral pressure. *J Arthroplasty.* 2017; 32: 280-5.
- Barrack RL, Schrader T, Bertot AJ, Wolfe MW, Myers L. Component rotation and anterior knee pain after total knee arthroplasty. *Clin Orthop Relat Res.* 2001; 392: 46-55.
- Nicoll D, Rowley DI. Internal rotational error of the tibial component is a major cause of pain after total knee replacement. *J Bone Joint Surg Br.* 2010; 92(9): 1238-44.
- Camp CL, Heidenreich MJ, Dahm DL, Bond JR, Collins MS, Krych AJ. A simple method of measuring tibial tubercle to trochlear groove distance on MRI: description of a novel and reliable technique. *Knee Surg Sports Traumatol Arthrosc.* 2016; 24(3): 879-84.
- Diederichs G, Issever AS, Scheffler S. MR Imaging of patellar instability: injury patterns and assessment of risk factors. *Radio Graphics.* 2010; 30(4): 961-81.
- Chhabra A, Subhawong TK, Carrino JA. A systematized MRI approach to evaluating the patellofemoral joint. *Skeletal Radiol.* 2011; 40(4): 375-87.
- Cho WS, Woo JH, Park HY, Youm YS, Kim BK. Should the 'no thumb technique' be the golden standard for evaluating patellar tracking in total knee arthroplasty? *The Knee.* 2011; 18(3): 177-9.
- Strachan RK, Merican AM, Devadasan B, Maheshwari R, Amis AA. A technique of staged lateral release to correct patellar tracking in total knee arthroplasty. *J Arthroplasty.* 2009; 24(5): 735-42.
- Hochreiter B, Hirschmann MT, Amsler F, Behrend H. Highly variable tibial tubercle-trochlear groove distance (TT-TG) in osteoarthritic knees should be considered when performing TKA. *Knee Surg Sports Traumatol Arthrosc.* 2019; 27(5): 1403-9.
- Sahin N, Atici T, Ozkaya G. Tibial Tuberosity-Trochlear Groove distance shows no change in patients with or without knee osteoarthritis. *Eurasian J Med.* 2018; 50(1): 38-41.
- Pandit S, Frampton C, Stoddart J, Lynskey T. Magnetic resonance imaging assessment of tibial tuberosity-trochlear groove distance: normal values for males and females. *Int Orthop.* 2011; 35(12): 1799-803.
- Anley CM, Morris GV, Saithna A, James SL, Snow M. Defining the role of the Tibial Tubercle-Trochlear Groove and Tibial Tubercle-Posterior cruciate ligament distances in the work-up of patients with patellofemoral disorders. *Am J Sports Med.* 2015; 43(6): 1348-53.
- Carlson VR, Boden BP, Shen A, Jackson JN, Yao L, Sheehan FT. The Tibial Tubercle-Trochlear Groove distance is greater in patients with patellofemoral pain: implications for the origin of pain and clinical interventions. *Am J Sports Med.* 2017; 45(5): 1110-6.
- Canale ST. *Campbell's Operative Orthopaedics.* 10th ed. Elsevier, 2003.
- Kinds MB, Welsing PMJ, Vignon EP, Bijlsma JWW, Viergever MA, Marijnissen ACA et al. A systematic review of the

association between radiographic and clinical osteoarthritis of hip and knee. *Osteoarthritis Cartilage*. 2011; 19(7): 768–78.

20. Mosis EK, Paschos N, Pakos EE, Georgoulis AD. Review article: patellar instability after total knee arthroplasty. *J Orthop Surg*. 2009; 17(3): 351–7.

21. Worden A, Kaar S, Owen J, Cutuk A. Radiographic and anatomic evaluation of tibial tubercle to trochlear groove distance. *J Knee Surg*. 2016; 29(7): 589–93.

22. Petersen W, Rembitzki IV, Bruggemann GP, Ellermann A, Best R, Koppenburg AG et al. Anterior knee pain after total knee arthroplasty: a narrative review. *Int Orthop*. 2014; 38(2): 319–28.

23. Pennock AT, Alam M, Bastrom T. Variation in tibial tubercle–trochlear groove measurement as a function of age, sex,

size, and patellar instability. *Am J Sports Med*. 2014; 42(2): 389–93.

24. Schoettle PB, Zanetti M, Seifert B, Pfirrmann CWA, Fucentese SF, Romero J. The tibial tuberosity–trochlear groove distance; a comparative study between CT and MRI scanning. *Knee*. 2006; 13(1): 26–31.

25. Dornacher D, Reichel H, Kappe T. Does tibial tuberosity–trochlear groove distance (TT–TG) correlate with knee size or body height? *Knee Surg Sports Traumatol Arthrosc*. 2016; 24(9): 2861–7.

26. Otsuki S, Nakajima M, Okamoto Y, Oda S, Hoshiyama Y, Iida G et al. Correlation between varus knee malalignment and patellofemoral osteoarthritis. *Knee Surg Sports Traumatol Arthrosc*. 2016; 24(1): 176–81.

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EVALUATION OF RIGHT VENTRICLE SYSTOLIC AND DIASTOLIC FUNCTION IN PATIENTS WITH PAROXYSMAL ATRIAL FIBRILLATION

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Abstract: Objective: Atrial fibrillation (AF) is frequently an electrical sign of underlying structural heart disease. Structural remodelling may begin not only in ventricles but also in atrium secondary to AF. In this study, we sought to investigate the effect of paroxysmal atrial fibrillation (PAF) on right ventricle function.

Method: We prospectively analyzed 30 patients diagnosed with PAF and 25 control individuals. Cardiac risk factors and medical treatment of patients were obtained and recorded in both groups. Right ventricle tricuspid annular plane systolic excursion (TAPSE) and Tei indexes were measured as an indicator of right ventricular function.

Results: There was no statistical difference between groups in terms of demographic and clinical characteristics. Tei index was higher and TAPSE was lower in PAF group compared to control individuals ($p > 0.05$). There was no statistically significant difference between PAF and control groups in terms of right ventricular diastolic functions neither. Although isovolumic relaxation time (IVRT) was higher in PAF group, it did not give statistical significance.

Conclusion: In this study, even not being statistically significant Tei index, which assess right ventricular function was over upper limit in PAF patients. This may have been as the result of prolonged IVRT. This result may indicate that right ventricular diastolic functions may be effected in patients with PAF.

Key words: Atrial Fibrillation, Right Ventricle, 2D Echocardiography.

INTRODUCTION

Atrial fibrillation (AF), is the most prevalent type of sustained arrhythmic disease in clinical practice and one of the main cause of hospitalization associated with morbidity and mortality. Epidemiological studies have shown that the most common cause of AF is ischemic heart disease (1, 2). Framingham Heart Study has revealed that; left ventricular (LV) wall thickness increasing, LV systolic functions decreasing and increased left atrial (LA) dimensions are independent risk factors for the development of AF (3). Proliferation of myoblasts to fibroblasts in atrium resulting with fibrosis are the major histopathological changes in atrial tissue of patients with AF. This structural remodeling causes electrical decomposition within local conduction, resulting in retention of small re-entry rings. Due to these changes, especially in persistent AF, the absence of atrial contractions leads to increased atrial volume and pressure. Hemodynamic effects such as increased heart rate in atrial fibrillation, absence of atrial contraction and impaired simultaneous contraction of the atria and ventricles may result into ventricular dysfunction that eventually causes symptoms of heart failure (4, 5). Paroxysmal atrial fibrillation (PAF), which is described as usually self-terminating AF within 48 hours has intermittent clinical manifestation. Spontaneous conversion rate is low after 48 h time point that is deadline for electrical or medical cardioversion to prevent embolic complications. After that, rate control strategy and anticoagulant treatment must be considered (6). Right heart is difficult to evaluate by echocardiography

because of its complexity of anatomical structure. Quantitative evaluation of right ventricular dimensions and functions has been proven to have significant clinical value in both cardiac and pulmonary diseases. Right ventricular functions may be impaired by volume overload, pressure overload and myocardial dysfunction. Diastolic functions tend to deteriorate earlier than systolic functions unless severe volume overload occurs. As the right ventricular volume increases, the cardiac myofibrils become stretched leading into decrease in right ventricular functions. The right ventricular chambers begin to enlarge resulting into abnormal septal movements. Right atrial (RA) pressure increases and peripheral right heart failure signs appear due to volume overload.

There are several studies evaluating the functions of LA in AF patients (3, 7, 8). In patients with valvular disease and LA diameter > 40 mm, the incidence of AF increases. The rate of increase in LA diameter was significantly correlated with the transition from normal sinus rhythm to PAF and PAF to chronic AF (9). However, there are few studies assessing the on RA and RV global functions in patients with AF (10, 11). Houltz et al. found that RA size might be an important parameter in maintaining normal heart rhythm after intraoperative ablation for AF (10). In this study, we aimed to evaluate right ventricular functions by echocardiography in patients with PAF.

PATIENTS AND METHODS

Patient selection

Forty-one consecutive patients with PAF who were admitted to Cardiology outpatient clinic were included to the study at Inonu University Faculty of Medicine Turgut Ozal Medical Center between July 2011 to December 2011 and referred to Echocardiography Laboratory for transthoracic echocardiography. Patients who were included in the study were examined for baseline demographic and clinical parameters such as coronary artery disease, cardiovascular risk factors, other diseases, medications, body weight, height and recorded on a study chart. PAF was described as according to the guideline of HRS/EHRA/ECAS. AF was defined as an arrhythmia to be recorded by a 12-lead ECG that has irregularly irregular episode, and lasts sufficiently long or at least 30 seconds on a rhythm strip. PAF was defined as two or more episodes of symptomatic AF recurrence within the preceding 6 months that was not longer than 7 days (6). The patients were selected by; a) results of 24-hour rhythm holter (at least two episodes of PAF) b) two or more PAF episodes detected by emergency department c) during the routine follow up of patients with PAF in outpatient clinic. The exclusion

criteria were previous ablation for AF, a left diameter of more than 45 mm, left ventricular ejection fraction of less than 50%, moderate-to-severe mitral valve disease, an age of more than 65 years and secondary atrial fibrillation (hyperthyroidism, infection, postoperative AF). Control group consisted of 25 patients who were admitted to cardiology outpatient clinic with other cardiac symptoms without AF or other rhythm disorders. These individuals had similar baseline characteristics with PAF group such as age, sex and medical history. This trial was approved by the local ethic committee. Written informative acceptance was obtained from all patients regarding their participation in our study. Eleven patients were excluded due to having pulmonary embolism, hyperthyroidism, postoperative AF, moderate to severe valvular disease in the study.

Transthoracic Echocardiography

Transthoracic echocardiography was performed in all patients. Conventional echocardiographic parameters of left and right ventricles were measured according to the recommendations of the American Society of Echocardiography (12). Briefly, RV dimensions were calculated from right ventricle apical 4-chamber view at end-diastole. And after this measurement, diameter > 42 mm at the base and > 35 mm at the mid level was defined as RV dilatation. Also, RA dimensions were calculated from the apical 4-chamber at the same frame. RA length (the main dimension) > 53 mm, RA diameter > 44 mm and RA area > 18 cm², at end diastole was defined as RA enlargement. Systolic functions of the right ventricle were evaluated by right ventricular ejection fraction (EF), tricuspid annular plane systolic excursion (TAPSE), isovolemic acceleration and myocardial performance index (MPI). The MPI (Tei index) measured by isovolumic contraction time (IVCT), isovolemic relaxation time (IVRT), and ejection time (ET), was calculated with $IVRT + IVCT / ET$ formulation. Tei index > 0.55 measured by tissue doppler imaging indicates RV dysfunction (11). TAPSE is defined as to calculate the distance of systolic excursion of the RV annular segment along its longitudinal plane, from a standard four chamber window. It is measured from the tricuspid lateral annulus. TAPSE < 16 mm assumes RV systolic dysfunction. Myocardial acceleration during isovolumic contraction (IVA) is defined as the peak isovolumic myocardial velocity divided by time to peak velocity. Diastolic functions of the right ventricle were evaluated by Doppler velocities of the transtricuspid flow such as (E, A, and E/A), and tissue Doppler velocities of the tricuspid annulus (E/A), and IVRT from the apical 4-chamber view.

The diameters of left ventricle were measured from long-axis of parasternal view at the end of

diastole and systole. Left atrium diameter was measured from parasternal long-axis view. Systolic and diastolic functions of the left ventricle were evaluated by EF, MPI, IVA, tissue doppler of mitral valve parameters (E, A, St) and deceleration time which are measured from the 4-chamber apical view.

Statistical Analysis

All statistical analyses were performed using SPSS version 15.0 (SPSS, Inc., Chicago, Illinois) for windows software. Continuous variables were expressed as mean value $\pm$ standard deviation for parametric variables. Categorical variables were defined as counts and percentages and compared the groups using Fisher's exact chi-square test and Pearson's chi square test. The

Kolmogorov-Smirnov test was used for the assessment of normality and differences between the means were compared by unpaired t-test. P value < 0.05 was considered as statistically significant in every test.

RESULTS

Our study included 55 patients (30 patients diagnosed with PAF and 25 patients were taken as a control group). The mean age was 52.0 ± 6.2 years in the patient group and 48.1 ± 6.5 years in control group. All baseline skills such as clinical, demographic characteristics, and pathologies of the study population are presented in Table 1. And there were no statistically difference in respect to age, smoking, gender, diabetes mellitus, hypertension, coronary artery disease, and hyperli-

Table 1. Baseline characteristics of patients and control groups

Characteristics	Patient (n = 30)		Control (n = 25)	P value
Age	52.0 ± 6.2		48.1 ± 6.5	NS
Gender	Women	12 (%40)	10 (%40)	NS
	Men	18 (%60)	15 (%60)	
Diabetes Mellitus	7 (%23.3)		4 (%16)	NS
Hypertension	10 (%33.3)		7 (%28)	NS
Obesity	6 (%20)		1 (%4)	NS
Smoking	13 (%43.3)		9 (%36)	NS
BMI, kg/m ²	27.0 ± 3.7		26.4 ± 2.5	NS
Hyperlipidemia	9 (%30)		8 (%32)	NS
SVE	1 (%3.3)		0 (0)	NS
Valvulardisease	11 (%36.7)		10 (%40)	NS

BMI: Body mass index, CVE: cerebrovascular event.

Table 2. Left ventricle echocardiographic results (mean)

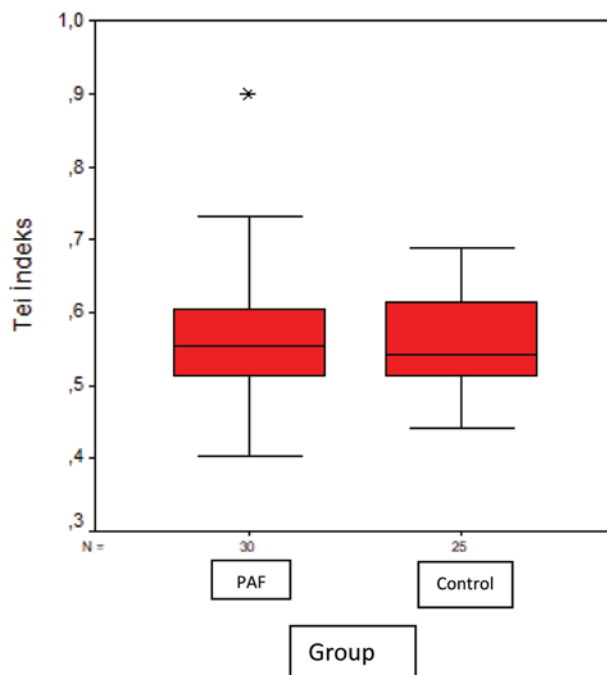
	Patients (n = 30)	Control (n = 25)	P value
LA (cm)	3.6 ± 0.5	3.5 ± 0.4	NS
LVEDd (cm)	4.6 ± 0.4	4.6 ± 0.3	NS
LVESd (cm)	3.0 ± 0.3	3.2 ± 0.4	0.048
EF (%)	60.1 ± 4.3	60.6 ± 3.0	NS
IVS (cm)	1.1 ± 0.1	1.0 ± 0.1	NS
PW (cm)	1.0 ± 0.1	1.0 ± 0.1	NS
E	73.3 ± 19.0	67.4 ± 15.1	NS
A	79.3 ± 21.8	68.4 ± 11.5	0.042
Dt	210.8 ± 64.3	194.2 ± 47.0	NS
St	10.5 ± 2.3	12.0 ± 2.5	0.022
Et/At	1.0 ± 0.5	1.1 ± 0.5	NS
E/E'	7.2 ± 3.6	5.9 ± 2.2	NS
MPI	0.5 ± 0.1	0.5 ± 0.1	NS
IVA	2.3 ± 0.5	2.4 ± 0.7	NS

LA: left atrium, LVEDd: left ventricular end diastole diameter, LVESd: left ventricular endsystolic diameter, IVS: interventricular septum, PW: posterior wall, EF: ejection fraction, E: early rapid filling, A: late filling after atrial contraction, Dt: deceleration time, MPI: myocardial performance index, IVA: Isovolumic acceleration, Dp/dt: rate of pressurerise in the ventricles.

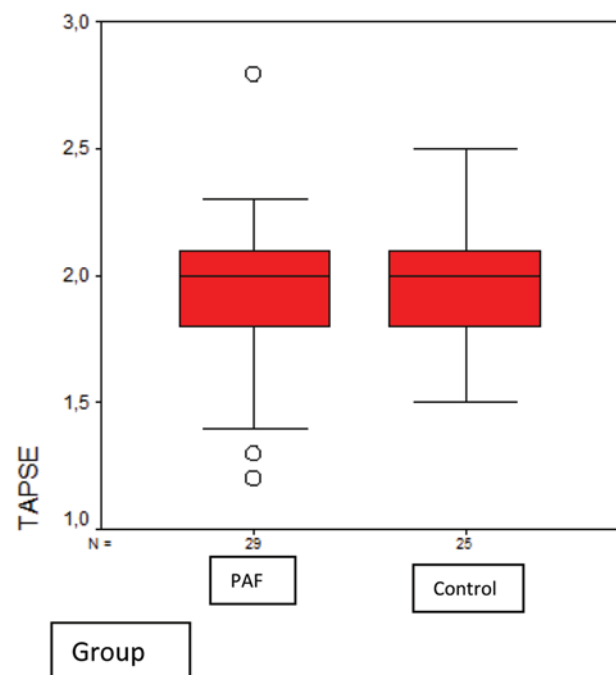
Table 3. Right ventricle echocardiografic results (mean)

	Patients (n = 30)	Control (n = 25)	Pvalue
RA (cm)	4.0 ± 0.5	3.9 ± 0.4	NS
RA area (cm ²)	16.6 ± 4.3	15.6 ± 2.7	NS
RV (cm)	3.9 ± 0.5	4.0 ± 0.3	NS
FAD	43.1 ± 10.4	44.0 ± 9.3	NS
E	50.1 ± 10.0	51.7 ± 12.2	NS
A	51.4 ± 13.8	52.2 ± 13.2	NS
Dt	233.0 ± 63.0	240.0 ± 62.0	NS
St	12.6 ± 3.1	14.1 ± 3.0	NS
Et/At	0.8 ± 0.4	0.9 ± 0.4	NS
E/E'	5.0 ± 1.5	4.6 ± 1.5	NS
MPI	0.6 ± 0.1	0.5 ± 0.1	NS
IVA	2.6 ± 1.1	2.6 ± 1.0	NS
TAPSE	1.9 ± 0.4	2.0 ± 0.2	NS
sPAP	31.50	29.46	NS
IVRT	85.0 ± 14.5	76.5 ± 12.0	NS

RA: Right atrium, RV: Right ventricle, MPI:myocardial performance index, TAPSE: Tricuspid annular plane systolic excursion, IVA: Isovolumic acceleration, IVRT: isovolumic relaxation time, sPAP: sistolic pulmonary artery pressure.

**Figure 1.** Comparising of right ventricle Tei index in patients with PAF and controls

pidemia between the groups. In addition, there was no difference in terms of mild regurgitation of mitral, aortic and tricuspid valves when the groups compared. All parameters of LV and RV such as systolic and diastolic functions are summarized in Table 2 and Table 3, respectively. There was no statistically significant difference in terms of RV systolic and diastolic functions between the groups. In the PAF group, the Tei index was higher than the upper limit of the reference values. This was as a result of prolongation of IVRT (Figure 1).

**Figure 2.** Comparising of right ventricle TAPSE in patients with PAF and controls

TAPSE was 1.9 ± 0.4 in the PAF group and 2.0 ± 0.2 in the control group ($p = 0.55$) (Figure 2). Also, RA dimension was higher in PAF group.

DISCUSSION

In this study, we could not found any statistically significant changing in right ventricular functions in patients with PAF though some parameters were higher in PAF group than the control group such as RA diame-

ter which might be an independent risk factor for the development of AF. As a consequent of these results, it can be speculated that intermittent occurrence of atrial fibrillation may not cause any functional disturbances on right ventricle during the AF free period. But, there were a few differences in PAF group that did not reach the statistically significance such as RA diameter and Tei index. We found that the RA diameter was higher in the PAF group but it was not reached to statistically significance between the groups. Also there was a decreased right ventricular systolic functions in PAF group, despite of being no statistical significant difference between the groups in terms of TAPSE and pulse tissue doppler St. In the current guidelines, the upper limit for Tei index measured by tissue doppler is 0.55 (13). In our study, the Tei index value in PAF group was found to be increased. This implies that; there might be a right ventricular dysfunction in the PAF group when evaluated with Tei index. Assessment of these data concluded that this elevation was due to the elongation of the right ventricular IVRT. Elongation in IVRT may reflect prolonged diastolic filling time, increased right ventricular end-diastolic pressure, or myocardial relaxation defect.

PAF could be an early sign of diastolic dysfunction of RV. In a similar study performed by Eidem et al. (14) found that; although right ventricular functions were normal in patients with right ventricular volume overload as the result of atrial septal defect, Tei index was higher than in normal individuals due to prolongation of IVRT. In addition, it was found that right ventricular dysfunction could be detected subclinically with Tei index as this was correlated with cardiac involvement in patients with chronic obstructive pulmonary disease. Moreover in this study, prolongation of IVRT was associated with the severity of the disease and therefore subclinically both systolic and diastolic dysfunction may occur in these patients (15). It has been found that Tei index had prognostic value in pulmonary hypertension and changing in Tei index could affect the clinical status of these patients (16, 17). Field et al. (18) found that right ventricular dysfunction detected by Tei index is a predictive factor for mortality, transplantation and left ventricular assist device use. In our study, these changes may occur as a result of atrial changes in PAF patients or it may occur as a result of changes in the ventricle together with ventricular response due to rapid and non-rhythmic ventricular stimulation during PAF episodes.

The risk of developing AF in patients with a history of valve disease is increased 1.8 times in men and 3.4 times in women (19). Similarly, a sustained hypertension and an increased pulse pressure are associated with an increased risk of AF (20). Due to these stress factors, the occurrence of ventricular hypertrophy and

atrial dilatation play an important role in the pathogenesis of AF. These subclinical changes develop to adapt changes initially induced by increased afterload or preload. These changes gradually leads to the decrease in ventricular and atrial functions. The relationship between atrial dilatation and AF is well known and well documented. Acar et al. (21) founded that increased in RA diameter could be an independent risk factor for the development of AF in patients on hemodialysis. Conversely, it might be speculated that this increasing in RA diameter could be a result of PAF even not reached to statistically significance in our study. Relevantly, in our study, the changes in right ventricular systolic and diastolic parameters were higher in the patients with PAF patients compared to the control group despite of being not statistically significant.

In PAF group patients, there were no statistical significant differences when left heart parameters were evaluated in accordance with current guidelines. However, we have found that there was statistically significance difference in st value. This might be resulted with left ventricular systolic and diastolic dysfunction in patients with PAF in a long time.

Limitations in our study

There are several limitations in the current study that should be addressed. Firstly, our study included limited number of patients. Another important limitation of the present study was the lack of datas on duration PAF and numbers of PAF episodes untill study participation. Lastly, intra-interobserver variability related to the parameters measured in echocardiography was not performed. Therefore, our findings may not be applicable to the entire PAF population. Therefore, large scaled and multicentered studies are needed.

CONCLUSION

In this study, we could not find any statistically significant changing in right ventricular functions in patients with PAF. But, there were a few differences in PAF group that did not reach the statistically significance such as RA diameter and Tei index. Tei index was detected over the normal references value because of delaying in IVRT. This result may indicate that right ventricular diastolic functions could be affected in patients with PAF. Moreover, increasing in RA diameter might be assumed that it could be a result of PAF in this patients. These results need to be supported by future studies including more patients.

Abbreviations

AF — Atrial fibrillation

PAF — paroxysmal atrial fibrillation

TAPSE — tricuspid annular plane systolic excursion

IVRT — isovolumic relaxation time
EF — ejection fraction
MPI — myocardial performance index

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Sažetak

PROCENA SISTOLNE I DIJASTOLNE FUNKCIJE DESNE KOMORE KOD PACIJENATA SA PAROKSIZMALNOM ATRIJALNOM FIBRILACIJOM

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Uvod: Atrijalna fibrilacija (AF) je često električni znak postojeće strukturne bolesti srca. Strukturno remodeliranje sekundarno može početi ne samo u komorama već i u pretkomorama zbog AF. U ovoj studiji, pokušali smo da istražimo efekat paroksizmalne atrijalne fibrilacije (PAF) na funkciju desne komore.

Metod: Prospektivno smo analizirali 30 pacijenata kod kojih je dijagnostikovana PAF i 25 u kontrolnoj grupi. Srčani faktori rizika i lečenje obe grupe pacijenata su dobijeni i sačuvani. Procena funkcije desne komore izvedena je pomoću parametara TAPSE i Tei indeksa.

Rezultati: Nije bilo statistički značajne razlike između grupa u smislu demografskih i kliničkih karakteristika. Tei indeks je bio viši, a TAPSE niži u PAF grupi

u poređenju sa kontrolnom grupom ($p > 0,05$). Nije nađena statistički značajna razlika između PAF i kontrolne grupe u pogledu dijasolne funkcije desne komore. Iako je vreme izovolemijske relaksacije (IVRT) bilo veće u PAF grupi, to nije dalo statistički značaj.

Zaključak: U ovoj studiji, iako nije od statističkog značaja, Tei indeks kojim se procenjuje funkcija desne komore bio je iznad gornje granice u PAF grupi. To je moglo biti rezultat produženog IVRT-a. Ovaj rezultat može ukazivati da dijasolna funkcija desne komore može biti izmenjena kod pacijenata sa paroksizmalnom atrijalnom fibrilacijom.

Cljučne reči: atrijalna fibrilacija, desna komora, 2D elektrokardiografija.

REFERENCES

1. Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S. Epidemiology of atrial fibrillation: European perspective. *Clin Epidemiol.* 2014; 6: 213-20.
2. Wilke T, Groth A, Mueller S, Pfannkuche M, Verheyen F, Linder R, et al. Incidence and prevalence of atrial fibrillation: an analysis based on 8.3 million patients. *Europace.* 2013; 15(4): 486-93.
3. Vaziri SM, Larson MG, Benjamin EJ, Levy D. Echocardiographic predictors of nonrheumatic atrial fibrillation. The Framingham Heart Study. *Circulation.* 1994; 89(2): 724-30.
4. Denham NC, Pearman CM, Caldwell JL, Madders GW, Eisner DA, Trafford AW, et al. Calcium in the pathophysiology of atrial fibrillation and heart failure. *Front Physiol.* 2018; 9: 1380.
5. Prabhu S, Voskoboinik A, Kaye DM, Kistler PM. Atrial fibrillation and heart failure — cause or effect? *Heart Lung Circ.* 2017; 26(9): 967-74.
6. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, et al. 2017 HRS/EHRA/ECAS/APHS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Europace.* 2018; 20(1): e1-e160.

7. Floria M, Blommaert D, Lacrosse M, Ambarus V, Dormal F, Dabiri Abkenari L, et al. Assessment of left atrial shape and volume in structural remodeling secondary to atrial fibrillation. *Journal of interventional cardiac electrophysiology : an international journal of arrhythmias and pacing.* 2009; 25(3): 167-70.

8. Sarvari SI, Haugaa KH, Stokke TM, Ansari HZ, Leren IS, Hegbom F, et al. Strain echocardiographic assessment of left atrial function predicts recurrence of atrial fibrillation. *Eur Heart J Cardiovasc Imaging.* 2016; 17(6): 660-7.

9. Jurin I, Hadzibegovic I, Durlen I, Jakšić Jurinjak S, Misković D, Ajduk M, et al. Left atrium size and red cell distribution width predict atrial fibrillation progression from paroxysmal or persistent to permanent. *Acta Clinica Belgica.* 2020; 75(3): 205-11.

10. Houtz B, Johansson B, Berglin E, Karlsson T, Edvardsson N, Wandt B. Left ventricular diastolic function and right atrial size are important rhythm outcome predictors after intraoperative ablation for atrial fibrillation. *Echocardiography.* 2010; 27(8): 961-8.

11. Donal E, Lip GY, Galderisi M, Goette A, Shah D, Marwan M, et al. EACVI/EHRA Expert Consensus Document on

the role of multi-modality imaging for the evaluation of patients with atrial fibrillation. *Eur Heart J Cardiovasc Imaging*. 2016; 17(4): 355-83.

12. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015; 28(1): 1-39.e14.

13. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2010; 23(7): 685-713.

14. Eidem BW, O'Leary PW, Tei C, Seward JB. Usefulness of the myocardial performance index for assessing right ventricular function in congenital heart disease. *Am J Cardiol*. 2000; 86(6): 654-8.

15. Ozben B, Basaran Y. [Echocardiography and other imaging modalities in pulmonary arterial hypertension]. *Anadolu Kardiyol Derg*. 2010; 0 (Suppl 1): 27-35.

16. Yücel M, Alp H, Yorulmaz A, Karaarslan S, Baysal T. Prediction of the development of pulmonary arterial hypertension with Tei Index in congenital heart diseases with left-to-right shunt. *Turk Kardiyol Dern Ars*. 2019; 47(6): 466-75.

17. Giusca S, Popa E, Amzulescu MS, Ghiorgiu I, Coman IM, Popescu BA, et al. Is right ventricular remodeling in pulmonary hypertension dependent on etiology? An echocardiographic study. *Echocardiography*. 2016; 33(4): 546-54.

18. Field ME, Solomon SD, Lewis EF, Kramer DB, Baughman KL, Stevenson LW, et al. Right ventricular dysfunction and adverse outcome in patients with advanced heart failure. *J Card Fail*. 2006; 12(8): 616-20.

19. Kavousi M. Differences in epidemiology and risk factors for atrial fibrillation between women and men. *Front Cardiovasc Med*. 2020; 7:3.

20. O'Neal WT, Soliman EZ, Qureshi W, Alonso A, Heckerbert SR, Herrington D. Sustained pre-hypertensive blood pressure and incident atrial fibrillation: the Multi-Ethnic Study of Atherosclerosis. *J Am Soc Hypertens*. 2015; 9(3): 191-6.

21. Acar G, Akcay A, Dogan E, Isik IO, Sokmen A, Sokmen G, et al. The prevalence and predictors of atrial fibrillation in hemodialysis patients. *Turk Kardiyol Dern Ars*. 2010; 38(1): 8-13.

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POSTOPERATIVE SURVIVAL RESULTS OF PATIENTS WITH STAGE I-II MALIGNANT PLEURAL MESOTHELIOMA IN AN ENDEMIC AREA

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Abstract: Introduction: The accepted treatment option for malignant pleural mesothelioma (MPM) is multimodality treatment including surgery, chemotherapy and radiotherapy. In this study, we aimed to evaluate the results of patients who underwent surgical resection for multimodality treatment due to MPM at our clinic between July 2015 and October 2019.

Method: The results of 13 patients who underwent surgical treatment for MPM in our clinic were evaluated retrospectively. Patients' demographic structure, regions where they live, symptom presentation, disease localization, biopsy diagnosis, type of surgical treatment, choice of neoadjuvant or adjuvant chemotherapy, postoperative complications and survival outcomes were evaluated.

Results: The mean survival time was 19.6 months. Six patients were still under follow-up. One patient whose postoperative pathology was reported as mixed type had the worst survival with 13 months and the best survival was 32 months in the patient who underwent postoperative hyperthermic chemotherapy with pleural decortication. Four patients died due to local recurrence and general condition disorder, and two patients died after peritonitis carcinomatosis and ascites.

Conclusion: Epitheloid type multimodality treatment and intrapleural hyperthermic chemotherapy may be a good choice in patients with the stage I and II malignant mesothelioma without surgical comorbidity.

Key words: mesothelioma, decortication, asbestos, pleura, malignant.

INTRODUCTION

Asbestos exhibits pathogenic properties depending on the diameter - length, exposure dose, duration of the asbestos fibers deposited on the pleural surface af-

ter exposure and the body's ability to break down asbestos. These results in benign asbestos plaques or malignant pleural mesothelioma (MPM) (1). MPM continues to be an endemic disease especially in our country. In Turkey, every year an average 500-600 patients are estimated to receive new diagnosis (2). Despite all advances in chemotherapy and oncologic treatment options, the survival time of the disease is still very short (3, 4).

Malignant pleural mesothelioma has three histological subtypes, epitheloid, sarcomatoid and mixed. It is the most common epitheloid type (55-60%) with the relatively good prognosis (5). Multimodality therapy, which includes thoracic surgery, oncology and radiation oncology, is the accepted world-wide option in the treatment of MPM (5). It is recommended that surgical + hyperthermic chemotherapy or radiotherapy to be applied only to surgery, followed by chemotherapy and incision areas together (6).

The aim of the surgery is to reduce the complaints such as shortness of breath and pain that may develop due to the disease, to improve the quality of life of the patient and to prolong the survival time. In addition, radical resection should be provided in macroscopic disease associated with lung parenchyma (7). In this study, we aimed to evaluate the results of patients who underwent surgical resection for MPM in our clinic between July 2015 and October 2019.

MATERIAL AND METHODS

The results of patients who underwent surgical treatment for MPM in our clinic were evaluated retrospectively from the hospital records. A total of 13 patients who underwent surgery was included in the study. Patients who received only chemotherapy and did not

undergo surgery were excluded. Patients' demographic structure, region of residence, symptom presentation, disease localization, biopsy, type of surgical treatment, choice of neoadjuvant or adjuvant chemotherapy, postoperative complications and survival outcomes were evaluated. In patients, preoperative and postoperative staging was performed according to TNM 8th edition. Before surgery, all patients were evaluated by a multidisciplinary team, including a thoracic surgeon, oncologist and radiation oncologist. As a result of the biopsies performed, surgery was planned for the patients whose pathology was epitheloid type. Surgical or neoadjuvant treatment decision in all patients was made in the oncological council. Neoadjuvant therapy was given in cases considered to be inappropriate for surgery and accepted as advanced stage.

RESULTS

Eleven patients were male and 2 was female. The mean age was found to be 63.1 ± 6.41 (53 - 77). Eleven

of the patients were from the endemic regions in terms of asbestos exposure in Elazig, Turkey and the surrounding provinces, and two patients came from Iraq. At the time of admission, the first symptom was dyspnea in 8 patients, back pain in 3 patients, and pleural effusion on chest X-ray in 2 patients. Posteroanterior and lateral chest radiographs of all patients were positive findings. Afterwards, patients underwent the contrast-enhanced thorax computed tomography (CT), and after MPM diagnosis the patients were staged with Positron Emission Tomography (Pet - CT). Chest radiography, thorax CT and Pet-CT were used as imaging methods in all patients. The mean SUV max was found to be 2.06 ± 4.08 (1.2 - 9.4). Localization included pleural effusion and pleural thickening on the right side in 10 patients and on the left side in 3 patients (Table I).

Eight patients (61.5%) presented with recurrent pleural effusion after tube thoracostomy and thoracentesis were diagnosed with video-assisted thoracoscopic surgery (VATS) and one patient (7.7%) with anteri-

Table 1. Demographic findings, presentation symptoms and tumor localization

		Patients number (n : 13)	%
Gender	Female	2	15.4
	Male	11	84.6
Symptoms at admission	No symptom	2	15.4
	Back pain	3	23.1
	Dyspnea	8	61.5
Tumor Localization	Left	3	23,1
	Right	10	76,9

Table 2. Diagnosis methods, neoadjuvant treatment, preoperative tumor stage, surgical methods and hyperthermic chemotherapy rate (VATS: Video-assisted thoracoscopic surgery, EPP: Extrapleural pneumonectomy, P/D: Total decortication, excisions of tumor tissue on the pericardium and diaphragm, TP/D: Total pleural decortication, iaphragm and pericardial resection)

		Patients number (n : 13)	%
Diagnostic methods	Thoracotomy	1	17,7
	Thoracentesis	4	30.8
	VATS	8	61.5
Neoadjuvant treatment		3	23.1
Preoperative Stage	Stage IA	5	38.4
	Stage IB	4	30.8
	Stage II	4	30.8
Surgical Method	EPP	1	7.7
	P/D	2	15.4
	TP/D	10	76.9
Hypertermic Chemotherapy		6	46,2

Table 3. Postoperative complications and tumor stage

		Patients number	%
Postoperative Complications (n : 6, %46.2)	Expansion defect and subcutaneous emphysema	1	7,7
	Atrial fibrillation	2	15,4
	Prolonged air leak	3	23.1
Postoperative Tumor Stage	Stage IA	2	15.4
	Stage IB	6	46.2
	Stage II	5	38.4

or mini thoracotomy. Four patients (30.8%) who applied for the first time were diagnosed with MPM after thoracentesis. All patients had a diagnosis of epitheloid type mesothelioma. Three patients had received 4 cycles of pemetrexed and cisplatin chemotherapy as a neoadjuvant treatment prior to surgery (Table 2). According to TNM 8th edition, 5 patients were Stage IA, 4 patients were Stage IB and 4 patients were Stage II in preoperative staging. ECOG scores were 2 in 8 patients, 1 in 3 patients, and 0 in 2 patients.

Standard posterolateral thoracotomy incision was opened to the patients. Two different thoracotomies were performed from the 5th and 8th intercostal spaces from the same incision. Ten patients (76.9%) underwent total pleural decortication, diaphragm and pericardial resection (TP, D group). One patient (7.7%) underwent extra pleural pneumonectomy (EPP group), diaphragm and pericardial resection, and two patients (15.4%) underwent total decortication, excisions of tumor tissue on the pericardium and diaphragm (P, D group) and primary repair after resection. The diaphragm and pericardial integrity were not impaired in this patient. Mesh was used for pericardial and diaphragmatic reconstruction in patients who underwent diaphragmatic and pericardial resection. Six patients received hyperthermic intrapleural chemotherapy with cisplatin at a dose of 100 mg/m² relative to the body surface (Table 2).

In the postoperative period, 3 patients had prolonged air leakage, and 2 patients had atrial fibrillation, 1 patient had expansion defect and subcutaneous emphysema. No side effects related to hyperthermic chemotherapy were seen in the postoperative period. The average length of stay in the intensive-care unit of the patients was 1.5 (1-4) days, and the average length of hospital stay was 6.1 days (5-9). Postoperative pathology was reported as epitheloid type in 12 patients and mixed type in 1 patient. According to TNM 8 staging system, Stage IA: 2 (15.4%) patients, Stage IB: 6 (46.1%) patients and Stage II: 5 (38.5%) patients were classified (Table III). In the postoperative period, 3 patients who were operated following neoadjuvant therapy we-

re given 2 cycles of chemotherapy, and 10 patients who underwent direct surgery were given 6 cycles of pemetrexed and cisplatin chemotherapy. Patients were routinely given radiotherapy to surgical incision lines. One patient with mediastinal recurrence and one patient with femoral metastasis received regional radiotherapy.

The patients were followed up with the thorax and abdominopelvic CT in the postoperative period. Patients with suspected recurrence in tomography images were rechecked with PET-CT. When all patients were evaluated, the mean survival time was 19.6 ± 4.76 (13-32) months. Seven patients were still under follow-up. One patient whose postoperative pathology was reported as mixed type had the worst survival with 13 months and the best survival was found to be 32 months in the patient who underwent postoperative hyperthermic chemotherapy with P,D group. Four patients died due to local recurrence and general condition disorder, and two died after peritonitis carcinomatosis and ascites.

DISCUSSION

Malignant pleural mesothelioma is a malignancy with high mortality and predominance of asbestos exposure (8). In our series, the mean survival was 19.6 months which is consistent with the literature. The majority of patients present with dyspnea due to pleural effusion. In our series, the most common presenting symptom was dyspnea at 66.7%. Chest radiography, Thorax CT or Pet - CT are the recommended methods for diagnosis (9).

Minimal invasive techniques should be used when selecting the biopsy method. Thoracentesis should be the first choice in diagnosis, but the diagnostic value has been reported to be very low. In a study by Lovrenski et al. (10), fluid samples from 49 patients with MPM were examined and as a result, only 29% of the patients were diagnosed as pathological malignant. This necessitates invasive biopsy techniques in patients with suspected malignancy and asbestos exposu-

re. Eren et al. (11), in their study in Diyarbak2r, an endemic region for asbestos, and in 28 undiagnosed patients with pleural effusion, suggested VATS as a diagnostic method with a high diagnostic value of 96.5% and a low complication rate. In our series, VATS was the most frequently used diagnostic method in 8 (61.5 %) patients.

The International Mesothelioma Interest Group (IMIG) recommends the treatment of multimodality in malignant pleural mesothelioma. They are reported that the combination of surgery, radiotherapy and chemotherapy may increase the success of treatment (12, 13). Because of the aggressive nature of MPM, patients in the group that may benefit from surgery should be carefully selected when planning multimodality treatment (14, 15). It has been shown that long-term survival in MPM is impossible if metastasis to the mediastinal lymph nodes is detected (16, 17, 18). In one of our patients, subcarinal lymph node involvement was detected in the postoperative pathology and the survival time was 13 months. However, the fact that the pathology result was mixed in this patient prevented us to determine whether lymph node positivity or pathological subtype had an effect on the course of the disease.

Different options may be preferred for surgical treatment in patients. One of them is extra pleural pneumonectomy, which is the en - block resection of the lung, parietal pleura decortication, pericardium and diaphragm. Thus, there are some who argue that a radical cytoreductive surgery is performed in MPM, and the same study emphasizes that it is not possible to perform R0 resection (19). On the other hand, there is a group that argues that macroscopic resection is sufficient to replace the morbidity and complications imposed by EPP (20, 21). In this case, extended pleural decortication or partial resection are recommended according to the diaphragm and pericardial involvement along with the total pleural decortication of the surgery (22). When we look at the preferred surgical technique in our patients, we saw that we performed total pleural decortication, diaphragm and pericardial resection surgery in general (76.9 %). In the literature, the survival of these patients is short and therefore, parenchymal protective surgical techniques should be preferred more (21-24).

In recent years, there have been published articles suggesting an increasing rate of intrapleural hyperthermic chemotherapy. Cisplatin (25, 26) is the most commonly used and recommended active substance for this

purpose. In a study conducted by Burt et al. (27) in which 104 patients completed the treatment and published Phase I, it was shown that Ciplastin and Gemcitabine could be combined. We used Cisplatin-based chemotherapy in 3 patients who underwent hyperthermic chemotherapy; however, due to the limited number of patients, no statistical evaluation was made in terms of contribution to survival. In our patient series, early postoperative mortality was not seen, and the complication rate was 46.2% in accordance with the literature. In the postoperative period, no patient required transfusion due to perioperative bleeding. In our study, no significant finding was found in terms of prognostic factors.

Because of the small number of patients in our study, its retrospective nature and the patient series did not meet a certain standard, and we had some limitations. These limitations indicate that we are not sufficient to evaluate the effect of surgery + hyperthermic chemotherapy or surgery alone on survival, and randomized controlled trials are needed in this area. It is difficult to reach larger series in terms of mesothelioma surgery, and therefore the necessity of multicenter studies is obvious.

CONCLUSION

Malignant pleural mesothelioma, which is still endemic disease in our country and which is expected to increase with the urban transformation, is still a public health problem. As seen in the literature, there is no recommended treatment option for MPM at the level of definitive evidence. Multimodality therapy and intrapleural hyperthermic chemotherapy may be a good choice in selected patients.

Abbreviations

SUVmax — Maximum standardized uptake value

TNM — Tumor Node Metastasis

ECOG — Eastern Cooperative Oncologic Group

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Sažetak

REZULTATI POSTOPERATIVNOG PREŽIVLJAVANJA PACIJENATA SA PLEURALNIM MALIGNIM MEZOTELIOMOM STADIJUMA I-II U ENDEMSKOM PODRUČJU

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Uvod: Lečenje malignog pleuralnog mezotelioma (MPM) je multimodalno i uključuje hirurško lečenje, hemoterapiju i radioterapiju. U ovoj studiji cilj nam je bio da evaluiramo rezultate pacijenata koji su podvrgnuti hirurškoj resekciji u cilju multimodalnog lečenja MPM na našoj Klinici, u periodu između jula 2015. i oktobra 2019. godine.

Metod: Rezultati 13 pacijenata koji su podvrgnuti hirurškoj terapiji MPM na našoj Klinici su retrospektivno evaluirani. Analizirani su demografske karakteristike pacijenata, mesto boravka, simptomi bolesti, lokalizacija bolesti, nalaz biopsije, tip hirurškog tretmana, izbor neoadjuvantne i adjuvantne hemoterapije, postoperativne komplikacije i preživljavanje.

Rezultati: Srednji period preživljavanja bio je 19,6 godina. Šest pacijenata se još uvek pratilo. Jedan

pacijent čiji je postoperativni patološki nalaz potvrdio mešoviti tip tumora je imao najkraći period preživljavanja od 13 meseci, a najduže preživljavanje od 32 meseca bilo je kod pacijenta koji je podvrgnut postoperativnoj hipertermičnoj hemoterapiji sa pleuralnom dekontakcijom. Četiri pacijenta su umrli zbog lokalne rekurentne pojave tumora i opšteg poremećaja zdravstvenog stanja. Dva pacijenta su umrli nakon peritonealne karcinomatose i ascitesa.

Zaključak: Epiteloidni tip multimodalnog tretmana i intrapleuralna hipertermička hemoterapija mogu biti dobar izbor lečenja kod pacijenata sa stadijumom I-II malignog mezotelioma bez hirurških komorbiditeta.

Cljučne reči: mezoteliom, dekontakcija, azbestoza, pleura, maligni.

REFERENCES

1. Senyigit A, Coskunsal M, Topcu F, Is2k R, Babayigit C. Malignant pleural mesothelioma: evaluation of clinical, radiological and histological features in 136 cases. *Tuberkuloz ve Toraks Dergisi*. 2000; 48(1): 26-34.
2. Metintas S, Metintas M, Ucgun I, Oner U. Malignant mesothelioma due to environmental exposure to asbestos: follow-up of a Turkish cohort living in a rural area. *Chest*. 2002; 122(6): 2224-9.
3. Turk F, Yuncu G, Ozturk G. Mezoteliyomada tani ve tedavi amacli cerrahi yaklasimlar. *Pam Med J*. 2012; 5(3): 105-9.
4. Kang SR, Bok JS, Lee GD, Choi SH, Kim HR, Kim DK, et. al. Surgical options for malignant mesothelioma: a single-center experience. *Korean J Thorac Cardiovasc Surg*. 2018; 51(3): 195-201.
5. Bozlar U, Ors F, Yildirim D, Battal B, Saglam M, Nural MS. Atypical malignant mesothelioma characterized with massive effusion: computed tomography findings. *Firat Med J*. 2009; 14(1): 78-80.
6. Sugarbaker PH. Intra-abdominal manifestations of pleural mesothelioma. *Ann Transl Med*. 2017; 5(11): 231.
7. Waller DA. Lung-sparing total pleurectomy: the surgical option of choice in malignant pleural mesothelioma? *Eur J Cardiothorac Surg*. 2013; 44(1): 123-4.
8. Tanrikulu AC, Abakay O, Sezgi C, Sen HS, Abakay A. Comparison of supportive treatment and pleurodesis in patients with malignant pleural mesothelioma. *Dicle Med J*. 2012; 39(4): 509-12.
9. Armato SG 3rd, Francis RJ, Katz SI, Ak G, Opitz J, Gudmundsson E, et. al. Imaging in pleural mesothelioma: A re-

view of the 14th International Conference of the International Mesothelioma Interest Group. *Lung Cancer*. 2019; 130: 108-14.

10. Lovrenski A, Panjkovic M, Tegeltija D, Latinovic LT, Krcecinac J. The role of cytological evaluation of pleural fluid in diagnosing malignant mesothelioma. *Med Pregl*. 2012; 65(1-2): 5-8.

11. Eren S, Balci AE, Ulku R, Esme H, Eren MN. Role of Video-Assisted Thoracoscopic Surgery (VATS) in pleural effusions. *Tuberk Toraks*. 2002; 50(1): 53-8.

12. MacRae RM, Ashton M, Lauk O, Wilson W, O'Rourke N, Simone CB 2nd, et. al. The role of radiation treatment in pleural mesothelioma: Highlights of the 14th International Conference of the International mesothelioma interest group. *Lung Cancer*. 2019; 132: 24-7.

13. Schröder C, Opitz I, Guckenberger M, Stahel R, Weder W, Förster R, et. al. Stereotactic Body Radiation Therapy (SBRT) as salvage therapy for oligorecurrent pleural mesothelioma after multi-modality therapy. *Front Oncol*. 2019; 9: 961.

15. Noiret B, Eveno C. Bidirectional chemotherapy allowing surgery and HIPEC for malignant peritoneal mesothelioma. *Pleura Peritoneum*. 2019; 4(2): 20190011.

15. Franceschini D, De Rose F, Cozzi S, Renna I, Franzese C, Di Brina L, et. al. Volumetric modulated arc therapy after lung sparing surgery for malignant pleural mesothelioma: a single institution experience. *Clin Lung Cancer*. 2020; 21(1): 86-93.

16. Tokat AO, Kutlay H. Gene therapy in malignant mesothelioma. *Tuberk Toraks*. 2003; 51(4): 456-60.

17. Hassan M, Mercer RM, Maskell NA, Asciak R, McCracken DJ, Bedawi EO, et. al. Survival in patients with malignant pleural effusion undergoing talc pleurodesis. *Lung Cancer*. 2019; 137: 14-8.

18. Kai Y, Tsutani Y, Tsubokawa N, Ito M, Mimura T, Miyata Y, et. al. Prolonged post-recurrence survival following pleurectomy/decortication for malignant pleural mesothelioma. *Oncol Lett.* 2019; 17(3): 3607-14.
19. Rokicki W, Rokicki M, Wojtacha J, Rydel MK. Malignant mesothelioma as a difficult interdisciplinary problem. *Kardiologich Torakochirurgia Pol.* 2017; 14(4): 263-7.
20. Scherpereel A, Astoul P, Bass P, Berghmans T, Clayson H, de Vuyst P, et. al. Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of malignant pleural mesothelioma. *Eur Respir J.* 2010; 35(3): 479-95.
21. Hasegawa S. Extrapleural pneumonectomy or pleurectomy/decortication for malignant pleural mesothelioma. *Gen Thorac Cardiovasc Surg.* 2014; 62(9): 516-21.
22. Opitz I, Weder W. A nuanced view of extrapleural pneumonectomy for malignant pleural mesothelioma. *Ann Transl Med.* 2017; 5(11): 237.
23. Kostron A, Friess M, Inci I, Hillinger S, Schneider D, Gelpke H, et. al. Propensity matched comparison of extrapleural pneumonectomy and pleurectomy/decortication for mesothelioma patients. *Interact Cardiovasc Thorac Surg.* 2017; 24(5): 740-6.
24. Shahin Y, Wellham J, Jappie R, Pointon K, Majewski A, Black E. How successful is lung-preserving radical surgery in the mesothelioma and radical surgery-trial environment? A case-controlled analysis. *Eur J Cardiothorac Surg.* 2011; 39(3): 360-3.
25. Richards WG, Zellos L, Bueno R, Jaklitsch MT, Jänne PA, Chirieac LR, et al. Phase I to II study of pleurectomy/decortication and intraoperative intracavitary hyperthermic cisplatin lavage for mesothelioma. *J Clin Oncol.* 2006; 24(10): 1561-7.
26. Ambrogi MC, Bertoglio P, Aprile V, Chella A, Korasidis S, Fontanini G, et. al. Diaphragm and lung-preserving surgery with hyperthermic chemotherapy for malignant pleural mesothelioma: A 10-year experience. *J Thorac Cardiovasc Surg.* 2018; 155(4): 1857-66.
27. Burt BM, Richards WG, Lee HS, Bartel S, Dasilva MC, Gill RR, et.al. A phase I trial of surgical resection and intraoperative hyperthermic cisplatin and gemcitabine for pleural mesothelioma. *J Thorac Oncol.* 2018; 13(9): 1400-9.

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FACTORS AFFECTING THE ARRIVAL TIME TO HOSPITAL OF PATIENTS WITH ACUTE ISCHEMIC STROKE

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Abstract: Objective: It is known that intravenous thrombolytic therapy in ischemic stroke is beneficial in selected patients who arrived within the first 4.5 hours after the onset of the symptoms and the effectiveness of the treatment depends on early arrival to the hospital. The more patients arrival to the hospital within this time zone, the more they will have the chance to receive thrombolytic therapy. This study aims to investigate the factors that cause delay in the arrival of patients with ischemic stroke to the hospital.

Methods: Patients diagnosed with acute ischemic stroke who applied to the neurology outpatient clinic and emergency room between February and May 2019 were included in the study. A **direct interview** survey was conducted to investigate the factors that delay the arrival to patients or relatives of the patients arrival to Bursa Yuksek Ihtisas Training and Research Hospital due to acute stroke. According to the time of arrival to the hospital after the onset of stroke symptoms, patients were classified as early (≤ 4.5 hours) and late arrival (> 4.5 hours). Based on this grouping, factors causing delay in patients' access to hospital were compared statistically.

Results: A total of 251 patients and / or patient relatives who arrived to the emergency and neurology outpatient clinic were interviewed. Of the 251 patients included in the study, 119 (47.4%) were female and the mean age was 70 (34-94) years. Approximately 72.5% of the patients were arrived in the first 4.5-hour slice after the onset of stroke symptoms. Factors causing late arrival were determined as being female, having low NIHSS score and not using ambulance in transportation.

Conclusion: Due to the delay in arrival of 27.5% of the patients, there is no chance to apply thrombolytic

therapy to eligible ones. The factors resulting in the delay were discovered as female gender, low severity of the stroke and transportation without ambulance. In this respect, community-oriented trainings are required.

Key words: Ischemic stroke, late arrival, emergency room, thrombolytic therapy.

INTRODUCTION

Stroke is one of the leading causes of death and disability worldwide. It is known that intravenous (IV) administration of thrombolytic therapy is helpful in selected patients in the first 4.5 hours following the onset of the symptoms and the earlier the treatment is started, the more effective it is. The more patients that arrived to the hospital within this time zone, the more patients will have the chance to receive thrombolytics (1, 2, 3).

The delay from the onset of stroke to arrival at the hospital reduces the rate of these patients to be treated with thrombolytic and/or mechanical thrombectomy. For this reason, the effect of a variety of factors in the arrival time to hospital of stroke patients were examined in previous studies. These factors include living alone, stroke onset time, age, gender, education level, place of arrival at the hospital, income level, distance to the hospital, stroke symptoms, stroke risk factors, level of consciousness, way to reach the hospital, National Health Stroke Scale (NIHSS), contact with the local doctor, recognition of stroke symptoms by healthcare professionals, patients and the relatives. It has been observed that the time of arrival to the hospital varies according to the development level of the countries, geographic, sociodemographic and organizational factors (4-21). In our study, we aimed to investigate the

causes leading to delay in the arrival of stroke patients to the hospital.

MATERIAL AND METHODS

This study included patients older than 18 years who arrived to the neurology outpatient clinic and emergency room between February and May 2019, presented stroke symptoms compatible with neuroimaging and were diagnosed with acute ischemic stroke. Patients with intracerebral hemorrhage and in-hospital stroke were excluded from the study. Stroke onset time was recorded as the time of appearance of stroke symptoms. In the wake-up strokes, the moment when the patient was last seen as healthy was evaluated as the stroke onset time. A questionnaire was filled in by interviewing each patient or the relative who agreed to participate in the study. Using the NIHSS, stroke symptom onset, hospital arrival time, age, gender, level of education and financial status, stroke severity at arrival were determined. Stroke onset time was divided into two intervals as day (07:00-19:00) and night time (19:00-07:00). The distance patients covered was determined using regional road maps. Neurological deficits during discharge were evaluated with modified ranking scale (mRS) scores. Having $mRS \leq 2$ during discharge was recorded as a good functional outcome and $mRS > 2$ as bad. Education levels of the patients were classified as secondary education or less, high school and university graduate. Income status was grouped as low, medium and high according to the economic situation perceived by the patient.

Whether the hospital arrival was direct or from another hospital, previous knowledge of the patients and their relatives about thrombolytic therapy was questioned and patients treated with thrombolytic therapy were recorded. As a result of the neurological examination, the consciousness levels of the patients were determined as conscious and unconscious (somnolence /stupor). Stroke symptoms were recorded as aphasia, dysarthria, hemianopsia, hemiparesis, hemihypoesthesia. Vascular risk factors, hypertension, diabetes mellitus (DM), hyperlipidemia, coronary artery disease (CAD), atrial fibrillation (AF), smoking and family history of stroke were determined. Transportation to the hospital, by ambulance or other private vehicles was questioned. According to the time of arrival to the hospital after the onset of stroke symptoms, patients were grouped as early (≤ 4.5 hours) and late arrival (> 4.5 hours). Factors related to the delay in the arrival of patients were compared statistically based on this grouping. The study was approved by Bursa Yuksek Ihtisas Training and Research Hospital Ethics Committee with the decision numbered 2011-KAEK-25 2019 / 02-26.

Statistical Analysis

Data were presented as the number of patients, percentage, mean, standard deviation and median, and the suitability of the data to normal distribution was evaluated. The variables that fit the normal distribution are given as mean $\pm$ standard deviation and those that do not fit the normal distribution are given as median (minimum-maximum). Parametric methods were used to relate data that match normal distribution, and non-parametric statistical methods were utilized to compare data that did not match normal distribution.

Parametric data in independent groups were compared with t-test and non-parametric data with Mann Whitney U test. The significance of the difference between categorical variables was evaluated by chi-square and Fisher's exact test. Multivariate logistic regression analysis was applied for variables that were statistically significant ($p < 0.05$) in univariate analyzes. Data were analyzed at 95% confidence interval. All statistical analysis was carried out using SPSS 24.0 (IBM Corp.; Armonk, NY, USA) programme.

RESULTS

Of the 251 patients included in the study, 132 were male (52.6%), 119 (47.4%) were female, and the mean age was 70 years (34-94). 182 patients (72.5%) applied to the hospital in the first 4.5 hours of stroke after the onset of the symptoms. There were 69 patients (27.5%) applying over the first 4.5-hour slice. The socio-demographic characteristics of the patients are presented in Table 1. Stroke symptoms were most common during

Table 1. Socio-demographic characteristics of stroke patients ($n = 251$)

Socio-demographic characteristics	n (%)
Age	70 (34-94)
Gender	
- Male	132 (52.6)
- Female	119 (47.4)
Education	
- Secondary school or less	208 (82.9)
- High School	32 (12.7)
- University	11 (4.4)
Place of arrival at the hospital	
- City	179 (71.3)
- District	59 (23.5)
- Country	13 (5.2)
Income Level	
- Low	125 (49.8)
- Middle	120 (47.8)
- High	6 (2.4)
Distance (km)	5 (1-160)

daytime with 155 patients (61.8%). Hemiparesis was the most common stroke symptom in 169 patients (67.3%). Hypertension was the most common stroke risk factor in 167 patients (66.5%). NIHSS averages of the patients at the time of admission were calculated as 4 (1-32). The number of patients transferring to the hospital by ambulance was 160 (63.7%). Only 16 patients (6.4%) knew about the application of thrombolytic therapy priorly. The consciousness of 185 patients (73.7%) was normal at the time of admission to the hospital.

The number of patients who applied to our hospital directly was 179 (71.3%). Good functional outcome

Table 2. Patients' stroke related features (n=251)

Patients' stroke related features	n (%)
Symptom onset time	
- Night (19:00-07:00)	96 (38.2)
- Day (07:00-19:00)	155 (61.8)
Symptom door time (min.)	104 (15-5500)
Stroke Symptoms	
- Hemiparesis	169 (67.3)
- Hemihypoesthesia	91 (36.3)
- Hemianopsia	36 (14.3)
- Aphasia	115 (45.8)
- Dysarthria	60 (23.9)
Stroke Risk Factors	
- Stroke History	76 (30.3)
- Hypertension	167 (66.5)
- Smoking	66 (26.3)
- Diabetes	90 (35.9)
- Hyperlipidemia	54 (21.5)
- CAD	76 (30.3)
- AF	47 (18.7)
- Family History	72 (28.7)
NIHSS (During application)	4 (1-32)
Transfer to Hospital	
- Ambulance	160 (63.7)
- Other	91 (36.3)
Information about thrombolytic therapy	16 (6.4)
Consciousness Level	
- Normal	185 (73.7)
- Somnolence	47 (18.7)
- Stupor	19 (7.6)
Arrival to Hospital	
- Direct arrival	179 (71.3)
- Transfer from another center	72 (28.7)
mRS (at discharge)	
≤ 2	140 (55.7)
>2	111 (44.3)

AF: Atrial fibrillation, CAD: Coronary artery disease, NIHSS, National Institutes of Health Stroke Scale, mRS: modified Rankin Scale

Table 3. Comparison of patients' socio-demographic and clinical characteristics by the time of arrival at the hospital (n = 251)

	Admission		P
	(≤ 4,5 hours), n = 182	(> 4,5 hours)t, n = 69	
Age	70 (36-92)	68,56 ± 12.43	0.77
Gender			
- Female	78 (42.9)	41 (59.4)	0.03*
Education			
- Secondary School or less	151 (83)	57 (82.6)	0.70
- High School	22 (12.1)	10 (14.5)	
- University	9 (4.9)	2 (2.9)	
Place of arrival to the hospital			
- City	128 (70.3)	51 (73.9)	0.79
- District	44 (24.2)	15 (21.7)	
- Country	10 (5.5)	3 (4.3)	
Income Level			
- Low	83 (45.6)	42 (60.9)	0.12
- Medium	94 (51.6)	26 (37.7)	
- High	5 (2.7)	1 (1.4)	
Distance (km)	5 (1-90)	5 (2-160)	0.83
Symptom Onset time			
- Day (07:00-19:00)	111 (61)	44 (63.8)	0.6
- Night (19:00-07:00)	71 (39)	25 (36.2)	
Stroke Symptoms			
- Hemiparesis	129 (70.9)	40 (58)	0.06
- Hemihypoesthesia	64 (35.2)	27 (39.1)	0.44
- Hemianopsia	28 (15.4)	8 (11.6)	0.67
- Aphasia	90 (49.5)	25 (36.2)	0.08
- Dysarthria	49 (26.9)	11 (15.9)	0.06
Stroke Risk Factors			
- Stroke History	50 (27.5)	26 (37.7)	0.07
- Hypertension	116 (63.7)	51 (73.9)	0.10
- Smoking	53 (29.1)	13 (18.8)	0.08
- Diabetes	69 (37.9)	21 (30.4)	0.22
- Hyperlipidemia	38 (20.9)	16 (23.2)	0.50
- CAD	58 (31.9)	18 (26.1)	0.50
- AF	37 (20.3)	10 (14.5)	0.26
- Family History	55 (30.2)	17 (24.69)	0.33
Consciousness Level			
- Normal	129 (70.9)	56 (81.2)	0.09
- Somnolence/Stupor	53 (29.1)	13 (18.8)	
Transfer to Hospital			
- Ambulance	126 (69.2)	56 (81.2)	0.005*
- Other	34 (18.8)	13 (18.8)	
Arrival to Hospital			
- Direct Arrival	130 (71.4)	49 (71)	0.98
- Transfer from another Center	52 (28.6)	20 (29)	
NIHSS (During application)	5 (1-32)	3 (1-17)	0.01*
Information about thrombolytic therapy	14 (7.7)	2 (2.9)	0.15

Table 4. Multivariable logistic regression analysis

	Wald	p-value	OR	%95(GA) Min
Gender(female)	6.92	0.009	2.21	1.22
Transportation				
Private vehicle	3.32	0.068	1.80	0.96
Other	0.02	0.867	1.10	0.31
NIHSS	10.37	0.001	0.91	0.85

OR: Odds ratio, CI (Confidence Interval)

(mRS score $mRS \leq 2$) in 140 patients (55.7%) and poor functional outcome in 111 patients (44.3%) (mRS score > 2) were observed during discharge. Stroke-related features of the patients are reflected in Table 2. In comparing the socio-demographic and clinical characteristics of the patients according to the time of arrival, female gender ($p < 0.03$), having a low NIHSS score ($p < 0.03$) and not using ambulance in transportation ($p < 0.03$) affect the time of arrival to the hospital adversely (Table 3).

In the multivariable logistic regression analysis model, effective factors like gender, transportation to hospital and NIHSS variables were included, and the results of the analysis are presented in Table 4. The logistic regression model was found significant ($p < 0.001$) and the data set was seen to be compatible with the model ($p = 0.587$). When the table is examined, women have a 2.21 times higher risk of late admission to the hospital than men. The mode of transportation could not be determined as a risk factor on the duration of the arrival, and an increase in one unit to be observed in the NIHSS score reduced the risk of late arrival to the hospital by 9%.

DISCUSSION

In our study, we examined the conditions causing a delay in the period from the onset of stroke to the arrival of patients at a training and research hospital with a stroke center. We found that 182 patients (72.5%) arrived to the emergency ward of our hospital in the first 4.5 hours after the onset of the symptoms.

In the study carried out in Turkey by Memis et al. (4), 67% of the patients were reached the hospital diagnosed with acute ischemic stroke and in the study conducted by Guveli et al. (5) 30.7% of them reached the hospital within 3 hours after the onset of stroke symptoms. In another research supervised by Kocak et al. (6), 29.5% of patients reached the hospital ≤ 4 hours. In the study of Atay (22) in the district hospital, it was reported that 44.4% of the patients applied to the hospital within the first three hours and 48.9% within

the first 4.5 hours of the treatment period. Dimitriou et al (19) stated in their study that 68.7% of the patients were diagnosed with acute ischemic stroke, in the study conducted by Fladt et al. (23), 58% were reported to have applied to the hospital within the first 4.5 hours. In a city such as Bursa, where the traffic density is high and distances are remote, both public and healthcare staff trainings in favor of early treatment intervention may have played a role in the high rate of patients arriving within the first 4.5 hours. In addition, due to the fact that our hospital has been recognized as a stroke center, acute stroke patients can be primarily brought directly to our hospital by emergency medical service. This proves us that as long as a rapid in-hospital organization can be provided, eligible patients will not miss the chance to undergo thrombolytic therapy.

In some scientific studies, low income level has been reported as a factor related to the delayed arrival of patients with acute stroke (7). In some of the studies, no relation was observed between the income status and arrival at the hospital (8). In our study, we could not see a relationship between the income status and the arrival of the patients.

The relationship between the education level and the arrival time was also examined. In some studies, it was found that the level of education was low and this delayed the arrival of patients (7, 8, 9), and in some, there was no relationship between these two factors (10, 11, 12). In our study, no relation was found between the education level and the arrival of patients.

Another remarkable point in our study was that the distance was not related to a delay in arrival. Ashraf et al. (8) and Arulprakash et al. (12) found a distance of 15 km to the hospital was linked with a delay in transportation to the hospital in acute stroke patients. In another study by Nepal et al. (7), > 20 km distance was associated with a delay.

Arulprakash et al. (12) reported that urban residents were more likely to arrive to the hospital earlier, but we did not find residing in a city as a significant factor for early arrival. This may be due to the information provided to the patients and their relatives in advance and far-flung and vigorous effort of the emergency service teams throughout the city.

In the literature, some studies have found that female gender affects the time of arrival to the hospital (13-16) adversely, while some studies have stated that female gender affects hospital arrival (8, 17) positively. In some studies, there was no relationship between these two factors (9, 11, 12). In our study, we figured out that female gender affects the time of arrival to the hospital adversely. This may be due to the absence of a family member during the day who would activate the ambulance service while many of the patients are at

home alone or dealing with children or household chores. The fact that stroke cases in males are more frequent during the daytime, when they are actively involved in work life and socialized, may explain the early access to the hospital due to the presence of another person to call the ambulance directly.

In previous studies, using ambulance/emergency medical service has been shown to shorten the arrival time to the hospital (10, 13, 14, 15, 18, 19). The rate of ambulance use in acute stroke cases was reported to be 16.3% in the study of Memis et al (4) carried out in Aydın in our country. In the study conducted by Tekin Guveli et al. (5), the rate of ambulance use was reported as 30%. In these studies, the absence of using an ambulance in acute stroke cases was associated with delayed arrival at the hospital, similar to our study. In our study, 160 (63.7%) patients who were diagnosed with acute ischemic stroke were transferred to our hospital by ambulance. This rate shows that Emergency Health Services Ambulance System (112) is well organized in our city and the referral chain works regularly.

There are studies in the literature showing that the onset of the stroke symptoms at night delay the arrival of the hospital compared to the onset of daytime (7, 20). In our study, no relation was observed between the onset of symptoms as day and night and the time of arrival at the hospital.

Nepal et al. and Ashraf et al. (7, 8) stated that presence of stroke in patients' history did not shorten the arrival time to the hospital as in our study. This proves that there is a serious lack of awareness of stroke symptoms even in stroke patients. Training these patients and their relatives in recognizing the symptoms in hospital discharge and citing the importance of avoiding pre-hospital delays may reduce such hold-up situations.

Although some studies have found a link of a history of coronary heart disease related to early arrival at the hospital (8, 10), we did not detect a statistically significant relationship between the presence of stroke risk factors in the history such as hypertension, diabetes, coronary heart disease, and hospital arrival time.

We figured out that both lack of consciousness and low NIHSS score ($p < 0.03$) negatively affect the arrival time in our patients. In the literature, there are studies reporting that stroke duration of patients who are in a coma is shorter than other patients (10, 21, 23). This may be due to the vigorous efforts of the relatives

to deliver their patients with serious clinical conditions to a healthcare facility speedily. One of the remarkable points was that transfer from another center in our study was not a factor affecting the arrival time at the hospital. In some studies, it has been stated that the patient's first contact with the local doctor and the referral from another center is a cause linked with late arrival at the hospital (7, 8, 23).

Our study also contains some limitations. It may not be generalized because it represents a training and research hospital experience with a stroke center and the sample size is small. In addition, it included patients or relatives who were diagnosed with ischemic stroke and who agreed to participate in the study. These are the limitations of this research. Therefore, further studies involving more centers are required.

CONCLUSION

In conclusion, comparing the socio-demographic and clinical features of the patients according to the time of arrival at the hospital we can state that female gender ($p < 0.03$), low NIHSS score ($p < 0.03$) and the absence of an ambulance in transportation ($p < 0.03$) affect the time of arrival to the hospital adversely. In this respect, identifying these factors can also guide us in terms of solving problems resulting from time. This study also aims to increase the awareness of the use of emergency medical services.

Abbreviations

NIHSS — National Health Stroke Scale

mRS — Modified ranking scale

DM — Diabetes mellitus

CAD — Coronary artery disease

AF — Atrial fibrillation

OR — Odds ratio

CI — Confidence Interval

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Sažetak

FAKTORI KOJI UTIČU NA VREME PRIJEMA U BOLNICU PACIJENATA SA AKUTNIM ISHEMIJSKIM MOŽDANIM UDAROM

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Uvod: Poznato je da intravenska trombolitička terapija kod ishemijskog moždanog udara je od koristi kod odabranih pacijenata koji se jave u toku prvih 4,5 sata nakon pojave simptoma i efikasnost tretmana zavisi od brzog prijema u bolnicu. Što je više prijema pacijenata u ovom vremenskom okviru, veća je i šansa da će primiti trombolitičku terapiju. Cilj studije je da ispita faktore koji su uzrok kasnog prijema pacijenata sa ishemijskim moždanim udarom.

Metod: U studiju su uključeni pacijenti koji su se javili u neurološku ambulantu i hitnu službu u periodu između februara i maja 2019. i dijagnostikovani su akutni ishemijski moždani udar. Sproveden je odgovarajući direktni intervju kako bi se ispitali faktori koji su odlagali dolazak pacijenata ili rođaka pacijenata u Bursa Yuksek Ihtisas Training and Research Hospital zbog moždanog udara. Prema vremenu dolaska u bolnicu nakon pojave simptoma moždanog udara pacijenti su podeljeni kao rani ($\leq 4,5$ sati) i kasni dolazak ($> 4,5$ sati). Na osnovu ovog grupisanja, faktori koji izrokuju

kašnjenje u dolasku pacijenata u bolnicu su statistički poređeni.

Ukupno 251 pacijenata i/ili rođaka pacijenata koji su došli u prijemnu neurološku ambulantu su intervjuisani. Od 251 pacijenata uključenih u studiju, 119 (47,4%) je bilo ženskog pola i prosečne starosti 70 (34-94) godina. Od prilike 72,5% pacijenata se javilo u bolnicu u toku prvih 4,5 sata od pojave simptoma moždanog udara. Faktori koji su uzrokovali kasniji dolazak u bolnicu su ženski pol, nizak NIHSS skor i nekorišćenje ambulantskog vozila za transport.

Zaključak: Zbog kasnog dolaska u bolnicu 27,5% pacijenata, nije bilo moguće primeniti trombolitičku terapiju kod onih koji su ispunjavali uslove za nju. Kao faktori koji su razlog kasnog dolaska u bolnicu otriveni su ženski pol, manje težak moždani udar i transport bez ambulantskog vozila. S tim u vezi, potrebni su treninzi orijentisani prema zajednici.

KLjučne reči: ishemijski moždani udar, kasni dolazak u bolnicu, hitna služba, trombolitička terapija.

REFERENCES

1. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, et al. Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD 2010) and the GBD Stroke Experts Group. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet*. 2014; 383(9913): 245-54.
2. Lahr MM, Luijckx GJ, Vroomen PC, van der Zee DJ, Buskens E. Proportion of patients treated with thrombolysis in a centralized versus a decentralized acute stroke care setting. *Stroke*. 2012; 43(5): 1336-40.
3. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al. Effect of treatment delay, age and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta analysis of individual patient data from randomised trials. *Lancet*. 2014; 384(9958): 1929-35.
4. Memis S, Tugrul E, Evci ED, Ergin F. Multiple causes for delay in arrival at hospital in acute stroke patients in Aydin, Turkey. *BMC Neurol*. 2008; 8:15.
5. Tekin Guveli B, Yatmazoglu M, Acar E, Senadim S, Coban E, Dayan C, et al. Pre-hospital obstacles in thrombolytic therapy and suggested solutions. *Turkish Journal of Cerebrovascular Diseases*. 2015; 21(3): 194-97.
6. Kocak S, Dogan E, Kokcam M, Girisgin AS, Bodur S. Limitations in thrombolytic therapy in acute ischemic stroke: *Pak J Med Sci*. 2012; 28(4): 586-90.
7. Nepal G, Yadav JK, Basnet B, Shrestha TM, Kharel G, Ojha R. Status of prehospital delay and intravenous thrombolysis in the management of acute ischemic stroke in Nepal. *BMC Neurol*. 2019; 19(1): 155.
8. Ashraf VV, Maneesh M, Praveenkumar R, Saifudheen K, Girija AS. Factors delaying hospital arrival of patients with acute stroke. *Ann Indian Acad Neurol*. 2015; 18(2): 162-6.
9. Chen CH, Huang P, Yang YH, Liu CK, Lin TJ, Lin RT. Pre-hospital and in-hospital delays after onset of acute ischemic stroke: a hospital-based study in southern Taiwan. *Kaohsiung J Med Sci*. 2007; 23(11): 552-9.
10. Jin H, Zhu S, Wei JW, Wang J, Liu M, Wu Y et al. Factors associated with prehospital delays in the presentation of acute stroke in urban China. *Stroke*. 2012; 43 (2): 362-70.
11. Hong ES, Kim SH, Kim WY, Ahn R, Hong JS. Factors associated with prehospital delay in acute stroke. *Emerg Med J*. 2011; 28(9): 790-3.
12. Arulprakash N, Umaiorubahan M. Causes of delayed arrival with acute ischemic stroke beyond the window period of thrombolysis. *J Family Med Prim Care*. 2018; 7(6): 1248-52.

13. Saver JL, Smith EE, Fonarow GC, Reeves MJ, Zhao X, Olson D, et al. The “golden hour” and acute brain ischemia: presenting features and lytic therapy in > 30,000 patients arriving within 60 minutes of stroke onset. *Stroke*. 2010; 41(7): 1431–9.
14. Tong D, Reeves MJ, Hernandez AF, Zhao X, Olson DM, Fonarow GC, et al. Times from symptom onset to hospital arrival in the Get with the Guidelines – Stroke Program 2002 to 2009: temporal trends and implications. *Stroke*. 2012; 43(7): 1912–17.
15. Mandelzweig L, Goldbourt U, Boyko V, Tanne D. Perceptual, social, and behavioral factors associated with delays in seeking medical care in patients with symptoms of acute stroke. *Stroke*. 2006; 37(5): 1248–53.
16. Smith MA, Lisabeth LD, Bonikowski F, Morgenstern LB. The role of ethnicity, sex, and language on delay to hospital arrival for acute ischemic stroke. *Stroke*. 2010; 41(5): 905–09.
17. Lichtman JH, Watanabe E, Allen NB, Jones SB, Dostal J, Goldstein LB. Hospital arrival time and intravenous t-PA use in US Academic Medical Centers, 2001–2004. *Stroke*. 2009; 40(12): 3845–50.
18. Inatomi Y, Yonehara T, Hashimoto Y, Hirano T, Uchino M. Pre-hospital delay in the use of intravenous rt-PA for acute ischemic stroke in Japan. *J Neurol Sci*. 2008; 270(1-2): 127–32.
19. Dimitriou P, Tziomalos K, Christou K, Kostaki S, Angelopoulou SM, Papagianni M et al. Factors associated with delayed presentation at the emergency department in patients with acute ischemic stroke. *Brain Inj*. 2019; 33(9): 1257–61.
20. Soto-Cámara R, González-Santos J, González-Bernal J, Martín-Santidrian A, Cubo E, Trejo-Gabriel-Galán JM. Factors associated with shortening of prehospital delay among patients with acute ischemic stroke. *J Clin Med*. 2019; 8(10): E1712.
21. Lee SJ. Association between Prehospital Delay Status and Stroke Severity in Acute Ischemic Stroke: Shift-Analysis Approach. *J Nurs Care*. 2018; 7:452. doi: 10.4172/2167-1168.1000452.
22. Atay V. Acute stroke through the perspective of a county hospital: problems and opportunities. *Turk J Neurol*. 2016; 22(1): 13-8.
23. Fladt J, Meier N, Thilemann S, Polymeris A, Traenka C, Seiffge DJ et al. Reasons for Prehospital Delay in Acute Ischemic Stroke. *J Am Heart Assoc* 2019; 8(20): e013101.

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ROLE OF FACET JOINT ORIENTATION AND FACET TROPISM IN NONSPECIFIC LOW BACK PAIN

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Abstract: Background: Low Back Pain is a complaint at least once we experience all through our life. Although low back pain can be caused by several reasons, mostly low back pain due to nonspecific reasons can be encountered. In this study, our main goal is to examine facet tropism types and facet joint orientation in patients with nonspecific low back pain we have grouped according to age and determine if there is a relationship between the low back pain and facet joint morphology.

Patients and methods: We have retrospectively examined magnetic resonance imaging of 135 patients who applied to the neurosurgery clinic with low back pain complaint in the period of 2017-2018 year. For each phenomenon, facet joint angles have been measured at all vertebra levels. Average values of facet joint angles have been taken and facet orientation has been determined. The difference between right and left facet joint angle has been calculated; degree and type of facet tropism have been determined.

Results: It has been observed that facet joint orientation at L1-2 level was more coronalized in age group of 70-80 when compared to age group of 10-20. 'No type' facet tropism has been observed in majority of the phenomenon and no significant difference has been observed between lumbar levels and age groups.

Conclusion: As a result of our study; it has been concluded that facet joint orientation and facet tropism are not effective in the etiology of nonspecific low back pain. Furthermore, facet tropism is not related to age and maybe it is an inborn characteristic.

Key words: Lumbar vertebra, Low back pain, Magnetic resonance imaging, Facet joint angle, Facet Tropism.

INTRODUCTION

Low Back Pain (LBP) is a common complaint that occurs at least once in a lifetime and affects more than

80% of the entire population. LBP in women and through elderly age group encountered more frequently (> 40 age) (1). Plenty of causes are responsible for low back pain. Only below 1% portion, low back pain encompasses a specific cause (spinal stenosis, lumbar discopathy, infection, compression fracture, spondyloarthritis, radicular pain, cancer, visceral diseases eg) (2). Non-specific causes impactful in vast majority of LBP cases. Among the non-specific causes discogenic and facet joint originated pains while constituted the diagnostic cohort, in one cohort none of any mechanic cause issue may be set forth (3).

Facet joints located over the spine dorsolateral surface refers to diarthrodial joint and by the virtue of their complex anatomy and biomechanic features strongly contribute to spinal mechanic functions (4). Movements of facet joints; restricted by their articulations, orientations and capsular outcomes and therefore (facet joints) constraints the rotational movements of vertebra (5). Calculating the right and left facet joint angles average ratios facet joint orientations are determined. In vertebral segment dispersion in between right and left facet joint angles and a facet joint's more sagittal orientation in comparison to an alternative joint has been referred as facet tropism (5, 6). Asymmetric orientation in facet joint orientation while observed predominantly in thoracic vertebra not always observed in lumbar vertebra (6). Facet tropism and increased facet joint sagittal orientation are thought to cause intensified axial and rotational compression over the lumbar vertebra, associated with the developments of spinal deformations such as intervertebral disc degeneration, herniation, degenerative spondylolisthesis and scoliosis (7). Degenerative facet joint illness and facet joint osteoarthritis while correlated with chronic low back pain (8), facet joint orientation and facet tropism

function in link with low back pain remains unclear. In that present study, among patients segments classified on the basis of age factor with none of any neurosurgical pathology defining the low back pain, reviewing the facet joint orientation and facet tropism types, challenged to find out any association in between the low back pain progression and facet joint morphology.

PATIENTS AND METHODS

In our study, in between the years of 2016-2018 magnetic resonance imaging (MRI) images of 135 patients applied to our neurosurgery clinic with low back pain complaint and anamnesis records reviewed retrospectively. During the MRI imaging process of the entire cases, the patient was in supine position on the cassette and axial images received in parallel to the end plate. In our study inclusion criterion consisted of 1) in the age range of 10-80 years of age subject to admittance with backache attack, 2) neurologic detection of the case remaining under normal limits, 3) in 2 weeks or longer time period despite pain relief medication use lack of any decrease in pain and pain causing to constraints in daily life events, 4) As per radiologic inspections (X-ray or MRI) having lumbar lordotic preservation of shooting from different angles in normal limits. In our study exclusion criteria; 1) To have been undergone back surgery previously by any cause, 2) In MRI images having any pathology being diagnosed necessitating surgery attempt (lumbar discal hernia, spondylolisthesis, spondylolysis, tumor, scoliosis, fractures, infections, etc), 3) in the case presence of any low back pain leading congenital deformity, muscular, rheumatologic or neurodegenerative disease. MRI images of the cases analysed by two independent persons (one radiologist and one neurosurgeon). For each of the cases, along the entire levels of lumbar vertebra (L1-2, L2-3, L3-4, L4-5, L5-S1) facet joint measurements were made. On each level, mean values of facet joint angles (between the right and left facet joint) were calibrated finding out the facet orientation. Identified method of Noren et al., also used for facet joint angle measurement. For each facet joint; one line was drawn tangential to the superior articular process, and one line was drawn in the midsagittal plane of the vertebra, and the angle between facet joint and the central line has been measured (9). In pursuant to the method put forward by Boden; calculating the dispersion between the right and left joint angles facet tropism grade and its type were found out (5). According to Boden; no facet tropism (FT) with asymmetry in the facet joint orientation as defined difference of the angles between the right and left facet $\leq 6^\circ$; mild FT as defined difference of the angles between the right and left facet 6-10E;

moderate FT as defined difference of the angles between the right and left facet 11-16 $^\circ$; severe FT as defined difference of the angles between the right and left facet $> 16^\circ$ (5). In 7 age based diversified groups, along the all vertebral levels mean facet joint angles and facet tropism types were compared with each other.

Statistical analysis

For statistical analysis NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used. During the evaluation of study data descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) were applied. Qualitative data normal distribution longitudes were examined by Kolmogorov-Smirnov, Shapiro-Wilk test and graphical assessments. In the comparisons of normal distribution exhibiting three and over three groups One-way Anova Test and in bilateral comparisons Bonferroni test were implemented. Significance at least evaluated on $p < 0.05$ level.

RESULTS

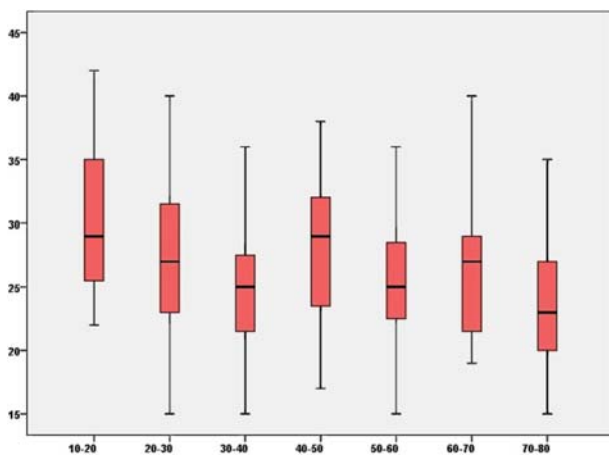
Applied to neurosurgery clinic with low back pain complaint and as we analysed in MRI inspections out of 135 patients 56.3% ($n = 76$) were female and 43.7% ($n = 59$) were male. Ages of the cases varied in the range of 12 and 77, on average corresponds to 45.53 ± 18.07 years of age; among the cases 11.9% ($n = 16$) remained in 10-20 ages, 11.1% ($n = 15$) remained in 20-30 years of age; 20.7% ($n = 28$) remained in the age of 30-40, 14.1% ($n = 19$) remained in the age of 40-50; 14.8% ($n = 20$) remained in the age of 50-60 years of age, 17.0% ($n = 23$) remained in the age of 60-70 and 10.4% ($n = 14$) remained in the age of 70-80 (Table 1). In age based L1-2 levels of the cases, mean FJA measurements revealed a statistically significant weighted variation ($p = 0.031$; $p < 0.05$) (Figure 1). Searching out to determine the group that leads to dispersion as a

Table 1: Distribution of cases by age and sex

Age (year)	n (%)	
	Min-Max (Median)	12-77 (44)
	Mean $\pm$ Std	45.53 $\pm$ 18.07
	10-20	16 (11.9)
	20-30	15 (11.1)
	30-40	28 (20.7)
	40-50	19 (14.1)
	50-60	20 (14.8)
	60-70	23 (17.0)
	70-80	14 (10.4)
Sex	Female	76 (56.3)
	Male	59 (43.7)

Table 2. Evaluation of mean facet joint angle values at lumbar vertebral levels according to age groups

Age Groups		FJA L1-2	FJA L2-3	FJA L3-4	FJA L4-5	FJA L5-S1
10-20¹ (n = 16)	Min-Max (Median)	22-42 (29)	23-43 (30)	28-46 (32)	29-57 (40)	28-58 (45,5)
	Mean $\pm$ Std	30.44 $\pm$ 6.24	30.56 $\pm$ 5.01	34.75 $\pm$ 6.20	41.38 $\pm$ 6.02	45.69 $\pm$ 7.01
20-30² (n = 15)	Min-Max (Median)	15-40 (27)	17-40 (29)	20-54 (33)	24-56 (42)	35-50 (45)
	Mean $\pm$ Std	26.87 $\pm$ 7.02	29.00 $\pm$ 6.73	34.27 $\pm$ 8.09	41.00 $\pm$ 7.91	43.07 $\pm$ 5.28
30-40³ (n = 28)	Min-Max (Median)	15-36 (25)	15-41 (28,5)	18-52 (35,5)	20-64 (43,5)	36-66 (45,5)
	Mean $\pm$ Std	25.25 $\pm$ 5.02	29.25 $\pm$ 6.29	35.29 $\pm$ 8.24	42.14 $\pm$ 8.08	47.14 $\pm$ 8.58
40-50⁴ (n = 19)	Min-Max (Median)	17-38 (29)	15-42 (28)	17-48 (34)	31-58 (41)	32-66 (46)
	Mean $\pm$ Std	28.11 $\pm$ 6.15	28.26 $\pm$ 6.10	34.16 $\pm$ 8.37	41.89 $\pm$ 6.66	46.95 $\pm$ 9.61
50-60⁵ (n = 20)	Min-Max (Median)	15-36 (25)	19-35 (27,5)	26-42 (31,5)	20-58 (43)	36-65 (45,5)
	Mean $\pm$ Std	25.05 $\pm$ 5.90	27.55 $\pm$ 5.37	32.15 $\pm$ 5.58	41.40 $\pm$ 8.05	47.40 $\pm$ 7.38
60-70⁶ (n = 23)	Min-Max (Median)	19-40 (27)	18-42 (27)	22-42 (36)	25-53 (43)	34-64 (45)
	Mean $\pm$ Std	26.78 $\pm$ 5.74	28.35 $\pm$ 5.33	34.22 $\pm$ 6.07	41.74 $\pm$ 6.99	46.22 $\pm$ 8.11
70-80⁷ (n = 14)	Min-Max (Median)	15-35 (23)	13-41 (27,5)	23-43 (34,5)	27-53 (43)	42-57 (49)
	Mean $\pm$ Std	23.79 $\pm$ 5.04	26.79 $\pm$ 7.15	32.50 $\pm$ 5.46	41.50 $\pm$ 7.25	49.43 $\pm$ 5.17
^a <i>p</i>		0,031*	0,661	0,786	0,999	0,461
^b <i>Post Hoc test;</i> <i>p</i>		$p_1 > p_7$	-	-	-	-

^aOne-way ANOVA Test^bBonferroni Test* $p < 0.05$ **Figure 1.** Age based L1-2 level 'mean facet joint angle' measures distribution

result of the performed bilateral comparisons; 10-20 age group cases L1-2 levels mean FJA measurements are higher than 70-80 age group ($p = 0.047$; $p < 0.05$). Among the other group's L1-2 levels mean FJA measurements none of statistically weighted diversions was found. Age based L2-3, L3-4, L4-5 and L5-S1 levels of the cases mean facet joint angle calculations are not statistically significant (Table 2). As a result of these data only at L1-2 levels facet joint orientation found to be significantly differentiated in the age group of 10-20

Table 3. Distribution of Mean facet joint angle values by vertebral levels according to gender

	Female Group FJA		Male Group FJA	
	Mean	Std	Mean	Std
L1-2	27.4	6.2	25.4	5.5
L2-3	29.2	5.9	27.7	5.8
L3-4	34.8	7.0	33.1	7.1
L4-5	42.6	7.7	40.4	6.3
L5-S1	46.0	7.5	47.4	7.8

and in the age group of 70-80 was significantly different and in the age group of 70-80 L1-2 facet joint orientation was monitored to be more coronalized. In the light of other level's mean facet joint angle ratios, based on ages facet joint orientations found not to have had any significant dispersion (Table 2).

On the basis of gender issues when the facet joint angle rates were compared; only at L4-5 levels in between the male and female gender groups found in statistical significance ($p = 0.02$; $p < 0.05$) and except L5-S1 level in all groups female mean facet joint angle value found higher than male gender and as a result of these figures on female at L4-5 level, facet joint sagitalization found to be more predominant (Table 3, Figure 2).

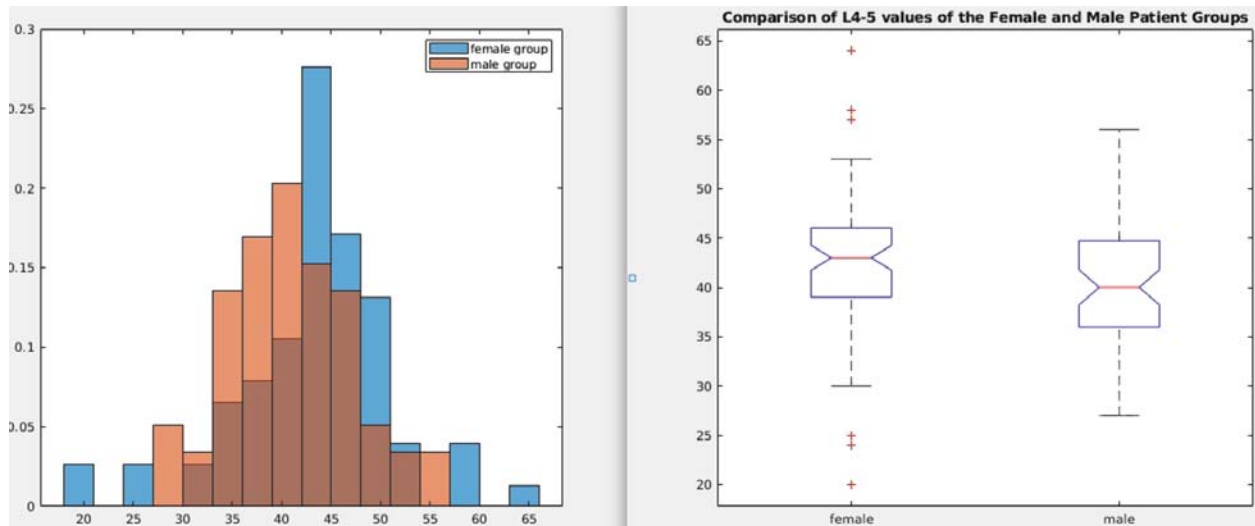


Figure 2. Comparison of L4-5 mean FJA angle values of the male and female patient groups

Table 4. Facet Tropism Types According to Lumbar Vertebral Levels

		Facet Tropism Types According to Lumbar Vertebral Levels				
Age Groups	FT Type	L1-2 # of patients	L2-3 # of patients	L3-4 # of patients	L4-5 # of patients	L5-S1 # of patients
10-20	None	16 (100%)	13 (81%)	13 (81%)	13 (81%)	11 (69%)
	Mild	0 (0%)	3 (19%)	3 (19%)	1 (6%)	0 (0%)
	Moderate	0 (0%)	0 (0%)	0 (0%)	2 (13%)	4 (25%)
	Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (6%)
20-30	None	13 (87%)	10 (67%)	11 (73%)	15 (100%)	14 (93%)
	Mild	2 (13%)	5 (33%)	3 (20%)	0 (0%)	1 (7%)
	Moderate	0 (0%)	0 (0%)	1 (7%)	0 (0%)	0 (0%)
	Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
30-40	None	21 (75%)	28 (100%)	28 (100%)	24 (86%)	18 (64%)
	Mild	7 (25%)	0 (0%)	0 (0%)	4 (14%)	7 (25%)
	Moderate	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (7%)
	Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)
40-50	None	14 (74%)	15 (79%)	16 (84%)	17 (90%)	12 (63%)
	Mild	5 (26%)	3 (16%)	2 (11%)	1 (5%)	6 (32%)
	Moderate	0 (0%)	1 (5%)	1 (5%)	1 (5%)	1 (5%)
	Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
50-60	None	14 (70%)	17 (85%)	17 (85%)	18 (90%)	12 (60%)
	Mild	6 (30%)	2 (10%)	1 (5%)	1 (5%)	4 (20%)
	Moderate	0 (0%)	1 (5%)	2 (10%)	1 (5%)	2 (10%)
	Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (10%)
60-70	None	18 (78%)	20 (87%)	20 (87%)	16 (70%)	15 (66%)
	Mild	4 (17%)	2 (9%)	3 (13%)	6 (26%)	4 (17%)
	Moderate	1 (5%)	1 (4%)	0 (0%)	1 (4%)	4 (17%)
	Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
70-80	None	12 (86%)	11 (79%)	10 (71%)	8 (57%)	8 (57%)
	Mild	0 (0%)	1 (7%)	1 (7%)	2 (14%)	3 (22%)
	Moderate	2 (14%)	2 (14%)	3 (22%)	1 (7%)	2 (14%)
	Severe	0 (0%)	0 (0%)	0 (0%)	3 (22%)	1 (7%)
Total Group	None	108 (80%)	114 (84%)	115 (85%)	111 (82%)	90 (67%)
	Mild	24 (18%)	16 (12%)	13 (10%)	15 (11%)	25 (18%)
	Moderate	3 (2%)	5 (4%)	7 (5%)	6 (4%)	15 (11%)
	Severe	0 (0%)	0 (0%)	0 (0%)	3 (3%)	5 (4%)

Upon the assessment of facet tropism type cases; through the entire vertebral levels and along the entire age cohorts 'none type facet tropism' found to be dominant (Table 4). L1-2 level when reviewed based on age groups, "none type facet tropism" found to be at utmost dominant in the age groups of 10-20 years of age. Severe type facet tropism, vast majority having been accumulated in L5-S1 level found to be only on L4-5 and L5-S1 age groups (Table 4).

DISCUSSION

Low back pain is one of the most frequently met illnesses in daily practice and 70% of the people experience low back pain at least once in their lifetime. LBP is more frequent in women and through the advanced ages (40-69) its incidence is enhanced, none of any difference has been encountered in terms of its incidence between the rural and urban area (2). Over the vast majority of LBP patients since the pain has gone away spontaneously hospitalization frequency is seldom and most of the hospitalization admittance is detected in women cases (10). Minor age and adolescence low back pains are seldom and in a study incorporated encompassing wide-range of case numbers adolescence low back pains found in 37% frequency and adolescent low back pains found higher over the girls in comparison with boys (11). During the adolescence and minor age period cases undergone low back pain are anticipated to experience low back pain in adults (11). In finalized systemic reviews determined low back pains associated risk factors: known as lifting, smoking, obesity, anthropometric measures, posture, depressive symptoms (12). Principally, during the adolescence, psycho-social factors play a significant role in low back pains (13). Low back pain is faced by us due to specific and unspecific underlying factors. Specific underlying factors are known as pathologies impacting the vertebra (epidural abscess, compression fracture, spondyloarthropathy, cauda equine syndrome, discopathy, spinal stenosis, malignity, visceral diseases, eg) (3). Most of the low back pains (90%) originated from non-specific causes. Whereas nonspecific low back pain may be diversified as diagnosable and non-diagnosable and several structures likewise intervertebral disc and facet joints may be the underlying cause factors (14). Diagnosable group; while progressed in association with facet joint associated pains, sacroiliac pathologies, discogenic issues; non-diagnosable group are progressed depending on psycho-social or other causes and in terms of radiologic detections a pathology is not detected (2, 3). In our present research we have analysed the cases with non-diagnosable nonspecific low back pain.

Since low back pain is very often encountered problem; spine surgeons are concentrated on the pre-

vention of low back pain, determination of potential risk factors and upon the selection of efficient therapeutic approach. In due course, plenty of studies are present incorporated in association with facet joints.

Final orientations of facet joints; in combination with vertical loading and flexion-extension movements anticipated to be formed during early childhood (15), however, in plenty of researches lifelong remodelling reported to have been sustained (16). Coronal oriented facet joints reported to play role in abundant magnitude of lumbar vertebra pathologies, whereas contrarily sagittialized facet joints reported in wide-spread of studies playing roles in a lot of events such as degenerative spondylolisthesis, spinal stenosis, disc herniation (16, 17). Boden et al., have shown that degenerative spinal changes are 25 times more in patients with facet joint sagittal orientation of over 45 degrees (5). From the second decade of life predominantly on intervertebral disc vertebra degenerative processes are launched and low back pain principal cause refers to degenerative causes (18). Emerging in line with advanced age as one of degenerative event facet joint osteoarthritis is one of chronic low back pain cause (18). Kalichman et al (12) in between the age and facet orientation principally at L4-5 level found an association and reported the facet's reinforcing potential for sagitalizations subject to age advancements and proved the fact that this case is associated with facet joint osteoarthritis. In our present study, selecting facet joint non-osteoarthritis and non-discopathy cases, we have intended to exclude the low back pain degenerative causes in advance aged cases. In our study; non-facet joint osteoarthritis form diversified based on age levels in non-specific low back pain cases according to lumbar vertebra levels between the facet joint orientations and mean facet joint angle values none of weighted variation was monitored and only in cases in age groups of 70-80 age and 10-20 ages L1-2 level facet joints found in significant difference and again only in age group of 70-80 age L1-2 level facet joints have been found in more coronalized pattern. But, since none of significant dispersions are found in between other levels and age groups; we have aspired that facet joint orientations is not correlated with age factor.

Facet tropism is one of the factors accelerating the development of spinal degeneration (5, 19, 20). Brailford (21) defined facet tropism as a more sagittal oriented form of a one side facet joint and as an asymmetry between the right and left facet joint angles. Karacan et al. (22) identified facet tropism, as an angle gauge differentiation over 10 degree between the two of facet joint. In the same study, lumbar movement segment facet tropism ratio defined in the range of 14-28% (22). During the vertebra sagittal movement

(flexion and extension) zygapophyseal joint of every joint displaced by sliding motion overlapping on each other. One of the each facet joints if placed more closer towards the coronal space prevent front and retro plane movements and cause rotation of vertebra against the facet joint closer to sagittal space (23). Ishihara et al (24) compared the facet joint asymmetry and tropism of adolescents and adults with lumbar disc hernia and in the adolescents found 5 times higher facet joint asymmetry. Some of the researchers suppose that facet tropism may be genetic and not associated with age, gender and ethnic origin (25). In the same way, some of the studies exist reporting facet joint sagitalization may be progressed with age and therefore also facet tropism is progressed in line with advancing age (26). In our study according to genders we have not determined any significant variation between FT types and in vast majority of the cases we have identified 'none type FT'. Mean facet joint angle values was statistically higher in female gender and at L4-5 level facet orientation was more sagitalized. Moreover, we have identified none of association in between the advancing age and facet tropism development and type.

In literature, none of any studies were found exploring facet tropism role over non-specific low back pain over the cases classified according to ages in which discal pathology or degenerative spinal variations underestimated. In our study FT type of all levels in all patient groups have been found to be at similar frequencies and through the vast majority of cases 'no type FT' was determined.

CONCLUSION

As a result of our study; as a result of mean facet joint angle measurement only in 70-80 age group in comparison with 10-20 age group L1-2 facet joint angles monitored in more coronalized form. On the other levels and according to ages due to lack of significant dispersion facet joint orientation found to have none of role related to non-specific low back pain. In female gender at L4-5 level mean facet joint angle measurements found to be elevated compared to males. In that circumstance, only concerning L4-5 level facet joint orientation exhibited gender variation and in females, L4-5 facet joints were in a more sagitalized pattern. Additionally, we have supported the fact that FT is not correlated with age and gender and perhaps it is a congenital pattern. In cases with non-specific low back pain without any surgical pathology, it has been proved that there is no cause factor to explain the FT low back pain.

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Sažetak

ULOGA ORIJENTACIJE FASETNIH ZGLOBOVA I FASETNI TROPIZAM KOD NESPECIFIČNOG BOLA U DONJEM DELU LEĐA

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Uvod: Bolove u donjem delu leđa smo svi osetili barem jednom u životu. Iako bolovi u donjem delu leđa mogu biti uzrokovani mnogobrojnim faktorima, najčešće se javljaju zbog nespecifičnih razloga. Glavni cilj ove studije bio je da se ispita tip fasetnog tropizma i orijentacija fasetnog zglobova kod pacijenata sa nespecifičnim bolom u donjem delu leđa koje smo grupisali prema godinama i da se utvrdi postoji li veza između bolova u donjem delu leđa i morfologije fasetnog zglobova.

Pacijenti i metode: Retrospektivno smo sagledali nalaze magnetnih rezonanci 135 pacijenata, koji su se javili u Neurohiruršku Kliniku sa bolom u donjem delu leđa u periodu od 2017-2018. te godine. Za svaki feno-

men, uglovi fasetnih zglobova su bili mereni na svakom kičmenom pršljenu. Srednja vrednost uglova fasetnih zglobova kao i fasetna orijentacija su bile određivane. Procenjivana je dalje razlika između levog i desnog ugla fasetnih zglobova, kao i stepen uglova i tip fasetnog tropizma.

Rezultati: Uočeno je da orijentacija fasetnih zglobova na nivou L1-2 je više koronalizovana u starijoj grupi od 70-80 godina u poređenju sa grupom pacijenata od 10-20 godina. Fasetni tropizam grupe „Bez određenog tipa“ je bio registrovan kod najvećeg broja pacijenata i nije utvrđena značajna statistička razlika između lumbalnih nivoa, niti između starosnih grupa.

Zaključak: Kao rezultat studije, može se zaključiti da zglobna orijentacija fasetnih zglobova, kao i tropizam fasetnih zglobova nisu efektivni u određivanju etiologije nespecifičnog bola u donjem delu leđa. Šta više tropizam fasetnih zglobova nije povezan sa godi-

nama, što može ukazivati na moogućnost urođenih karakteristika.

Ključne reči: lumbalni pršljenovi, bol u donjem delu leđa, magnetna rezonanca, ugao fasetnih zglobova, tropizam fasetnih zglobova.

REFERENCES

1. Henschke N, Maher CG, Refshauge KM, Herbert RD, Cumming RG, Bleasel J, et al. Prevalence of and screening for serious spinal pathology in patients presenting to primary care settings with acute low back pain. *Arthritis Rheum.* 2009; 60(10): 3072-80.
2. Maher C, Underwood M, Buchbinder R. Non-specific low back pain. *Lancet.* 2017; 389(10070): 736-47.
3. Deyo RA, Rainville J, Kent DL. What can the history and physical examination tell us about low back pain? *JAMA.* 1992; 268(6): 760-5.
4. An HS, Masuda K, Inoue N. Intervertebral disc degeneration: biological and biomechanical factors. *J Orthop Sci.* 2006; 11(5): 541-52.
5. Boden SD, Riew KD, Yamaguchi K, Branch TP, Schellinger D, Wiesel SW. Orientation of the lumbar facet joints: association with degenerative disc disease. *J Bone Joint Surg Am.* 1996; 78(3): 403-11.
6. Varlotta GP, Lefkowitz TR, Schweiter M, Ericco TJ, Spivak J, Bendo JA, et al. Lumbar facet joint: a review of the current knowledge: Part 1: Anatomy, biomechanics, and grading. *Skeletal Radiol.* 2010; 40(1): 13-23.
7. Chadha M, Sharma G, Arora SS, Kochar V. Association of facet tropism with lumbar disc herniation. *Eur Spine J.* 2013; 22(5): 1045-52.
8. Jelec V, Turner R, Franic M, Korusic A, Rotim K. Facet orientation and tropism: Association with accelerated degeneration of stabilizing structures in lower lumbar spine. *Acta Clin Croat.* 2016; 55(1): 117-24.
9. Hirsch C. Etiology and pathogenesis of low back pain. *Isr J Med Sci.* 1966; 2: 362-70.
10. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries. 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet.* 2015; 386(9995): 743-800.
11. Swain MS, Henschke N, Kamper SJ, Gobina I, Ottona-Jordan V, Maher CG. An international survey of pain in adolescents. *BMC Public Health.* 2014; 14: 447.
12. Kalichman L, Suri P, Guermazi A, Li L, Hunter DJ. Facet orientation and tropism: association with facet joint osteoarthritis and degeneratives. *Spine.* 2009; 34(16): 579-85.
13. Kamper SJ, Henschke N, Hestbaek L, Dunn KM, Williams CM. Musculoskeletal pain in children and adolescent. *Braz J Phys Ther.* 2016; 20(3): 275-84.
14. Hancock MJ, Maher CG, Latimer J, Spindler MF, McAuley JH, Laslett M, et al. Systematic review of tests to identify the disc, SIJ or facet joint as the source of low back pain. *Eur Spine J.* 2007; 16(10): 1539-50.
15. Mahato NK. Facet dimensions, orientation and symmetry at L5-S1 junction in lumbosacral transitional states. *Spine.* 2011; 36(9): 569-73.
16. Masharawi YM, Alperovitch-Najenson D, Steinberg N, Dar G, Peleg S, Rothschild B, et al. Lumbar facet orientation in spondylolysis: a skeletal study. *Spine.* 2007; 32(6): 176-80.
17. Wang J, Yang X. Age related changes in the orientation of lumbar facet joints. *Spine.* 2009; 34(17): 596-8.
18. Quint U, Wilke HJ. Grading of degenerative disk disease and functional impairment: imaging vs patho-anatomical findings. *Eur Spine J.* 2008; 17(12): 1705-13.
19. Arnoldi CC, Brodsky LE, Cauchoix J, Crock HV, Dommissie GF, Edgar MA, et al. Lumbar spinal stenosis and nerve root entrapment syndromes: definition and classification. *Clin Orthop Relat Res.* 1976; 115: 4-5.
20. Noren R, Trafimow J, Andersson GB, Huckman MS. The role of facet tropism and facet angle in disc degeneration. *Spine.* 1991; 16(5): 530-2.
21. Brailsford JH. Deformities of the lumbosacral region of the spine. *Br J Surg.* 1928; 16: 562-627.
22. Karacan I, Aydin T, Sahin Z, Cidem M, Koyuncu H, Aktas I et al. Facet angles in lumbar disc herniation: their relation to anthropometric features. *Spine.* 2004; 29(10): 1132-6.
23. Fujiwara A, Tamai K, An HS, Lim TH, Yoshida H, Kurihashi A et al. Orientation and osteoarthritis of the lumbar facet joint. *Clin Orthop Relat Res.* 2001; 88:94.
24. Ishihara H, Matsui H, Osada R, Ohshima H, Tsuji H. Facet joint asymmetry as a radiologic feature of lumbar intervertebral herniation in children and adolescents. *Spine.* 1997; 22(17): 2001-4.
25. Pinheiro MB, Ferreira ML, Refshauge K, Ordonana JR, Machado GC, Prado LR, et al. Symptoms of depression and risk of new episodes of low back pain: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken).* 2015; 67(11): 1591-603.
26. Kong MH, He W, Tsai YD, Chen NF, Keorochana G, Do DH et al. Relationship of facet tropism with degeneration and stability of functional spinal unit. *Yonsei Med J.* 2009; 50(5): 624-9.

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THE ASSOCIATION OF RECURRENT ABDOMINAL PAIN AND HELICOBACTER PYLORI INFECTION IN CORRELATION WITH ESOPHAGOGASTRODUODENOSCOPY FINDINGS

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Abstract: Aim: The aim of this research was to determine the association of recurrent abdominal pain and *Helicobacter pylori* (*H. pylori*) infection in childhood, in correlation with the finding of an upper endoscopy.

Introduction: Recurrent abdominal pain (RAP) was defined according to Apley and Naish's criteria from the year 1959 as at least three or more episodes of abdominal pain lasting longer than three months in children older than 3 years, and severe enough to prevent normal activities in child. The association of RAP and *H. pylori* has been analyzed in several different researches, and there are conflicting results about their interconnection.

However, the ethiological association of the presence of *H. pylori* with the onset and development of acute and chronic active gastritis and duodenal ulcer is known.

Material and method: The research protocol included a total of 77/183 (42.07%) children divided by age into three subgroups: preschool age (3 to 6.9 years), school age (7 to 10.9 years) and adolescent age (11 to 15 years) in whom the diagnosis of RAP was determined by meeting the criteria according to Apley and Naish (1959), and the American Academy of Pediatrics (2005). *H. pylori* infection was confirmed by enzyme-linked immunosorbent assay (ELISA), while esophagogastroduodenoscopy was performed by the device for upper endoscopy type Olympus GIF Type Q156, in the endoscopic cabinet of the Clinic for Internal Medicine, University Clinical Center Tuzla.

Results: Of the total number of examined children (77), the analysis of *Helicobacter pylori* infection presence showed the biggest number of positive findings in school age 91.3%, in adolescent age 78.0%,

while the smallest number was in preschool age (25.0%). The most common findings of upper endoscopy and microscopic findings were described as: antritis acuta in 16%, gastritis chronica activa et erosiva in 32%, and duodenitis acuta (12%).

Conclusion: A significant association of *H. pylori* infection and RAP are confirmed by positive finding of esophagogastroduodenoscopy, leading to conclusion that immunological testing for the presence of this bacteria is justified. After obtaining a positive finding with confirmed infection, it is necessary to start with the treatment.

Key words: recurrent abdominal pain, *Helicobacter pylori*, esophagogastroduodenoscopy.

INTRODUCTION

For many years recurrent abdominal pain (RAP) has been defined in the world literature according to generally accepted criteria proposed by Apley and Naish in the year 1959 as follows: at least three or more episodes of abdominal pain lasting longer than three months in children older than 3 years, and severe enough to prevent normal activities in child (1).

Abdominal pain is one of the most common childhood symptom occurring in 9% to 16% of children, and accounts for 35% to 45% of all examinations in specialists gastroenterology ambulatory (2, 3). Although the exact RAP prevalence cannot be determined, this diagnosis is considered to be responsible for 2% to 4% of all visits to a specialist pediatrician in America, while 13% to 19% of all school children experience this painful episode at least once a week. As Andrews et al. point out, RAP combined with other symptoms greatly disturbs not only school activities and psychosocial

function, but also disturbs the overall quality of life of the child and his family (4).

Most basic printbooks cite the entire array of possible causes of abdominal pain on the basis of which the division of RAP into organic, functional (nonspecific) and psychogenic is made (5, 6, 7). Organic causes of pain have their etiology intraabdominally, and they are the result of the presence of abnormal anatomical, structural or disordered physiological processes such as inflammatory, metabolic, infectious and neoplastic changes (7, 8).

Seng Hock Quak (8) and Bufler et al. (9) defined the most common organic causes of recurrent abdominal pain:

- food intolerance (primary or secondary lactose intolerance, fructose malabsorption)
- gastroesophageal reflux and esophagitis (eosinophilic esophagitis),
- peptic ulcer with or without *Helicobacter Pylori* infection,
- chronic inflammatory bowel disease (Crohn's disease, ulcerative colitis),
- gluten enteropathy,
- diseases of the hepatobiliary tract,
- pancreatitis,
- anatomical malformations (Mekel's diverticulum, intestinal malrotations and duplications, annular pancreas),
- infectious intestinal diseases (*Yersinia enterocolica*, *Yersinia pseudotuberculosis*, *Entamoeba histolytica*, parasitosis)
- neoplasms,
- dysmenorrhea,
- urinary tract infection (8, 9).

The association of RAP and *H. pylori* infection has been analyzed in several different studies, and there are conflicting results about their interconnection (10, 11, 12).

The etiological association of the presence of *H. pylori* with the onset and development of acute and chronic active gastritis, duodenal ulcer and malignant diseases such as gastric lymphomas and adenocarcinomas is known (13, 14). Although opinions on the presence of *H. pylori* in children with RAP are divided (15, 16), recent studies that have been made worldwide suggest their significant association (2, 11, 12, 17).

Helicobacter pylori is a gram-negative, microaerophilic, spiral-shaped bacteria of high motility from the spirillaceae family, and it has 4-6 unipolar flagella. This bacteria lives within the gastric mucus layer overlying the gastric epithelial cells. To survive in the hostile acid environment of the stomach, *H. pylori* produces the enzyme urease which converts urea from gastric acid into ammonia and carbon dioxide, whereby reduces acidity

and creates favorable conditions for life of this bacteria. This feature of *H. pylori* forms the basis for some diagnostic tests such as rapid urease test and urea breath test.

Many recent studies have confirmed that the only known source of *H. pylori* infection are humans. The route of transmission of the infection is mainly by oro-oral, faeco-oral and gastric-oral route. *H. pylori* is mainly transmitted within families, from parents to children, respectively from the elderly of the third generation to their children, as well as between siblings. Researches data confirm that transmission from children to children is most common in overcrowded schools, also in institutions for care of children with disabilities. Immigrants who arrived from underdeveloped countries, American-born children whose parents are immigrants, and even children who are adopted from developing countries form a group of a high risk individuals carrying the bacteria *H. pylori* (17, 18).

The role of *H. pylori* infection in the onset of RAP is not significant because it is considered that this bacteria does not cause stomach pain (13, 14), while research from the year 2012 suggests that there is no direct connection of RAP with *H. pylori* infection. There was no statistically significant difference between the group of *H. pylori* positive and negative children in the symptoms of RAP, as well as the symptoms of vomiting and sideropenic anemia (18). According to Nasphgan's recommendation, the aim of diagnostic procedures in the onset of RAP in children is to determine the cause of present symptoms before determining the presence of *H. pylori* infection (7, 19).

Significance of esophagogastroduodenoscopy in the differential diagnosis of recurrent abdominal pain

Esophagogastroduodenoscopy (EGD) has become a common procedure in the evaluation of RAP in children. According to the research results by the Pediatric Endoscopy Databases System-Clinical Outcomes Research Initiative (PED-CORI), endoscopy finding was positive in 38% of children with a positive anamnesis of recurrent abdominal pain, whereby this endoscopic procedure was justified (20). Most authors state that EGD is not recommended in the evaluation of RAP without clearly defined symptoms of the disease (21, 22, 23).

The definition of functional gastrointestinal pain in children based on the Rome II criteria fully meets the RAP criteria set by the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) (5). They state that negative EGD does not confirm the functional etiology of RAP, respecti-

vely it does not exclude the possibility of organic basis for disease of the gastrointestinal tract (21).

According to NASPGHAN there is no significant justification for EGD in children with RAP who do not show warning symptoms such as: involuntary weight loss ($> 10\%$ of body weight), delayed linear growth, gastrointestinal bleeding, significant vomiting, chronic diarrhea, nocturnal pain that disrupts child's sleep, positive family history on inflammatory bowel disease, unexplained fever, delayed puberty, reproductive system disturbances, dysuria, arthritis (7,9,24), or warning signs such as: enlargement of the abdomen, presence of pathological peristalsis, any abnormal palpation finding of the abdomen and typical localization of pain in the right upper and the lower quadrant of the abdomen (9).

The importance of EGD is not only based on adequate diagnosis, but also on the need to eliminate the symptoms and signs of RAP, respectively in the application of therapeutic treatment that will enable recovery from the underlying pathogen and allow the child and his family to return to everyday activities (2). Frank et al. in their study highlight the importance of eradicating *H. pylori* infection for the prevention of gastric and duodenal ulcers in childhood and the possibility of gastric cancer in adulthood (25). The aim of this research was to determine the association of recurrent abdominal pain and *Helicobacter pylori* infection in childhood, in correlation with the finding of an upper endoscopy.

PATIENTS AND METHODS

The prospective research in the examined period from 1st December 2011. to 1st December 2012., conducted in an Outpatient clinic for gastroenterology and the Department for gastroenterology, Clinic for children's diseases, University Clinical Center Tuzla (UCC) included 1013 children aged 3-15 years old, of whom RAP had 183/1013 (18.6%) children. From total number of respondents, 106 children did not meet the research criteria. All data of our patients were acquired based on available medical documentation (illness history and medical charts), questionnaire, physical examination and laboratory findings. Data for questionnaires was gathered from parents of patients, with their consent in accordance with procedure in UCC Tuzla.

Inclusion criteria for the research were:

- The diagnosis of RAP was established by meeting Apley and Naish (1) and the American Academy for Pediatrics (24) criteria, which included more than three episodes of abdominal pain that occur over at least three months in children older than 3 years, severe enough to affect the child's ability to perform normal activities, and require intervention by the doctor (1, 24).

- that the patients are up to 15 years of age on the day of examination.

The study included 183 children of whom two groups were formed; examined group $N = 70$ with a positive finding of esophagogastroduodenoscopy and control group $N = 7$ children with a negative finding of esophagogastroduodenoscopy. Respondents of both groups were also divided according to age into three subgroups:

- preschool age (from 3 to 6.9 years)
- school age (from 7 to 10.9 years) and
- adolescence (from 11 to 15 years)

Criteria for **excluding** respondents from the study were: failure to meet the criteria for the diagnosis of RAP according to the stated criteria, that the ages are under 3 years and over 15 years on the day of the examination, children with cystic fibrosis, children with organ transplants, Down syndrome, cerebral palsy, microcephaly and neurodegenerative diseases because in these children the etiology of pain differs significantly from the general population, have used proton pump inhibitor therapy, metronidazole or clarithromycin for at least two weeks before the test, children after thoracic and abdominal surgery, respondents for whom we did not obtain written consent for inclusion in the survey.

Indications for esophagogastroduodenoscopy in children with RAP were based on the following criteria: anamnestic data on the presence of at least two warning signs and/or one warning sign, one or more positive immunological finding.

Specific serological tests were determined by common methods at the Polyclinic for laboratory diagnostics- Department for microbiology- Department for immunology, University Clinical Center Tuzla. Confirmation of *H. pylori* infection was done by enzyme-linked immunosorbent assay (ELISA) (Enzyme IgA, IgM, IgG, SIMENS, Marburg, Germany).

Esophagogastroduodenoscopies were performed in the endoscopic cabinet, Clinic for Internal Medicine, University Clinical Center Tuzla by the device for upper endoscopy type Olympus GIF Type Q156. Diagnostically significant endoscopic and pathohistological finding of biopsy were those that potentially have diagnostic and therapeutic value. In cases when the upper endoscopy finding was pathologically altered (esophagus, ventricle or duodenum) at least one biopsy sample was taken from the altered area. The justification of this methodological approach to children with RAP is also confirmed by the results of research in which no statistical significance of biopsy in the case of normal endoscopy finding was recorded (11, 26, 27, 28).

The descriptions of endoscopic findings such as: mucosal erythema, reduced or absent vascular pattern of mucosa or redness, as well as the descriptions of pat-

hological findings defined as reactive changes, mucosal edema or moderate inflammatory changes were not included in this research (11).

A biopsy finding of the endoscopically altered mucosa of the esophagus, ventricle (antrum, and fundus) or duodenum was classified as negative, suspected, and positive. Interpretation of the histological finding was performed blindly by a pathologist who was unfamiliar with the history of the disease, the endoscopic finding, and the immunological values of the antibody.

1. Negative score was defined as a pathohistological change based on the following characteristics, for esophagus: normal type of mucosa without the presence of basal hyperplasia and absent intraepithelial eosinophils; for antrum and ventricular fundus: normal type of mucosa; for duodenum: normal villous.

2. Ambiguous or suspicious score referred to moderate pathohistological changes, for esophagus: minimal or moderate basal hyperplasia, vascular ectasia and rare intraepithelial lymphocytes or eosinophils; for antrum and ventricular fundus: rare occurrence of lymphoids in groups; for duodenum: villi fragmented distributed with sparse inflammatory cells.

3. Positive score was defined as significant pathohistological changes, for esophagus: basal hyperplasia, vascular ectasia and numerous intraepithelial eosinophils and lymphocytes; for antrum and ventricular fundus: lymphocyte aggregation; for duodenum: crypt hyperplasia, villous atrophy and increased number of intraepithelial lymphocytes.

Statistical analysis was performed with biomedical application software called "MedCalc for Windows, version 114.4". For statistical significance of value "p" the usual level of significance, $p < 0.05$, was chosen (29).

RESULTS

A positive finding of esophagogastrroduodenoscopy on the whole sample had 70 (91%) children, while 7 (9%) had a negative finding. The ratio of a pos-

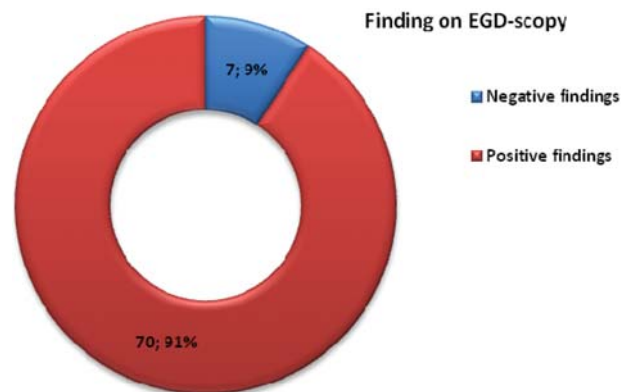


Figure 1. EGD finding in patients with RAP symptoms

itive and negative findings was 9: 1. The results of this part of research are shown in Figure 1.

Of the 77 children who entered the study protocol, 47 (61%) were female and 30 (39%) were male. Female subjects were more represented, with a statistically significant difference (61 vs 39; $p = 0.009$). The most common causes of RAP in children recorded in our research were EGD pathological findings, of which the most common were gastropathies (erythematous and/or erosive) in total of 24/30 or 80% boys and 35/47 or 74.5% girls.

Endoscopic findings of duodenogastric reflux were present in 11/30 or 36.6% of boys and 17/47 or 36.2% of girls, while hiatal hernia was found much rare and was recorded in 8/30 or 26.6% of male and 8/47 (17.2%) female subjects.

By analyzing the presence of *H. pylori* infection in children with symptoms of RAP by age groups, we found the biggest number of positive findings in school age in 21/23 (91.3%) children aged from 7 to 11,9 years, some less in adolescent group in 39/50 (78.0%) children aged from 12 to 15 years, while in the pre-school group we found the smallest number 1/4 (25%) child. The results are shown in Table 1.

Table 2 shows the pathological values of serologic tests associated with a positive EGD finding in patients with RAP.

Table 1. Positivity of *H. pylori* infection findings according to the examined age groups of children with RAP

			Group by age			Total
			Preschool age	School age	Adolescent age	
H. pylori	Neg	N	3	2	11	16
		%	75.0%	8.7%	22.0%	20.8%
	Pos	N	1	21	39	61
		%	25.0%	91.3%	78.0%	79.2%
Total		N	4	23	50	77
		%	100.0%	100.0%	100.0%	100.0%

Table 2. The pathological values of serologic tests associated with a positive EGD finding in children with RAP symptoms

Parameter		Frequency	%	p-value
H. pylori	Positive	61	79.2	0,053
	Negative	16	20.8	
	Not done	0	0	

*H. pylori (Helicobacter pylori)

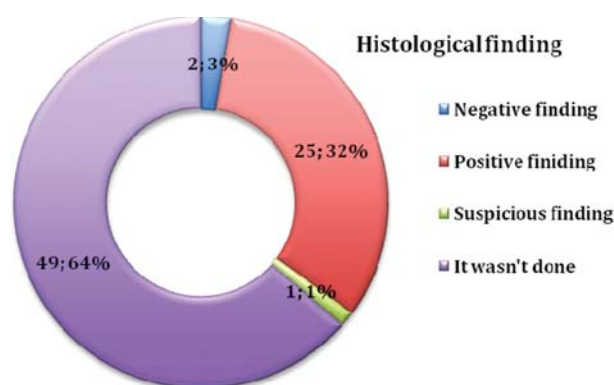
Table 3. Relationship of positive histological and EGD findings in subjects with RAP symptoms

			Positive histological findings				Total
			Pos	Neg	Susp	Wasn't done	
Positive EGD	Neg	N	0	0	0	7	7
		%	0.0%	0.0%	0.0%	100.0%	100.0%
	Pos	N	25	2	1	42	70
		%	35.7%	2.9%	1.4%	60.0%	100.0%
Total		N	25	2	1	49	77
		%	32.5%	2.6%	1.3%	63.6%	100.0%

Endoscopically confirmed antral and prepyloric gastritis in our research was recorded in 22 H. pylori positive children and 10 H. pylori negative children, while infection and alteration of the corporal and antral mucosa with prepyloric area was recorded in 7 H. pylori positive children, and 6 H. pylori negative children.

The descriptions of endoscopic findings such as: mucosal erythema, reduced or absent vascular pattern of mucosa or redness, as well as the descriptions of pathological findings defined as reactive changes, mucosal edema or moderate inflammatory changes were not included in this research. In our endoscopic findings of a large number of patients, gastropathy of antral and prepyloric area was described as altered hyperemic, edematous or stripped mucosa with single or molten erosive and hemorrhagic fields.

Gastric mucosal biopsy is not always indicated in EDG and it was done in 28 (36.4%) children, of whom 25 (89.3%) had a positive pathohistological (PHD) finding. The most common microscopic findings were described as antritis acuta in 4 (16%) children, gastritis chronica non atrophica et non erosiva in 2 (8%) children, gastric chronica activa et erosiva in 8 (32%) children, duodenitis acuta in 3 (12%) children, and duodenitis chronica ulcerosa in 5 (20%) children, while other children with a positive mucosal biopsy findings had a combination of active chronic gastritis with or without ulcerations and erosions. Of the total number of positive EGD findings (70), a small number of biopsies were recorded, a total of 28, of which six were biopsy of the small intestinal mucosa and confirmed gluten enteropathy.

**Figure 2.** Histological finding of duodenal biopsy in children with RAP symptoms who underwent EGD

A biopsy finding of the endoscopically altered mucosa of the esophagus, ventricle (antrum, and fundus), or duodenum was classified as negative, suspected, and positive. Figure 2 and Table 3 provide a comparative presentation of the histological findings and the findings on EGD-scopy.

DISCUSSION

In this research we have examined and/or hospitalized 1013 children in an Outpatient clinic for gastroenterology and/or the Department for gastroenterology, Clinic for children's diseases, University Clinical Center Tuzla. Out of this number, 183 (18.06%) children had RAP. Dhroove et al. (28) recorded that out of 14,836 examined children in Germany, 20% of them had a RAP prevalence, which partially agrees with the results of our research (28). The best comparison of our

results and the results of other researches is related to the work of Apley and Naish (1), where in a group of 100 examined children, the incidence of RAP was 10.8% (9.9% boys and 12.3% girls), with the highest incidence at the age of 5 years, and between the age of 8 and 10 years (30).

By analyzing the presence of *H. pylori* infection according to age groups, we have found the biggest number of a positive findings in the school age group from 7 to 11.9 years (91.3%), slightly smaller number in the adolescent age group from 12 to 15 years (78.0%), while in the preschool age from 3 to 6.9 years was the smallest number (25.0%). Stordal et al. (30) conducted a research in which out of 44 patients the RAP organic etiology was confirmed in 45% of children, while only one child was positive for *H. pylori*, which partially agrees with the results of our research (30).

The research results from Kumar et al. (26) completely agree with our results, especially when compared with the adolescent age group. They show that out of 55 patients with RAP, 42 (75.36%) of them was positive for *H. pylori*. The prevalence of *H. pylori* infection was statistically significantly higher in children with gastritis and duodenal ulcer, while in patients with normal EGD findings *H. pylori* bacteria was positive in only 25% of the examined children (26).

In a research Mansoura et al. (27) there was no statistically significant association of *H. pylori* infection with RAP symptoms. In both examined groups (group I consisted of children with RAP, and group II as a control group consisted of healthy children) the number of *H. pylori* positive children was 42% and 45%. The only statistically significant difference between these two examined groups was the number of patients with symptoms of vomiting, typical localization of pain and hypochromic anemia. The results obtained by this research agree with the results from our research when it comes to the statistical significance of the association of *H. pylori* infection and warning symptoms and signs (vomiting, typical localization of pain) (27).

In our research the most common causes of RAP in children described in EGD findings were gastropathies (erythematous and/or erosive) in 24 (83.3%) boys and 35 (74.4%) girls. Endoscopic finding of duodenogastric reflux was found in 11 (36.6%) boys and 17 (36.1%) girls, while hiatal hernia was much rarer condition and it was found in 22 *H. pylori* positive children and 10 *H. pylori* negative children, while infection of the corpora mucosa with alteration of the antral and prepyloric area was found in 7 *H. pylori* positive children and 6 *H. pylori* negative children.

Frank et al. (25) in their research of patients aged 3 to 15 years old with RAP recorded the following results: mean age was 9.2 years, ratio between girls and

boys was the same, epigastric pain had 48% of children infected with *H. pylori*, diffuse abdominal pain had 52%, and vomiting as a symptom was present in 14% of children. Among patients with RAP symptoms who were *H. pylori* negative, epigastric pain had 43%, diffuse abdominal pain had 57%, while vomiting was present in 13% patients proving that there was no statistically significant difference in symptoms and signs in these two groups of examined children. It is noteworthy that there was a statistically significant difference in the upper endoscopy finding in children with positive and negative *H. pylori* findings. Nodular antral gastropathy was recorded in 69% of *H. pylori* positive and only in 2% *H. pylori* negative patients, a duodenal ulcer in four or 14% *H. pylori* positive patients. The pathohistological finding was not normal in any of patients who were positive to *H. pylori*, while in *H. pylori* negative patients there was 66% with normal pathohistological finding (25).

Baysoy et al. (31) in their research recorded that positive *H. pylori* finding had 28 patients out of a total of 52 children, and they underwent EGD. Different degrees of mucosal damage, classified according to the Sydney score for gastritis from mild to severe degree, were recorded in 26 patients. Antral gastritis had 15 (53.6%), corpus gastritis 3%, while pancarditis was recorded in 8 or 28.6% children (31).

The research of Akbulut et al. (32) also corresponds to results from our research. The importance of upper endoscopy as "the gold standard" remains an irreplaceable method for assessing the association of RAP and *H. pylori* infection in children, for it allows for a very clear and accurate diagnosis of the disease. Therefore, it is very important to advocate the development of this invasive procedure, especially in underdeveloped and developing countries (32, 33).

CONCLUSION

It is quite difficult to make the distinction between the organic cause of abdominal pain and the functional etiology of this disease in children. The organic cause of abdominal pain must be precisely defined by using necessary and different diagnostic procedures, just as in the case of functional etiology of the disease, unnecessary and sometimes very painful diagnostic test should be avoided.

In our research the significant association between *H. pylori* infection and RAP was recorded and confirmed by a positive esophagogastroduodenoscopy finding, suggesting that immunological processing for the presence of this bacterium is justified. It is necessary to start treatment and *H. pylori* eradication therapy right away after obtaining a positive finding of infection.

The importance of serological tests and EGD is not only based on adequate diagnosis, but also on the need to eliminate the symptoms and signs of RAP, respectively the application of therapeutic treatment that will cure the underlying pathogen and allow the child and his family to return to normal, everyday activities.

Abbreviations

RAP — Recurrent abdominal pain

ELISA — Enzyme-Linked Immunosorbent Assay

EGD — Esophagogastroduodenoscopy

NASPGHAN — North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

UCC — University Clinical Center Tuzla

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Sažetak

POVEZANOST REKURENTNOG ABDOMINALNOG BOLA I INFEKCIJE SA HELICOBACTER PYLORI U KORELACIJI SA NALAZOM EZOFAGOGASTRODUODENOSKOPIJE

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Cilj: Cilj ovog istraživanja je da ispita vezu između rekurentnog abdominalnog bola i infekcije sa *Helicobacter pylori* (H. pylori) kod dece, u korelaciji sa nalazom ezofagogastroduodenoskopije.

Uvod: Rekurentni abdominalni bol (RAB) je definisan prema kriterijumu iz 1959. godine, koji su dali Apley i Naish, kao najmanje tri ili više epizoda abdominalnog bola koje traju duže od tri meseca, kod dece starije od 3 godine i koje su toliko jake da sprečavaju uobičajene aktivnosti kod deteta. Veza između RAB i H. pylori je već analizirana u nekoliko različitih istraživanja i postoje konflikti rezultati o njihovoj međusobnoj vezi. Ipak, veza između H. pylori i pojave i razvoja akutnog i hroničnog gastritisa, i ulkusa duodenuma je poznata.

Materijal i metode: Istraživanjem je obuhvaćeno ukupno 77/183 dece koja su podeljena u tri grupe: predškolski uzrast (3-6 godina), školski uzrast (7-10,9 godina) i adolescenti (11-15 godina), kod kojih je dijagnoza RAP-a postavljena pomoću kriterijuma Apley-a i Naish-a (1959) i Američke Akademije Pedijatara (2005). Infekcija sa H. pylori je potvrđena ELI-

SA testom, dok je ezofagogastroduodenoskopija izvedena uz pomoć aparata za gornju endoskopiju Olympus GIF Type Q156, u endoskopskom kabinetu Klinike za internu medicinu, Univerzitetskog Kliničkog Centra Tuzla.

Rezultati: Od ukupnog broja pregledane dece (77), *Helicobacter pylori* pozitivnih je najviše bilo među decom školskog uzrasta 91,3%, kod adolescenata je bilo njih 78,0%, dok je najmanje pozitivnih na H. pylori bilo među decom predškolskog uzrasta (25,0%). Najčešći nalaz dobijen gornjom endoskopijom i mikroskopskom analizom bio je akutni antritis kod 16% slučajeva, hronični gastritis, aktivni i erozivni kod 32%, i akutni duodenitis (12%).

Zaključak: Značajna veza infekcije sa H. pylori i RAP-a potvrđena pozitivnim nalazom ezofagogastroduodenoskopije vodi ka zaključku da je imunološko testiranje na prisustvo ove bakterije opravdano. Nakon dobijanja pozitivnog nalaza sa potvrđenom infekcijom neophodno je započeti lečenje.

Cljučne reči: rekurentni abdominalni bol, *Helicobacter pylori*, ezofagogastroduodenoskopija.

REFERENCES

1. Apley J, Naish N. Recurrent abdominal pains: A field survey of 1000 school children. Arch Dis Child. 1958; 33(168): 165-70.
2. Kalach N, Bontems P, Raymond J. Helicobacter pylori infection in children. Helicobacter. 2017;22 (Suppl 1). doi: 10.1111/hel.12414.

3. Kaji E, Yoden A, Otani M, Okuhira T, Aomatsu T, Tamai H et al. Helicobacter pylori test-and-treat strategy for second-year junior high school students aimed at the prevention of gastric cancer in Takatsuki City. Helicobacter. 2020; 25: e12696.

4. Andrews ET, Beattie RM, Tighe MP. Functional abdominal pain: what clinicians need to know. Arch Dis Child. Published Online First: 09 March 2020. doi: 10.1136/archdischild-2020-318825.

5. Domsa AT, Lupusoru R, Gheban D, Serban R, Borzan CM. Helicobacter pylori Gastritis in Children-The Link between Endoscopy and Histology. *J Clin Med*. 2020; 9(3): 784.
6. Apley J. "Little belliches": Prognostic implication. *Pediatrics* IV, Gastroenterology. 1974; 7: 220-4.
7. Crandall WV, Barnard JA, Cohen MB, Colletti RB, Ferry GD, Harnsberger JK, et al. Pediatric Gastroenterology Work force Survey 2003-04. *J Pediatr Gastroenterol Nutr*. 2005; 40(4): 397-405.
8. Quek SH. Recurrent abdominal pain in children: a clinical approach. *Singapore Med J*. 2015; 56(3): 125-8.
9. Bufler P, Gross M, Urlic H. Recurrent abdominal pain in childhood. *Dtsch Arztebl Int*. 2011; 108(17): 295-304.
10. Yang HR. Updates on the diagnosis of Helicobacter pylori infection in children: What are the differences between adults and children? *Pediatr Gastroenterol Hepatol Nutr*. 2016; 19(2): 96-103.
11. Berger TD, Soffer S, Vuzel-Harel T, Silbermintz A, Fleishaker H, Shamir R, et al. The yield of upper gastrointestinal endoscopy at a Pediatric Tertiary Care Center. *Isr Med Assoc J*. 2020; 22(3): 164-8.
12. Nakayama Y, Horiuchi A, Kumagai T, S Kubota, Y Taki, S Oishi, et al. Psychiatric, Somatic and gastrointestinal disorder Helicobacter pylori infection in children with recurrent abdominal pain. *Arch Dis Child*. 2006; 91(8): 671-4.
13. Sherman PM. Appropriate strategies for testing and treating Helicobacter pylori in children: When and How. *Am J Med*. 2004; 117(Suppl 5A): 30-5.
14. De Giacomo C, Valdambri V, Lizzoli F, Gissi A, Palestro M, Tinelli C, et al. A population-based survey on gastrointestinal tract symptoms and Helicobacter pylori infection in children and adolescent. *Helicobacter*. 2002; 7(6): 356-63.
15. Perquin CW, Hunfeld J, Hazebroek-Kampschreur A, van Suijlekom-Smit LW, Passchier J, Koes BW, et al. The natural course of chronic benign pain in childhood and adolescent: a two-year population-based follow-up study. *Eur J Pain*. 2003; 7(6): 551-9.
16. El-Meki A, Kumar A, Alkaway B, O Al-Ammari, R Moosa, S Quli et al. Comparison of enzyme immunoassays detecting Helicobacter pylori specific IgG in serum and saliva with endoscopic and biopsy findings in patients with dyspepsia. *Indian J Med Microbiol*. 2011; 29(2): 136-40.
17. Czinn SJ. Helicobacter pylori infection; detection, investigation and management. *J Pediatr*. 2005; 146 (Suppl 3): 21-6.
18. Mansour MM, Al Hadidi Khm, Omar MA. Helicobacter pylori and recurrent abdominal pain in children: is there any relation? *Trop Gastroenterol*. 2012; 33(1): 55-61.
19. Gold BD, Colletti RB, Abbott M, Czinn SJ, Elitsur Y, Hassall E et al. Helicobacter pylori in children. Recommendation for diagnosis and treatment. *J Pediatr Gastroenterol Nutr*. 2000; 31(5): 490-7.
20. Gilger M. Gastroenterologic endoscopy in children: past, present and future, Current option in Pediatric. 2001; 13(5): 429-34.
21. Walker LS, Lipani T, Green JW, Caines K, Stutts J, Polk DB, et al. Recurrent abdominal pain: Symptom subtypes based on the Rome II criteria for pediatric functional gastrointestinal disorders. *J Pediatr Gastroenterol Nutr*. 2004; 38(2): 187-91.
22. Thakkar K, Gilger MA, Shulman RJ, El Serga HB. EGD in children with abdominal pain: a systematic review. 2007. In: Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews ŠInternetČ. York (UK): Centre for Reviews and Dissemination (UK); 1995-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK74647/>.
23. Agin M, Kayar Y. The effect of primary duodenogastric bile reflux on the presence and density of helicobacter pylori and on gastritis in childhood. *Medicina (Kaunas)*. 2019; 55(12): 775.
24. American Academy of Pediatric, North American Society For Pediatric Gastroenterology, Hepatology and Nutrition. Chronic abdominal pain in children. *Pediatrics*. 2005; 115(3): 812-5.
25. Frank F, Stricker T, Stallmach T, Braegger CP. Helicobacter pylori in Recurrent abdominal pain. *J Pediatr Gastroenterol Nutr*. 2000; 31(4): 424-7.
26. Kumar M, Yachha SK, Khanduri A, Prasad KN, Ayagari A, Pandey R. Endoscopic, Histologic and microbiologic evaluation of upper abdominal pain with special reference to Helicobacter pylori infection. *Indian pediatrics*. 1996; 33: 905-9.
27. Mansour MM, Al Hadidi Khm, Omar MA. Helicobacter pylori and recurrent abdominal pain in children: is there any relation? *Trop Gastroenterol*. 2012; 33(1): 55-61.
28. Dhroove G, Chogle A, Saps A. A million-dollar work-up for abdominal pain: is it worth it. *J Pediatr Gastroenterol Nutr*. 2010; 51(5): 579-83.
29. Buchan IE. *Arcus Quickstat (Biomedical)*. Cambridge: Addison Wesley Longman, 1997.
30. Stordal, K, Nygaard E, Bentsen B. Organic abnormalities in recurrent abdominal pain in children. *Acta Paediatrica*. 2001; 90(6): 638-42.
31. Baysoy G, Ertem D, Ademoglu E, Kotiloglu E, Keskin S, Pehlivanoglu E. Gastric histopathology, iron status and iron deficiency anemia in children with Helicobacter pylori infection. *J Pediatr Gastroenterol Nutr*. 2004; 38 (2): 146-51.
32. Akbulut UE, Emeksiz HC, Kocak FG, Livaoglu A. Diagnostic yield of esophagogastroduodenoscopy in children with chronic abdominal pain. *Arch Med Sci*. 2018; 14(1): 74-80.
33. Adeniyi OF, Odeghe EA, Lawal MA, Olowu AO, Ademuyiwa A. Recurrent abdominal pain and upper gastrointestinal endoscopy findings in children and adolescents presenting at the Lagos University Teaching Hospital. *PLoS One*. 2019; 23; 14(5): e0216394. <https://doi.org/10.1371/journal.pone.0216394>.

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SURGICAL TREATMENT OF CARDIAC TAMPONADE DEVELOPED IN TWO PATIENTS WITH TERMINAL STAGE LUNG CANCER

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Abstract: Introduction: Although tamponade due to pericardial effusion that develops in advanced stage lung cancer is rare, it is a life threatening complication. Case report: 59 and 72 years old 2 female patients diagnosed with cardiac tamponade were hospitalized in Cardiology Clinic of Balıkesir State Hospital. Massive pericardial effusion that caused diastolic collapse of right ventricle was detected in their echocardiographies. Inoperable lung cancer was diagnosed as a result of bronchoscopy performed due to pathologies observed in their radiograms. Despite repeated pericardiocentesis, fluid continued to accumulate rapidly. Hence, pericardioperitoneal window was formed through subxiphoid route to obtain continuous drainage in both patients. Significant pericardial effusion didn't develop in echocardiographies in the 2nd and the 6th month post-operative follow-ups. Conclusion: Subxiphoid pericardioperitoneal window is a simple, safe and effective surgical procedure. It may be performed in some patients with malignant tamponade.

Key words: Pericardioperitoneal window, lung cancer, pericardial tamponade.

INTRODUCTION

Chronic exudative pericarditis can cause cardiac tamponade. Although echocardiography guided with pericardiocentesis, especially in effusions related to malignancy, is helpful in some cases, fluids may accumulate again in a short time. In such case, pleuropericardial window can be the choice of treatment. But due to spread of the malignancy this may not be possible in patients with pleurodesis. In this case pericardial-peritoneal shunt is regarded as a solution. Pericardial spread that causes tamponade in lung cancer patients occurs in three ways. These are direct spreads that occur via lymphatic, hematogenous route spread and

spread from adjacent invasion (1). Tamponade may develop as a result of invasion of malignant cells to pericardium just as it may develop as a result of invasion of lymphatic or blood veins when pericardium is not directly involved (2). Furthermore, pericardial fluid may accumulate after radiotherapy.

Surgical Technique Performed in Patients

About 4 cm in length, midline incision below xiphoid was performed. Xiphoid was left uncut. Pericardium was opened and accumulated fluid was aspirated. Diaphragm and inferior pericardium was incised forming a window 5-6 cm in dimensions. The edges of pericardium and diaphragm were sutured using 5/0 Prolene. Also a chest tube was inserted via the first opening to pericardial cavity and it was removed soon as the drainage was diminished.

Case No 1

A 59 year-old female patient was hospitalized in cardiology clinic with symptoms including dyspnea, tachycardia and wide spread edema in lower extremities. Pericardial and pleural fluid was detected in the echocardiography. Following the examination of sample taken by bronchoscopy performed in Chest Diseases Clinic of our Hospital, squamous cell lung cancer was diagnosed (T4N1M0). Because of rapid fluid accumulation, despite pleural punctures, pleurodesis was performed and positive results were obtained. A month later patient's complaints recurred and she applied to the cardiology clinic of our hospital. Upon detection of pericardial effusion causing diastolic collapse in right ventricle in the echocardiography, clinical picture was adjusted by performing echocardiography guided peri-

cardiocentesis with diagnosis of cardiac tamponade. Because of the rapid accumulation of pericardial fluid pericardiocentesis became inefficient so surgical drainage was planned. Initially 900 cc hemorrhagic fluid was drained following subxiphoid intervention. Because there were severe adhesives, pericardioperitoneal window was formed with a diameter of 5 cm. Histopathological examination of resected pericardium showed the pericardial invasion. Malign cells were observed in the pericardial fluid and there was no reproduction in the culture. During post-operative 2 months follow-up period we didn't see effusion collection.

Case No 2

A 72 year-old female patient with dyspnea complaint was hospitalized in cardiology clinic. Upon detection of tamponade in echocardiography, patient was relieved with pericardiocentesis. Lung cancer was diagnosed (T4N2M1) following bronchoscopy performed in Chest Diseases Clinic of our hospital due to pathology detected in thorax radiography (Figure 1). Alt-

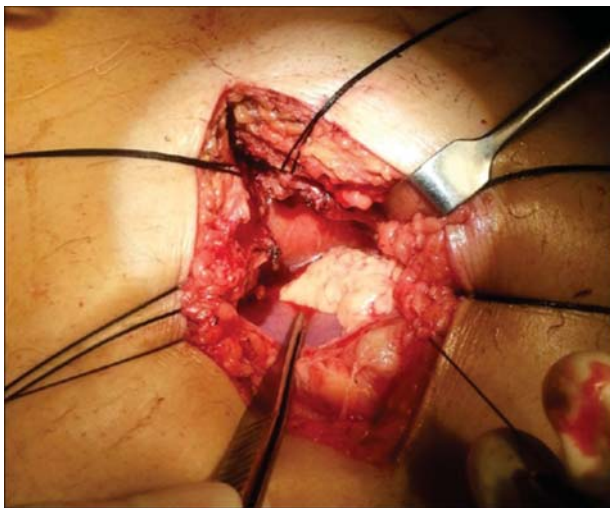


Figure 1. Intraoperative surgical approach



Figure 2. Preoperative chest X-ray

hough pericardiocentesis was applied again pericardial effusion was detected and drainage was planned. 1250 cc exudative fluid was drained from pericardium via subxiphoid incision under general anesthesia. Pericardioperitoneal window was created with approximately 6 cm of diameter (Figure 2). Malign cells were detected in pericardial fluid. There was no reproduction in the culture. The result of pericardium biopsy was adenocarcinoma. Patient was relieved in post-operative period. Tamponade did not recur in 6 months follow-up period.

DISCUSSION

Just as malign effusion may occur as a result of pericardial invasion of malign cells, pericardial fluid may also form by invasion of inflammation, lymphatic and blood veins without any pericardial invasion. This is called paramalign effusion (1, 2). Peritoneum cavity has a larger absorption surface than thorax cavity. Rodriguez et al. stated that creation of a pericardioperitoneal window was a simple, safe and efficient procedure and that it can be applied in most cases with malignant or non-infectious benign pericardial effusion and tamponade (3). Some authors stated that it was not clear why fluid drained from negative intrathoracic pressure area to abdominal cavity which has positive pressure (4). They thought that this window would quickly close due to adhesion between liver and omentum. But many researchers stated that this window is efficient and stayed open for a very long time (2). Pericardial window was created with also laparoscopic and thoracoscopic methods in patients with tamponade (5). But if there are advanced adhesivity like in our cases or in case pleurodesis is performed, pericardial window cannot be created laparoscopically. Although pericardioperitoneal window is considered to be dangerous in malign cases due to risk of peritoneal carcinomatosis, Alotti et al. (3) did not report any development of peritoneal carcinomatosis in any of their cases. Even though peritoneal carcinomatosis develops, this type of patients that have limited life expectancy will be able to spend the last phase of their life without the risk of tamponade. Tamponade can develop in 18% of the malignancy cases with cardiac involvement (6). Although tamponade is rarely considered as the first symptom for malignity, if a good anamnesis is taken it can be seen that symptoms secondary to malignity such as coughing, dyspnea, malaise, weight loss develops earlier (1). Wang et al. (6) stated that average life of patients with lung cancer following a pericardial drainage was 78 days and only 11,8% of the patients could live one year. In studies, no relationship between age, gender, tumor type, lymph node metastasis, pleural fluid, dis-

tant metastasis, symptoms, amount of drained fluid and lifetime are found in the relationship between lung malignancy and tamponade development. Wang et al. (6) reported that cytology of pericardial fluid did not have an effect on the lifetime in non-small cell lung cancer cases that developed tamponade. Video assisted thorascopic surgery (VATS) can only be performed in hemodynamically stable patients because it requires only lung anesthesia (7). When procedure is performed laparoscopically, great caution should be given in the opening of pericardium with cautery. Serious arrhythmia may develop. Intraabdominal pressure should be lowered when pericardium is opened in order to prevent the development of tamponade (7). It is reported that windows with diameters less than 3 cm, will close quickly, approximately in a year due to adhesion in the liver. Thus the need for a window opening over 4 cm is reported (5). Lymphatic system of heart is the major path in tumoral invasions in heart. Tumor that reaches mediastinal lymph nodes, retrogradely proceeds to lymphatic canals and blocks cardiac lymphatic system. Epicardial lymphatic veins are always attacked early. Due to its poor lymphatic structure, in many cases parietal layer of the pericardium is not attacked by tumoral diffusion in early stages. Even in the early stage where clinical symptoms related to primer tumor does not de-

velop and where tumor does not reach a significant size, pericardial effusion can develop due to early invasion of mediastinal lymphnodes (8). Positive results were reported with echocardiography guided percutaneous catheter drainage in cases with tamponade. But in some maligncases repeated effusion has been reported (9). Even though advanced malignancy is responsible from the bad prognosis in malign cases, sudden tamponade development especially after the discharge can causedeath.

CONCLUSION

In conclusion pericardioperitoneal window should be thought as protective factor against sudden deaths that might occur following tamponade in repeated malign pericardial effusions.

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

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Sažetak

HIRURŠKO LEČENJE TAMPONADE SRCA RAZVIJENE KOD DVA PACIJENTA SA KARCINOMOM PLUĆA TERMINALNOG STADIJUMA

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Uvod: Iako je tamponada usled perikardijalne efuzije koja se razvija kod karcinoma pluća u poodmaklom stadijumu retka, to je komplikacija opasna po život. **Prikaz slučaja:** Dve pacijentkinje ženskog pola, starosti 59 i 72 godine, hospitalizovane su na Klinici za kardiologiju državne bolnice Balıkesir zbog dijagnostikovane srčane tamponade. Na njihovim ehokardiogramima je otkrivena masivna perikardijalna efuzija koja je dovela do dijastolnog kolapsa desne komore.

Inoperabilan karcinom pluća je dijagnostikovao bronhoskopijom koja je izvedena zbog patoloških promena viđenih na radiografiji pluća. Uprkos ponovlje-

nim perikardiocentezama tečnost se akumulirala rapidly. Zbog toga je formiran perikardioperitonealni prozor subksifoidnim putem da bi se dobila kontinuirana drenaža kod oba pacijenta. Značajan perikardijalni izliv nije se razvio na ehokardiografijama drugog i šestog meseca postoperativnog praćenja. **Zaključak:** Subksifoidni perikardioperitonealni prozor je jednostavna, sigurna i efektivna hirurška procedura. Može se izvesti kod nekih pacijenata sa malignom tamponadom.

Cljučne reči: perikardioperitonealni prozor, karcinom pluća, perikardijalna tamponada.

REFERENCES

1. Patel N, Rafique AM, Eshaghian S, Mendoza F, Biner S, Cercek B et al. Retrospective comparison of outcomes, diagnostic value and complications of percutaneous prolonged dra-

inage versus surgical pericardiotomy of pericardial effusion associated with malignancy. Am J Cardiol. 2013; 112(8): 1235-9.

2. Burazor I, Imazio M, Markel G, Adler Y. Malignant pericardial effusion. Cardiology. 2013; 124(4): 224-32.

3. Lepska L, Pisiak S, Dudziak M. A case of carcinoid pericardial metastases and massive effusion. *Kardiol Pol.* 2013; 71(8): 881.
4. Degirmencioglu A, Karakus G, Güvenc TS, Pinhan O, Sipahi I, Akyol A. Echocardiography-Guided or "Sided" Pericardiocentesis. *Echocardiography.* 2013; 30(9): 997-1000.
5. Fredriksen RT, Cohen LS, Mullins CB. Pericardial windows or pericardiocentesis for pericardial effusions. *Am Heart J.* 1971; 82(2): 158-62.
6. Wang JL, Hsieh MJ, Lee CH, Chen CC, Hsieh IC, Lin JD et al. Hypothyroid cardiac tamponade: clinical features, electrocardiography, pericardial fluid and management. *Am J Med Sci.* 2010; 340(4): 276-81.
7. Wang LS, Cheng GQ, Chen C, Cao Y. Cardiac tamponade due to fatal pneumopericardium after commercial flight: transportation of a premature infant with chronic lung disease. *J Trop Pediatr.* 2013; 59(1): 70-1.
8. Rafique AM, Patel N, Biner S, Eshaghian S, Mendoza F, Cercek B et al. Frequency of recurrence of pericardial tamponade in patients with extended versus nonextended pericardial catheter drainage. *Am J Cardiol.* 2011; 108(12): 1820-5.
9. Nogueira RB, de Resende RM, Muzzi RA, dos Reis Mesquita L. Alterations in peripheral circulation in dogs with cardiac tamponade. *Vet Rec.* 2011; 169(11): 280.

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TRANSURETHRAL REMOVAL FOR SUCCESSFUL DIAGNOSIS OF BLADDER MALAKOPLAKIA: A RARE CASE REPORT

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Abstract: Introduction: Malakoplakia is a rare granulomatous inflammatory disorder of infectious etiology that most often involves the urinary tract. Because it is so rare and can present in several different ways, malakoplakia poses a difficult diagnostic challenge.

Case report: We report an unusual clinical case of bladder malakoplakia in a 75-year-old man. He presented to urologist with hematuria, burning on urination, urinary urgency and frequency. Cystoscopy evaluation revealed yellowish polypoid lesion with easy bleeding in the trigone of the bladder. Microscopic evaluation showed acidophilic, foamy histiocytes (Von Hanseman cells) admixed with Michaelis-Gutmann inclusions. The final postoperative diagnosis was malakoplakia of the bladder.

In conclusion, we reported a case of malakoplakia of the bladder diagnosed with minimally invasive approach by transurethral resection. It is important to be aware of this rare granulomatous disease as accurate diagnosis with antibiotic treatment can prevent possible complications.

Key words: Malakoplakia, Bladder, Transurethral resection.

INTRODUCTION

Malakoplakia is a rare granulomatous inflammatory disorder of infectious etiology, that usually affects genitourinary system, mainly bladder in 60-80 % of cases (1). The prevalence is unknown; however more than 700 cases have been studied so far (2). This rare disease should be considered in patients with recurrent coliform urinary infections, in immunocompromised patients and transplant recipients. It can be asymptomatic, or presents with painless hematuria, urinary tract infections, septicemia, acute renal failure or complica-

tions of end stage renal failure (3). The pathophysiology of malakoplakia is uncertain, it is believed that it represents an unusual granulomatous response to bacterial infection (3). Clinically, as well as radiologically malakoplakia produces tumor-like lesions that are able to mimic malignant neoplasms, thus confirmation can only be achieved histologically.

The current report represents malakoplakia of bladder which presented histologically after a transurethral removal of bladder lesion. Malakoplakia represents a differential diagnosis which needs to be considered in these cases, since despite an appropriate early antibiotic long-term use; this type of infection might increase fast and significantly.

CASE REPORT

We report an unusual clinical case of bladder malakoplakia in a 75 year old man. He presented to urologist with a four-month history of hematuria, burning on urination, urinary urgency and frequency. Patient also had significant history of recurrent urinary tract infections (UTI) with *Escherichia coli* in the last nine months. His past medical history was positive for essential hypertension in the last four years, for which he was on atenolol. He denied any family history of genitourinary malignancy.

On admission, laboratory examinations (Table 1) were in the reference range. Urine analyses showed no signs of proteinuria but increase number of leukocytes and erythrocytes. Urine culture grew *Escherichia coli*, sensitive to quinolones. His blood pressure was 130/80 mm Hg, with a pulse rate of 74 beats/min. An initial ultrasound scan of the urinary tract showed presence of 2,5 mm tumor mass of the posterior bladder wall (Figure 1), without signs of ureteral obstruction. The contrast CT scan revealed hyperdense focus in the bladder



Figure 1. Ultrasound of the bladder shows mass of the posterior bladder wall

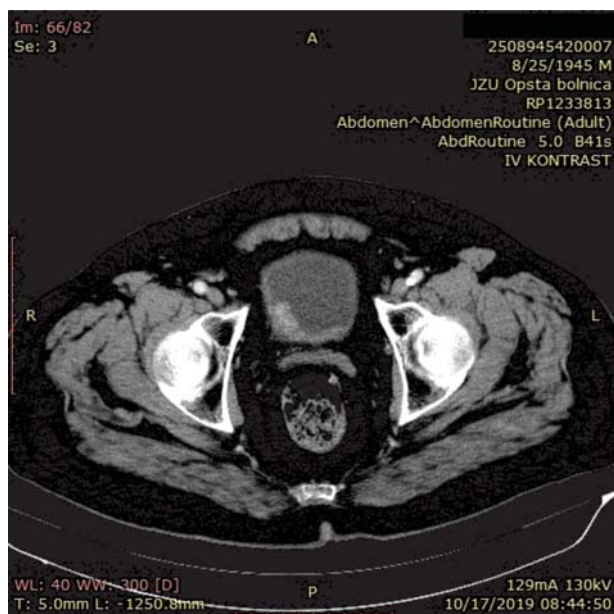


Figure 2. CT scan shows hyperdense focus of the bladder

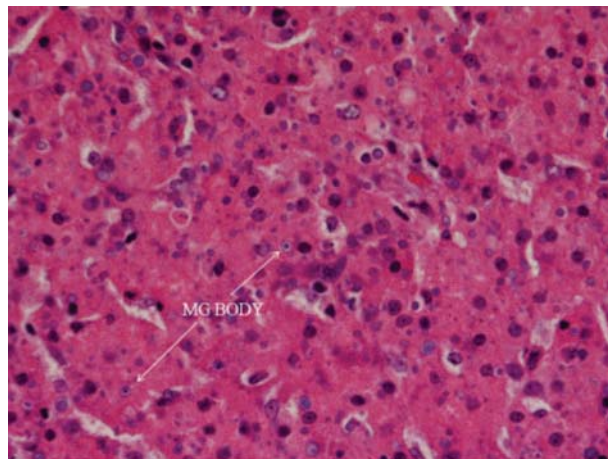


Figure 3. Foamy macrophages and Michaelis-Gutmann (MG) bodies. (H&E stain magnification 400x)

measuring 2,5 x 1,5 mm (Figure 2). Cystoscopy evaluation revealed atypical yellowish polypoid lesion with easy bleeding in the trigone of the bladder. Malignancy was suspected and transurethral resection of the lesion was performed under spinal anesthesia. The patient was discharged home on first postoperative day with advice of antibiotic use with ciprofloxacin for 4 days and monthly follow-up. Microscopic evaluation showed acidophilic, foamy histiocytes (Von Hanseman cells) admixed with Michaelis-Gutmann inclusions (Figure 3). The final postoperative diagnosis was malakoplakia of the bladder.

DISCUSSION

Malakoplakia is benign and very rare chronic inflammatory granulomatous disease that mostly occurs

Table 1. Laboratory findings

Test	Result	Reference range
WBC (white blood cells) $\times 10^9/L$	6.4	4.00-9.00
RBC (red blood cells) $\times 10^{12}/L$	4.48	4.20-5.50
Haemoglobin g/L	148	120-180
Haematocrit (rv)	0.460	0.37-0.54
PLT (platelet count) $\times 10^9/l$	261	150-450
Glucose (mmol/l)	5.07	3.5-6.5
Urea (mmol/l)	4.8	2.7-7.8
Creatinine (umol/l)	78	45-109
Potassium (mmol/l)	5.2	3.8-5.5
Sodium (mmol/l)	139	137-145
Chlorides (mmol/l)	106	99-108
CRP mg/L	5	< 6

in the genitourinary system. Malakoplakia mostly affects the bladder, prostate, ureter, kidney, female genital tract and retroperitoneal tissue (3). In general, malakoplakia of the urinary tract more frequently affects men above 50 years old (4). Cases of malakoplakia with involvement of the gastrointestinal tract and other visceral organ like lungs, bones, brain, conjunctiva, skin and tonsils has been described in the literature (5, 6, 7).

Diagnosis of malakoplakia is still challenge because it presents clinically with wide spectrum of symptoms depending on organs involved. The symptoms of bladder malakoplakia, as in our case are hematuria, and signs of urinary tract infection, mimicking malignancy (2). Bladder malakoplakia has also been found in association with bladder tumors with or without a history of infection (8). Urethral malakoplakia can manifest with urethral obstruction and formation of structure. Renal malakoplakia may present with fever, flank pain and tumor-mass. Extensive pelvic malakoplakia has the potential to spread throughout the retroperitoneum and can cause renal failure if both ureters are compromised (9).

Bacterial infection and immunocompromised status are believed to be related to the development of malakoplakia. *Escherichia coli* is the most commonly isolated bacteria in urine culture in approximately 80% of cases (10). In addition to this microorganism, other possible factors are described, such are *Klebsiella*, *Proteus*, *Mycobacterium*, *Staphylococcus* and fungi (6). The pathophysiology of malakoplakia is uncertain, it included certain microorganism involvement such as gram-negative coliforms and defective phagocytosis in monocytes and macrophages (11). This results in accumulation of bacterial degradation products in monocytes and macrophages and developing granulomas. The bacterial degradation products persist in phagolysosomes and become mineralized; resulting in characteristic intracellular inclusions called Michaelis-Gutmann bodies (11). Intraluminal protrusion of bladder mucosa occurs due to accumulation of mac-

rophages in the lamina propria (2), as in this case. Since this disease is rare and presents with hematuria, it is often misdiagnosed as malignancy.

Most bladder lesions may be detected by radiographic techniques (ultrasound, computed tomography and magnetic resonance). Contrast computed tomography is an important diagnostic investigation in upper urinary tract malakoplakia and can be presented with hydroureter and multiple hyperdense masses.

The diagnosis of malakoplakia is verified by biopsy and histopathological examination. The treatment consists of transurethral resection of the affected site and appropriate antibiotics according to result of antibiogram test from urine culture. The best antibiotics are those that achieve high intracellular antibiotics levels such as fluoroquinolones and trimethoprim-sulfamethoxazol (12). Persistence of malakoplakia may require resection.

CONCLUSION

In conclusion, we reported a case of malakoplakia of the bladder diagnosed with minimally invasive approach by transurethral resection. It is important to be aware of this rare granulomatous disease as accurate diagnosis with long term antibiotic treatment can prevent possible complications.

Abbreviations

CT — computed tomography.

H&E — hematoxylin and eosin stain.

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

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Sažetak

TRANSURETRALNA RESEKCIJA MOKRAĆNE BEŠIKE ZBOG USPEŠNE DIJAGNOZE MALAKOPLAKIJE: PRIKAZ SLUČAJA

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Uvod: Malakoplakija je redak granulomatozni inflamatorni poremećaj infektivne etiologije koji najčešće obuhvata urinarni trakt. Obzirom da je rećka bolest i može se manifestovati na više različitih

načina, malakoplakija predstavlja ozbiljan dijagnostički izazov.

Prikaz slućaja: Prikazujemo redak klinićki slućaj malakoplakije bećike kod 75-godišnjeg mućkarca.

Upućen je kod urologa sa hematurijom, peckanjem pri mokrenju, urgentnom i učestalom mokrenju. Cistoskopski je detektovana žućkasta polipoidna lezija sa lakim krvarenjem na trigonumu bešike. Histopatološka evaluacija pokazala je acidofilne, penaste histiocite (Von Hanseman čelije) pomešane sa Michaelis-Gutmann-ovim inkluzijama. Konačna postoperativna dijagnoza bila je malakoplakija bešike.

REFERENCES

1. Badillo LGF, Aguileria BI, Prada CS, Pedroza LVR, Lanzabal JDS. Renal malakoplakia. A case report. *Rev Colomb Radiol.* 2018; 29(3): 4987-91.
2. Kim SH, Choi YS, Kim ES, Lee K, Lee JH, Kang HG et al. Bladder malakoplakia mimicking bladder cancer. *Korean J Med.* 2017; 92(5): 476-9.
3. Dong H, Dawes S, Philip J, Caudhri S, Subramonian K. Malakoplakia of the urogenital tract. *Urol Case Rep.* 2014; 3(1): 6-8.
4. Wong SHL, Yeung VHW, Lee WK, Lee YK, Chan MTY, Cheng CH et al. Malakoplakia of the urinary tract: A benign disease with a possible malignant outcome. *J Case Rep.* 2016; 6: 254-8.
5. Niknejad N., Nili F., Shirkhoda M. Malakoplakia in association with adenocarcinoma of sigmoid colon: A case report. *Iran J Pathol.* 2019; 14(3): 258-60.
6. Kyriakou G, Gialeli E, Vryzaki E, Koumoundourou D, Glentis A, Georgiou S. Malakoplakia of the skin: overview of a rare clinical entity. *Dermatol Online J.* 2019; 25(6): 232-7.
7. Fudaba H, Ooba H, Abe T, Kamida T, Wakabayashi Y, Fujiki M, et al. An adult case of cerebral malakoplakia success-

Zaključak: Ukratko, prikazali smo slučaj malakoplakije bešike koja je dijagnostikovana transuretralnom resekcijom. Važno je da budemo svesni ove retke granulomatozne bolesti, jer tačna dijagnoza sa lečenjem antibioticima može sprečiti moguće komplikacije.

Cljučne reči: Malakoplakia, Bešika, Transuretralna resekcija.

fully cured by treatment with antibiotics, bethanechol and ascorbic acid. *J Neurol Sci.* 2014; 342(1): 192-6.

8. Lee SL, Teo JK, Lim SK, Salkade HP, Mancera K. Coexistence of malakoplakia and papillary urothelial carcinoma of the urinary bladder. *Int J Surg Pathol.* 2015; 23(7): 575-8.

9. Patnayak R, Reddy MK, Subramanian S, Jena A, Ravisankar G, Dandu RS. An unusual case of bilateral hydronephrosis caused by uretero-vesico malakoplakia in a young male: a case report and review of the literature. *Cases J.* 2009; 2(1): 7527.

10. Papilomata E, Agarwala N, Ioannidis M, Vorous MI, Balaxis AD, Filindris NT, Chalambois NS et al. Malakoplakia of genitourinary tract: A report of 3 cases. *Urotoday Int J.* 2010; 3(4). Available from: <http://dx.doi.org/10.3834/uij.1944-5784>. 2010.08.12

11. Yousef GM, Naghibi B, Hamodat MM. Malakoplakia outside the urinary tract. *Arch Pathol Lab Med.* 2007; 131(2): 297-300.

12. Hina S, Hasan A, Iqbal N, Shabbir MU, Sheikh AAE. Malakoplakia of the urinary bladder and unilateral ureter. *J Coll Physicians Surg Pak.* 2019; 29 (6): 582-4.

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RARE PENILE KELOID AFTER CIRCUMCISION: CASE REPORT AND LITERATURE REVIEW

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Abstract: Objective: To report a case of keloid formation after circumcision and review the literature for similar cases to formulate possible risk factors contributing to its development as well as its treatment options.

Method: a literature review was done using PubMed and Google Scholar by searching the keyword “keloid”, “penis” and “circumcision”. Additional searches were done on references from related articles. The articles are then reviewed by the author, noting for possible predisposing factors to keloid formation, along with patient demographics and method of treatments. Findings were then tabulated and analyzed using Microsoft Excel (2018).

Results: Thirteen case reports on penile keloid after circumcision with a total of 16 patients were found dating from 1993 to 2017. Circumcision in four cases (25%) were complicated with infection or dehiscence. The median age during circumcision is 9 years old. Two patients (12.5%) were reported with the tendency for keloid. The ethnicity of the patients is as follows; Turkish (7 cases, 43.7%), African descent (4 cases, 25%), Chinese (3 cases, 18.75%), Indian (1 case 6.25%) and Caucasian (1 case, 6.25%). Ten (62.5%) cases were treated with a combination of excision and immediate injection of triamcinolone acetate. Others were treated with either excision alone, steroid injection alone or excision with topical steroid. Maintenance treatment includes topical steroid, intralesional injection of steroid, and silicone gel. Recurrence occurred in one patient.

Conclusion: The minuscule number of published reports of keloid formation after circumcision underscores the rarity of the complication. No specific risk factors can be attributed to stratify patients who may develop keloid after circumcision. Excision followed by triamcinolone acetate injection with maintenance

therapy until scar maturity is the preferred choice of treatment for penile keloid.

Keywords: Penile keloid, circumcision, keloidal scar.

INTRODUCTION

Excision of the penile foreskin, is one of the most frequently performed surgeries in men. It is projected that one-third of the total male population is circumcised (1). While there is no official data on the prevalence of circumcision in Malaysian men, it is estimated that at least 60% of Malaysian men are circumcised as it reflects the proportion of Muslim men in the country. It is performed due to various reasons, commonly due to religious beliefs and cultural rites. Medically, it is indicated for paraphimosis, balanitis and balanoposthitis and for the prevention of HIV and other sexually transmitted infections in a high-risk population (2).

Complications rates vary between regions and the age of circumcision. Common complications include bleeding, infection, wound dehiscence, and excess skin removal. Iatrogenic glans amputation is an uncommon but a severely debilitating complication (3). While the general understanding is that the penile skin heals well with favorable scarring, there has been a handful of anecdotal reports of pathological scarring, either hypertrophic or keloid scar stemming from circumcision. We report such a case, which to the best of our knowledge, the first in the Southeast Asian population.

CASE PRESENTATION

A 14 years old boy who is under our follow-up for keloid scar over his left pre-auricular region presents with a painless, rubbery nodule along his circumcision scar which was performed 3 years ago. He also carries a strong familial history of developing a keloid scar,

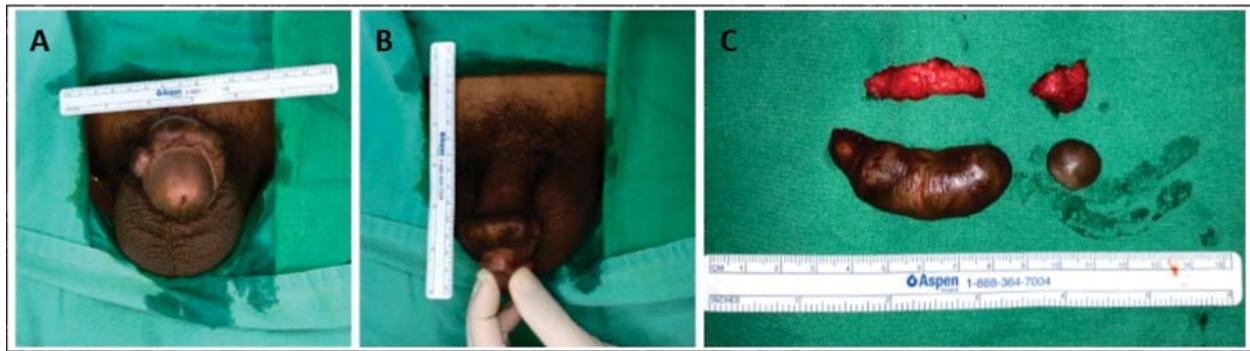


Figure 1. A: two keloidal nodule scar from front view; B: dorsal aspect of penile keloid; and C: excised keloidal scar shown with its measurement

claiming some males from the paternal side, including his brother. The circumcision was performed concurrently with excision of keloid scar over his left pre-auricular region at our center. Recovery following surgery was uneventful. While it is uncertain when the nodule appears following circumcision, it was claimed by the patient that it steadily increases in size.

Physical examination revealed two rubbery, mobile, non-tender nodules along the dorsal aspect of his circumcision scar (Figure 1A). It measures 5 x 2 x 2 cm and 1.5 x 1.5 x 2 cm (Length x Width X Height) (Figure 1B). The ventral aspect of the circumcision wound otherwise forms a hairline scar which is expected from an uncomplicated circumcision. The nodule was excised completely (Figure 1C) and closed tension-free with subdermal undyed Vicryl 5-0 and subcuticular Prolene 5-0. Suture removal (Prolene) was done on day 5 post-operation. Triamcinolone acetate injection was commenced at 2 weeks following surgery and scheduled for every six weeks until the scar fully matures. Histological examination revealed nodules of haphazardly arranged broad homogenous collagen bundles. Fibroblasts are seen arranged parallel to these collagen bundles. A moderate amount of lymphoplasmacytic cells are present in the dermis. These findings are consistent with keloid.

Literature Review

A literature search was done via PubMed and Google Scholar using the keywords “keloid”, “penis” and

“circumcision”. A total of 20 abstracts of relevant articles were found. Full-text articles were available to the author for all except one. A secondary search was performed on references from related articles. Only articles of keloid formation after circumcision are included for analysis. Information on patient’s ethnicity (Table 1), age at presentation, age of circumcision, family history/self-tendency to develop keloid scar, treatment methods and recurrence were tabulated and analyzed using Excel. Articles with missing data were excluded from the relevant analysis.

RESULTS

There is a total of 16 patients spreading across 13 articles (Table 2) with the earliest report was published in 1993 and the latest in 2017. Data on 4 patients were incomplete for age at circumcision and 3 patients were incomplete for the tendency for keloid scarring.

Out of 16 patients, 4 (25%) suffered complications following circumcision. In 13 patients in which family history/tendency to develop keloid scar was explored, 2 (15.4%) reports having a tendency for keloid scarring. The majority of the author’s employed a multimodal approach to penile keloid treatment (68.75%). Intralesional injection of triamcinolone is the preferred choice (80%) by most authors who opted for a single modality approach. Regardless of the treatment method, recurrence was reported in one case in which excision and triamcinolone injection were employed.

Table 1. Demographics of patients with keloid formation after circumcision

Median Age of Circumcision, Years (Youngest, Oldest)		9 (3, 31)
Median Age at Presentation, Years (Youngest, Oldest)		9.5 (13 months, 32 years)
Family History/Tendency for Keloid		2 of 10 cases
Ethnicity	Turkish	6 reports
	African Descent	4 reports
	Chinese	3 reports
	Indian	1 report
	Caucasian	1 report

Table 2. Reports on keloid formation after circumcision and its treatment

	Author, Year	Ethnicity	Age	Age at Circumcision	Complications	Keloid tendency	Treatment	Recurrence
1	Warwick et al, 1993(4)	African descent	10 yrs.	12 yrs.	No	Not stated	Intralesional triamcinolone	No
2	Gurunluoglu et al, 1996(5)	Turkish	12 yrs.	9 yrs.	No	Yes	Intralesional triamcinolone	No
3	Gurunluoglu et al, 1997(6)	Turkish	13 yrs.	-	No	Not stated	Intralesional triamcinolone	No
4	Bekerecioglu et al, 2005(7)	Turkish	13 yrs.	8 yrs.	No	No	Excision + triamcinolone injection	No
5	Erdemir et al, 2006(8)	Turkish	15 yrs.	14 yrs.	No	No	Excision + triamcinolone injection	No
6	Isken et al, 2008(9)	Turkish	10 yrs.	8 yrs.	No	Not stated	Topical steroid followed by excision	No
7	Lokhande et al, 2010(10)	Indian	9 yrs.	9 yrs.	No	No	Excision + triamcinolone	No
8	Demirdover et al, 2012(11)	Turkish	3 yrs.	3 yrs.	No	No	Intralesional triamcinolone followed by excision	No
9	Xie et al, 2013(12)	Chinese	32 yrs.	31 yrs.	Infection	Yes	Excision + triamcinolone injection	No
10		Chinese	10 yrs.	8 yrs.	Infection	No	Excision + triamcinolone injection	No
11		Chinese	12 yrs.	12 yrs.	Infection	No	Excision + triamcinolone injection	No
12	Yong et al, 2013(13)	African descent	19 months	-	Dehiscence	No	Excision	No
13	Cinpolat et al, 2015(14)	Turkish	9 yrs.	9 yrs.	No	No	Excision + triamcinolone injection	No
14	Ozinko et al, 2015(15)	Nigerian	13 months	-	No	No	Intralesional triamcinolone	No
15		Nigerian	2 yrs.	-	No	No	Excision + triamcinolone injection	Yes, Re-excised + triamcinolone
16	Sanal et al, 2017(16)	Caucasian	13 yrs.	11 yrs.	No	No	Excision + triamcinolone injection	No

Table 3. Published approach to penile keloid

Single Modality Approach		Multimodal Approach	
Intralesional triamcinolone	80% (4)	Excision + intralesional triamcinolone	81.8% (9)
Excision	25% (1)	Topical steroid followed by excision	9% (1)
		Intralesional triamcinolone followed by excision	9% (1)

DISCUSSION

The majority of patients reported presents with age within the range at which the occurrence of a keloid scar is most common (age 10 to 30 years old). This is further supported by the fact that the occurrence of keloid is linked with a period of a hormonal event such as puberty and pregnancy (17). Therefore, circumcision during the period of puberty may have led some of the published cases to develop keloid after circumcision.

A complicated course of recovery following circumcision, such as infection and dehiscence may not be a major factor in the formation of a keloid scar. The reported rate of such complications varies from 0.0034% to 7.4% in populations where circumcision is a common practice (3). Where else, keloid formation, judging from the minuscule number of reports, is almost negligible and does not demonstrate a cause-and-effect relationship with complicated circumcision wounds.

While certain ethnicity such as African and Chinese are more susceptible to developing keloids in general, the same is not reflected in the occurrence of penile keloid after circumcision. Not known to be a population susceptible to keloid, the high number of reports of the formation of keloids after circumcision originating from Turkey may be due to different factors entirely. The differences in the prevalence of keloid scar in general, or perhaps in a different region of the body between ethnicities highlight the role of multiple genetic risk factors as suggested by A.S. Halim et al (2012) (18). In regard to the case being reported, the patient has a history of developing a keloidal scar and carries a strong familial history of keloid. In retrospect, these factors should be taken into account prior to circumcision and with anticipation of keloid formation, should be closely observed for its development with early interven-

tion or consider a prophylactic injection of triamcinolone immediately the following circumcision.

Considering the size of the keloid nodule, it is without a doubt that it will incur a functional problem once the patient is sexually active. While the patient did not express any psychological distress caused by the scar, it remains a potential cause for impaired self-esteem as his sexuality matures. Therefore, the objective of our treatment is immediate excision of the keloid scar and prevention of recurrence. All of the published treatment methods were effective in addressing the penile keloid scar (Table 3). Excision and concurrent injection of triamcinolone is the popular method published, however, we opted for delayed injection of triamcinolone to allow for proper wound healing to take place and not risk wound dehiscence by altering the wound healing process.

Conclusion

The minuscule number of published reports of keloid formation after circumcision underscores the rarity of the complication. No definite risk factors can be recognized to stratify patients who may develop keloid following circumcision. Excision followed by triamcinolone acetate injection with maintenance therapy until scar maturity is the preferred choice of treatment for penile keloid.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms.

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Sažetak

RETKE PENILNI KELOIDI NAKON CIRKUMCIZIJE: PRIKAZ SLUČAJA I PREGLED LITERATURE

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Cilj: Prikazati slučaj keloida formiranog nakon cirkumcizije i pregled literature za slične slučajeve kako bi se formulirali mogući faktori rizika koji doprinose njihovom razvoju, kao i mogućnosti lečenja.

Metode: Pregled literature je izveden PubMed i Google Scholar pretraživanjem reči „keloid“, „penis“ i „cirkumcizija“. Dodatna pretraživanja su izvedena iz referenci relevantnih članaka. Članci su zatim pregle-

dani od strane autora, izdvajajući moguće predisponirajuće faktore za formaciju keloida, zajedno sa demografskim osobinama pacijenata i metoda lečenja. Podaci su zatim tabelirani i analizirani pomoću programa Microsoft Excel (2018).

Rezultati: Trinaest slučajeva prikaza penilnih keloida nakon cirkumcizije kod ukupno 16 pacijenata je nađeno u periodu od 1993 do 2017. Cirkumcizija u četiri

slučaja (25%) je komplikovana infekcijom i dehiscencijom. Prosečan uzrast tokom cirkumcizije je 9 godina.

Dva pacijenta (12.5%) su zabeležena sa sklonošću za keloide. Etnička pripadnost pacijenata je sledeća; tursko (7 slučajeva, 43.7%), afričko poreklo (4 slučaja, 25%), kinesko (3 slučaja, 18.75%), indijsko (1 slučaj 6.25%) i kavkazsko poreklo (1 slučaj, 6.25%). Deset (62.5%) slučajeva je lečeno kombinacijom ekscizije i neposrednog ubrizgavanja triamcionolon acetata. Ostali su bili lečeni samo sa ekscizijom, injekcijom steroida ili ekscizijom sa topikalnim steroidima. Terapija održavanja je uključivala topikalne steroide, intra-

lezione injekcije steroida i silikonski gel. Recidiv se javio kod jednog pacijenta.

Zaključak: Minimalan broj objavljenih prikaza keloida formiranih nakon cirkumcizije naglašava retkost komplikacije. Nijedan specifičan faktor rizika ne može biti pripisan grupi pacijenata koji su razvili keloid nakon cirkumcizije. Ekscizija praćena injekcijom triamcionolon acetata sa terapijom održavanja do sazrevanja ožiljka je najčešći izbor za lečenje penilnih keloida.

Ključne reči: Penilni keloid, cirkumcizija, keloidni ožiljci.

REFERENCES

1. Weiss H, Polonsky J, Bailey R, Hankins C, Halperin D, Schmid G. Male Circumcision: Global trends and determinants of prevalence, safety and acceptability. WHO Press. 2007.
2. Malone P, Steinbrecher H. Medical aspects of male circumcision. *BMJ*. 2007; 335(7631): 1206–9.
3. Krill AJ, Palmer LS, Palmer JS. Complications of circumcision. *Sci World J*. 2011; 11: 2458–68.
4. Warwick DJ, Dickson WA. Keloid of the penis after circumcision. *Postgr Med J*. 1993; 69: 236–7.
5. Gurunluoglu R, Bayramicli M, Numanoglu A. Keloid of the penis after circumcision. *Br J Plast Surg*. 1996; 49(6): 425–6.
6. Gurunluoglu R, Bayramicli M, Numanoglu A. Two Patients with penile keloids: a review of the literature. *Ann Plast Surg*. 1997; 39(6): 662–5.
7. Bekerecioglu M, Inaloz HS, Tercan M, Isik D. Keloid formation on an inconspicuous penis. *J Dermatol*. 2005; 32(10): 835–8.
8. Erdemir F, Parlaktas BS, Sanli O, Kadioglu A, Parlaktas BS, Uluocak N et al. A rare complication after circumcision: Keloid of the penis. *Int Urol Nephrol*. 2006; 38(3–4): 609–11.
9. Isken T, Sen C, Isil E, Iscen D, Sozubir S, Gurbuz Y. A very rare complication: keloid formation after circumcision, and its treatment. *J Plast Reconstr Aesthetic Surg*. 2008; 61(11): 1405–7.
10. Lokhande A, Wiblishauser M, Khubchandani J. Keloid and hypertrophic scar formation after male circumcision. *Gulf J Dermatology Venerol*. 2010; 17(1): 50–1.
11. Demirdover C, Sahin B, Vayvada H, Oztan HY. Keloid formation after circumcision and its treatment. *J Pediatr Urol*. 2013; 9(1): e54–6.
12. Xie LH, Li SK, Li Q. Combined treatment of penile keloid: A troublesome complication after circumcision. *Asian J Androl*. 2013; 15(4): 575–6.
13. Yong M, Afshar K, MacNeily A, Arneja JS. Management of pediatric penile keloid. *Can Urol Assoc J*. 2013; 7(9–10): e618–20.
14. Cinpolat A, Seyhan T, Rizvanovic Z, Demirturk P, Bektas G. A very rare complication: keloid formation after circumcision and its treatment: case report. *Turkiye Klin J*. 2015; 23(4): 444–6.
15. Ozinko MO, Otei OO, Ikpi EE. Penile paediatric keloids: a rare presentation. *Eur J Biomed Pharm Sci*. 2015; 2(5): 33–7.
16. Sanal M, Haerter B. Keloid on the penis after circumcision: a rare complication. *Clin Surg*. 2017; 2: 1705.
17. Niessen FB, Spauwen PHM, Schalkwijk J, Kon M. On the nature of hypertrophic scars and keloids: a review. *Plast Reconstr Surg*. 1999; 104(5): 1435–58.
18. Halim AS, Emami A, Salahshourifar I, Kannan TP. Keloid scarring: Understanding the genetic basis, advances, and prospects. *Arch Plast Surg*. 2012; 39(3): 184–9.

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DEEP VEIN THROMBOSIS AND RECURENT PULMONARY EMBOLISM IN A PATIENT WITH THROMBOPHILIC MUTATIONS AND GENERALIZED PSORIASIS: A CASE REPORT

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Abstract: Introduction: Genetic risk factors that increase venous thromboembolism risk are disorders in the synthesis or activity of coagulation factors. Factor V Leiden, prothrombin (20210-A), antithrombin deficiency, protein C and protein S deficiency, and hyperhomocysteinaemia are the most common venous thromboembolism-related gene mutations. When genetic factors are combined with non-provoking risk factors (obesity, psoriasis, smoking and previous venous thromboembolism) the result is increased venous thromboembolism risk for each factor individually. Previous venous thromboembolism is one of the strongest risk factors, even in patients actively treated with anticoagulant. Patients are more likely to have recurrent venous thromboembolism with longer duration. Psoriasis is a complex immune-mediated disease, associated with cardiovascular risk, hypercoagulability markers and elevated homocysteine. Lots of observational reports suggest increased incidence of venous thromboembolic events in patient with psoriasis.

Case presentation: We present patient with inherited thrombophilia and chronic diffuse plaque psoriasis complicated with deep venous thrombosis and pul-

monary embolism. DNA analysis indicates the presence of homozygosis for Factor V Leiden mutation as well as heterozygosis for Factor XIII V34L, PAI-1 5G/4G and MTHFR A1298C polymorphism. Dermatological anamnesis is positive for plaque psoriasis since 12 years ago.

Conclusion: The presentation of this case indicates an association between venous thromboembolism and chronic psoriasis. All patients with recurrent thromboembolism, hereditary thrombophilia, and moderate to severe psoriasis should be considered to be at higher risk for venous thromboembolism and appropriately treated.

Key words: Recurrent venous thromboembolism, thrombophilia, psoriasis, pulmonary embolism.

INTRODUCTION

Venous thromboembolism (VTE) comprising deep venous thrombosis (DVT) and pulmonary embolism (PE) is a common medical problem, which can be predisposed by several medical conditions as trauma, surgery, immobilization, chronic inflammation or cancer, or genetic mutations. Recently there are studies

about systemic chronic inflammation as potential risk factor for VTE. The relationships stems from the impact of the chronic inflammation on the aggregation of the platelets, activation of the coagulation cascade, and stimulation the pro-coagulant activity of the inflammatory cytokines and decrease of the activity of the anti-coagulant and fibrinolytic systems. Therefore some studies suggest that patients with elevated inflammatory markers (C reactive protein (CRP) and other inflammatory cytokines IL-6, IL-8 and TNF) have an increased risk of VTE (1). This positive association between inflammatory makers and VTE is highly suggestive but it's unclear whether the inflammation and its inflammatory cytokines are responsible and causative component for generating a VTE event. Several systemic inflammatory diseases has been linked with increased VTE risk, in a large epidemiologic studies, such as rheumatoid arthritis (RA), psoriasis, inflammatory bowel disease, systemic lupus erythematodous (2). Psoriasis is a chronic complex immune – mediated disease, wich activates both Th1 and Th 17 inflammatory pathways that afflicts not only the skin and joints but involves the endothelium as well and results in increased IL6 and TNF cytokines so the patients often has elevated CRP (3). Worldwide review revealed the prevalence of psoriasis ranged from 0,5-11,4 % in adult and 0-1,4 % in children (4). It's associated with cardiovascular risk, hypercoagulability markers and elevated homocysteine (Hcy) (5). A cohort study conducted by Ahlehoff et al., in Denmark demonstrated age and severity dependent increase in risk of cardiovascular mortality in psoriasis patients. In this report we present patient with inherited trombophilia and chronic diffuse plaque psoriasis complicated with DVT.

CASE REPORT

We present a case of a 40-year-old male patient in the intensive care unit admitted for severe breathing, suffocation approaches, chest pain, swelling and pain in the left calf, acute DVT in the left femoral and popliteal vein, given episode of DTV and PE 7 years ago. Anamnestic few days back, with pain and swelling in the left calf. From day one, chest pain, shortness of breath, dyspnea, inhalation pain and hemoptysis in two occasions. The symptoms intensify one hour before admission to ER. Examinations show increase in D-dimers 19000 µg/L, cO₂ -88%. Leukocytosis 11×10^9 /L, SE 45, CRP 65 mg/L, Hemostasis TT 13,2; INR 1. Venous doppler on the left calf: v. poplitea of increased size, partially compressible, with visible thrombotic substrate in the lumen. Left v. safena parva in upper half uncompressible, dilated, with visible thrombotic substrate, absent color doppler signal. The remaining deep veins to the left with neat dimensions, compressible re-

spiratory modulated, spontaneous flow. Left v.safena magna with neat dimensions, compressible, spontaneous flow. No reflux was observed at the left saphenofemoral joint. Right: normal finding. The finding on CT scan is in addition to extensive filling defects that correspond to thrombi in both major pulmonary arteries. Left in the segmental artery for the lower lobe, a highly suspected lingual defect in the filling is also present in the segmental artery for the upper lobe. In addition to the filling defect in the main artery there are also defect in segmental and sub-segmental arteries for the lower lobe as well as a small filling defect in the artery for the upper lobe, the transverse diameter of the truncus pulmonalis is 3 cm. Data for PE 7 years ago, (treated with the Acenocoumarol 4 mg pattern until two years ago, therapy was discontinued alone). Comorbidities: HTA, obesity, psoriasis, recurrent VTE. Personal history: single, smoking a pack of cigarettes a day. Family history: The patient did not have a history of recent trauma, immobilization, distant traveling, fever or history of cancer but had a positive family history of thrombosis. His mother had two miscarriages and history of trombophlebitis, and is set on a regular oral anticoagulant therapy. General status: Accepted conscious, oriented, afebril, distinctly dyspnoeic, hemodynamically compensated, obese with BMI 34.7 kg/m², skin and visible mucus pale color. Lungs: vesicular breathing. Heart: rhythmic action, tachycardia with HR 110/min, clear tones, TA 150/90 Extremities: pronounced swelling of left calf, warm skin with preserved coloration and pulse of a.dorsalis pedis. The patient is suffering from severe case of plaque psoriasis for the last 12 years. Diffusely distributed erythematous plaques with prominent hyperkeratosis on the trunk, extensor area of the extremities and scalp. His PASI score is 56. Itching is pronounced on the trunk. (Figure 1, 2 and 3.). He



Figure 1. Psoriatic squamous plaques



Figure 2. Psoriatic plaques on the lower leg

reports a worsening of psoriasis at the same time as VTE. Echocardiography: LVs 50 mm, LVd 34 mm, RV 28 mm, LA 38 mm, Ao 21/34 mm IVS 9 mm; PW 9 mm; EF 60%. Mild tricuspid regurgitation, without pulmonary hypertension (SPAP 29 mmHg). Treatment: After 48h of intravenous anticoagulant use, the anticoagulant was then shifted to Rivaroxaban. Antibiotics were administered parenteral the same. The following recommendation for home therapy is given: Tbl Rivaroxaban a 15 mg 2 x 1 three weeks, then Tbl Rivaroxaban a 20 mg 1 x 1; Tbl Atorvastatin a 10 mg 1 x 1; and regular therapy for HTA tbl Losartan 50 mg 2 x



Figure 3. Diffuse extensive thick plaques

1 and tbl Lerkandipin 10 mg, tbl Indapamid 1,5 mg Tbl Cefixime a 400 mg 2 x 1 seven days, as well as treatment for psoriasis in consultation with a dermatologist. Realized genetic studies of thrombophilic genes are shown in Table 1. Tests in this patient indicate homozygosity for Factor V Leiden mutation, as well as heterozygosity for Factor XIII V34L, PAI-1 5G/4G and MTHFR A1298C polymorphisms. Control CT angiography after 6 months with full resolution. Control vein Doppler after 3 months - deep veins are neat, compressible with spontaneous flow. Anticoagulant therapy in these patients with recurrent thromboembolism is lifelong with regular controls for all provocative factors and psoriasis.

DISCUSSION

About 20-30 single nucleotide polymorphisms (SNPs) are associated with the risk of VTE through the candidate gene discovered by genotyping methods, although for some mutations, the clinical relevance and underlying pathophysiological mechanism remain un-

Table 1. Thrombophilic gene mutations

Gen (according to HGNC)	Referent sequence	Mutation		Genotype according to HGVS of the investigated mutations
		Standard nomenclature (according to HGVS)	Traditional nomenclature	
F5	NM_000130.4	c.1601G > A	Factor V Leiden	c.[1601G > A]; [1601G > A]
		c.3980A > G	Factor V H1299R	[=]; [=]
F2	NM_000506.3	c.*97G > A	FactorIIIG20210A	[=]; [=]
F13A1	NM_000129.3	c.103G > T	Factor XIII V34L	c.[103G > T]; [=]
FGB	NM_005141.4	c.-463G > A	FFB 455 G/A	c.[-463G > A]; [=]
SERPINE1	NM_000602.4	c.-816A > G	PAI-1 5G/4G	c.[-816A > G]; [=]
MTHFR	NM_005957.4	c.665C > T	MTHFR C677T	c. [665C>T]; [=]
MTFHR	NM_005957.4	c.1286A > C	MTHFR A1298C	c.[1286A > C]; [=]
MTRR	NM_002454.2	c.66A > G	MTRR A66G	c.[66A > G]; [=]
MTR	NM_000245.2	c.2756A > G	MTR A2756G	c.[2756A > G]; [=]

clear. The most common are Factor V Leiden and Prothrombin gene mutation, with estimated prevalence of 4-5% and 2-4%, respectively (6). Individuals that are homozygous for Factor V Leiden are even more prone to VTE with nearly 40 times the risk compared to a 2-7 fold increase in risk in heterozygous individuals (7). This case is of interest because recurrence occurs as a result of this patient's provocative risk factors: BMI = 34.7 kg/m², smoking, previous DVT as one of the strongest risk factors and psoriasis as a generalized chronic inflammatory condition. The genetic profile predisposing the patient to thrombophilia and thromboembolism is also of interest: the mutations factor V Leiden and MTHFR A1298C are already known, and Factor XIII V34L, PAI-1 5G/4G heterozygous form has been recently proposed as a prothrombotic risk factor for venous thrombosis in Caucasian populations. The patient had a long history of psoriasis, treated only with topical creams, and has history of previous thrombophilia and DVT, was smoker, obese, hypertensive with metabolic Sy, and he has thrombophilic mutations. The first one who recorded this association in the dermatological literature was Bunch (8). Subsequently a lot of reports and growing evidence of VTE events in psoriasis appeared. A nationwide cohort study was conducted in Denmark, from 1997-2006, which indicated increased risk of VTE in psoriasis patients. A large prospective-population based study of almost 40.000 patients, revealed - that psoriasis is associated with 40% increased risk of incident VTE (9). Still the pathogenesis is unknown. One of the proposed hypothesis is the process of systemic chronic inflammation, via genetic mechanism, produces inflammatory proteins. Elevated levels of inflammatory mediators like CRP and cytokines, in psoriatic patients are related to the coagulation cascade and subsequently may lead to platelet aggregation and clot formation (10). Also the existing eosinophils in psoriasis acts as thrombogenic factors regulated by the inflammation which lead to hypercoagulable or prothrombotic state. The second hypothesis is elevated levels of homocysteine due to the condition or its treatment. Several mechanisms for hyperhomocysteinemia are proposed - Hcy is directly toxic to vascular and endothelial cells, decrease the NO bioavailability which contributes to thrombosis (11) or it blocks the binding of tissue plasminogen activator which leads to decrease in plasmin production and extravascular fibrin deposition. Another prothrombotic mechanism is related to decreased expression of thrombomodulin which is essential for activation of the anticoagulant protein C.

There are studies that demonstrate that deficiency in folic acid, Vit B12 and B6 which are involved in the synthesis of Hcy is the main reason for hyperhomocysteinemia. Persons carriers of MTHFR polymorphism predisposes elevated Hcy levels. The A1298C polymorphism in the MTHFR gene shows an association with the risk of cardiovascular event and subclinical atherosclerosis in patient with RA (12). Polymorphism in the Factor XIII gene, V34L, has a small, but significant protective effect against venous thrombosis. It has also been associated with lower risk for stroke and myocardial infarction. Plasminogen activator inhibitor-1 (PAI-1) is the major inhibitor of tissue type plasminogen activator (tPA). Increased plasma PAI-1 levels due to reduced fibrinolytic capacity plays an important role in the pathogenesis of disorders associated with thrombosis. This polymorphism has been studied extensively, the prevalence of 4G allele was found to be higher in disorders like coronary artery disease, severe pre-eclampsia, type 2 diabetic nephropathy, PE and arterial thrombosis associated with hereditary protein S deficiency (13).

CONCLUSION

The present case report suggests a relation between systemic inflammation, thrombophilia and risk of VTE, and it suggests that patients with even mild to moderate psoriasis may be at an elevated risk of a VTE event. Screening patients with psoriasis for additional risk factors that promote thrombosis should be considered. Until further evidence is available, all patients with mild to moderate psoriasis may be considered to be at a higher risk of venous thromboembolism and managed accordingly.

Abbreviation

DVT — deep venous thrombosis
PE — pulmonary embolism
VTE — venous thromboembolism

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Sažetak

DUBOKA VENSKA TROMBOZA I REKURENTNA PLUĆNA EMBOLIJA KOD PACIJENTA SA TROMBOFILICNIM MUTACIJAMA I GENERALIZOVANOM PSORIJAZOM: PRIKAZ SLUČAJA

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Uvod: Genetski faktori rizika koji povećavaju rizik venske tromboembolije su poremećaji u sintezi ili aktivnosti faktora koagulacije. Faktor V Leiden, protrombin (20210-A), antitrombinski deficit, deficit proteina C i proteina S i hiperhomocisteinemija najčešće su mutacije gena povezane sa venskom tromboembolijom. Kada se genetski činioci kombinuju sa neprovocirajućim faktorima rizika (gojaznost, psorijaza, pušenje i prethodna venska tromboembolija), rezultat je povećani rizik venske tromboembolije za svaki faktor pojedinačno. Prethodna venska tromboembolija je jedan od najjačih faktora rizika, čak i kod pacijenata koji su aktivno lečeni antikoagulantima. Pacijenti imaju veću verovatnoću da imaju ponavljajuću vensku tromboemboliju sa dužim trajanjem. Psorijaza je kompleksna imuno posredovana bolest, povezana sa kardiovaskularnim rizikom, markerima hiperkoagulabilnosti i povišenim homocisteinom. Mnogo izveštaja o opservacijama sugerise po-

većanu učestalost venskih tromboembolijskih događaja kod pacijenata sa psorijazom.

Prikaz slučaja: Predstavljamo pacijenta sa trombofilijom i hroničnom difuznom psorijazom komplikovani dubokom venskom trombozom i plućnom embolijom. DNA analiza ukazuje na prisustvo homozigota za mutaciju Faktora V Leiden, kao i heterozigota za polimorfizam Faktora XIII V34L, PAI-1 5G/4G i MTHFR A1298C. Dermatološka anamneza pozitivna je za plakarnu psorijazu od pre 12 godina.

Zaključak: Prikaz ovog slučaja ukazuje na povezanost venske tromboembolije i hronične psorijaze. Svi pacijenti sa ponavljajućom tromboembolijom, naslednom trombofilijom, umerenom do teškom psorijazom treba da se smatraju sa visokim rizikom od venske tromboembolije i da se na odgovarajući način leče.

Cljučne reči: ponavljajuća venska tromboembolija, trombofilija, psorijaza, plućna embolija.

REFERENCES

1. Fox EA, Kahn SR: The relationship between inflammation and venous thrombosis. A systematic review of clinical studies. *Thromb Haemost.* 2005; 94(2): 362-5.
2. Ogdie A, Kay McGill N, Shin DB, Takeshita J, Love TJ, Noe MH et al. Risk of venous thromboembolism in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a general population-based cohort study. *Eur Heart J.* 2018; 39(39): 3608-14.
3. Karabudak O, Ulusoy RE, Erikci AA, Solmazgul E, Dogan B, Harmaneri Y. Inflammation and hypercoagulable state in adult psoriatic men. *Acta Derm Venereol.* 2008; 88(4): 337-40.
4. Michalek IM, Loring B, John SM. A systematic review of worldwide epidemiology of psoriasis. *J Eur Acad Dermatol Venereol.* 2017; 31(2): 205-12.
5. Ahlehoff O, Gislason GH, Lindhardsen J, Charlott MG, Jorgensen CH, Olesen JB et al. Psoriasis carries an increased risk of venous thromboembolism: A danish nationwide cohort study. *PloS one.* 2011; 6(3): e18125.
6. Heit J, Sobell J, Li H, Sommer SS. The incidence of venous thromboembolism among Factor V Leiden carriers: a community-based cohort study. *J Thromb Haemost.* 2005; 3(2): 305-11.
7. Saemundsson Y, Sveinsdottir SV, Svantesson H, Svensson PJ. Homozygous Factor V Leiden and double heterozygosity for factor V Leiden and prothrombin mutation. *J Thromb Thrombolysis.* 2013; 36(3): 324-31.
8. Bunch JL. Psoriasis associated with thrombosis of the Inferior Vena Cava. *Proc R Soc Med.* 1914; 7: 257-8.
9. Lutsey P, Prizment A, Folsom A. Psoriasis is associated with a greater risk of incident venous thromboembolism: the

Iowa Women's Health Study. *J Tromb Haemost.* 2012; 10(4): 708-11.

10. Gisondi P, Malerba M, Malara G, Puglisi Guerra A, Salla R, Radaeli A, et al. C-reactive protein and markers for thrombophilia in patients with chronic plaque psoriasis. *Int J Immunopathol Pharmacol.* 2010; 23(4): 1195-202.

11. Hajjar KA, Mauri L, Jacovina AT, Zhong F, Mirza UA, Padovan JC et al. Tissue plasminogen activator binding to the annexin II tail domain. Direct modulation by homocysteine. *J Biol Chem.* 1998; 273(16): 9987-93.

12. Palomino-Morales R, Gonzalez-Juanatey C, Vazquez-Rodriguez TR, Rodriguez L, Miranda-Filloo JA, Fernandez-Gutierrez B, et al. A1298C polymorphism in the MTHFR gene predisposes to cardiovascular risk in rheumatoid arthritis. *Arthritis Res Ther.* 2010; 12(2): R71.

13. Zoller B, Garcia de Frutos P, Dahlback B. A common 4G allele in the promoter of the plasminogen activator inhibitor-1 (PAI-1) gene as a risk factor for pulmonary embolism and arterial thrombosis in hereditary protein S deficiency. *Thromb Haemost.* 1998; 79(4): 802-7.

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LOST KIDNEY IN GOODPASTURE SYNDROM - CASE REPORT

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Abstract: Introduction: Goodpasture syndrome is a rare autoimmune syndrome with alveolar hemorrhages and glomerulonephritis caused by circulating antibodies against the glomerular-basement-membrane. Anti-glomerular-basement-membrane were administered against a non-collagen (*NC-1*) $\alpha 3$ chain of collagen type IV, which was found at the highest concentration in the basal membrane of renal and pulmonary capillaries. The aim of case report is a clinical overview of this rare and severe syndrome.

Case report: The patient, 22-years-old was sent to Center of Urgent Medicine of Clinical Center Kragujevac from General Hospital of Paraćin because of blood poisoning, fever, symptoms and signs of renal and respiratory weakness, and suspected of Wegener's disease. Antibodies were taken on the basement membrane of the glomerulus were resulted of enormously high. After due to the clinical and immunology diagnosis of Goodpasture syndrome, plasmapheresis treatment was initiated. The standard hemodialysis was continued. Following the guidelines protocols, patient received pulse doses of cytostatics, corticosteroids, etc.

Conclusion: The case report of our patient points to the necessity of multidisciplinary approach of the expert team, consisting of a nephrologist, pulmonologist, clinical pharmacologist and other specialists. The prognosis is good, if treatment is started before irreversible pulmonary and/or renal changes (respiratory and/or renal insufficiency). Goodpasture syndrome often progresses rapidly, so it can be fatal if it's delayed with the diagnosis and the treatment. Patients with Goodpasture's syndrome require an adequate the socio-medical care as a rare and severe syndrome.

Key words: Goodpasture's syndrome, autoimmune diseases, anti-glomerular basement disease and antibody, pulmonary hemorrhage, glomerulonephritis.

INTRODUCTION

Goodpasture syndrome is a rare autoimmune syndrome with alveolar hemorrhages and glomerulonephritis caused by circulating antibodies against (anti) glomerular-basement-membrane (GBM) and most commonly affects genetically predisposed in younger men. The estimated incidence of Goodpasture syndrome is one case per million per year (1). Anti-GBM antibodies were administered against a non-collagen (*NC-1*) $\alpha 3$ chain of collagen type IV, which was found at the highest concentration in the basal membrane of renal and pulmonary capillaries (1). Exposure - the smoking, the viral infection of the upper respiratory tract, the inhalation of carbon dioxide waste, as well as pneumonia induction of the alveolar capillary to circulating antibodies, especially those with *HLA-DRw15 allele*, *-DR4* and *-DRB1 allele* (1). GBM circulating antibodies bind to basal membrane, fix complement, and stimulate the cellular inflammatory response, causing glomerulonephritis and/or pulmonary capillaritis. Symptoms and signs of disease include dyspnoea, cough, tiredness, hemoptysis, hematuria, proteinuria, increased body temperature, weight loss, peripheral edema, pale skin and visible mucous due to sideropenic anemia, arthralgia, uremia, hypertension, cotton wool deposits and vasculitis on retina, etc. For diagnosis of Goodpasture's syndrome, it is necessary to demonstrate serum of anti-GBM antibodies with indirect immunofluorescence or ELISA with recombinant or human *NC-1* $\alpha 3$ directly bound antibodies to the antigen-membrane glomeruli (1). Other serological tests, such as ANA for the detection of System Lupus, Chyrg-Strayss's disease, Bechcet's diseases and the antistreptolysin O-titer for the proving of poststreptococcal glomerulonephritis were used in the differential diagnosis (1). In the case of glomerulonephritis (hematuria, proteinuria, erythrocyte cylinders in urine and/or renal in-

sufficiency), the kidney biopsy is indicated. Progressive focal segmental necrotic zealous glomerulonephritis with sickle (crescentic) creatures was found in the biopate. The immunofluorescence coloring of lung and kidney samples shows diffusely distributed immunoglobulin deposits of IgG, sometimes IgA and IgM, along the basal membrane of alveoli capsules and glomeruli. In addition to the insufficiency of pulmonary function of the restrictive type with hypoxemia, the diffuse capacity for carbon monoxide has been increased due to the presence of blood in alveoli. It was treated with plasmapheresis, corticosteroids and immunosuppressants. It was treated daily or every other day by plasmapheresis 2 to 3 weeks to eliminate circulating anti-GBM antibodies, in combination with iv pulse doses of corticosteroids (usually methylprednisolone 1 g for 20 min every other day in 3 doses, and then 1 mg/kg of prednisone 1 x/day) and cyclophosphamide (in bolus and than 2 mg/kg 1 x/day) for 6 to 12 months to prevent the formation of new antibodies (1). After renal transplantation for renal insufficiency, this disease can be recidivated. The prognosis is good if treatment is started before irreversible pulmonary and/or renal changes, i.e. respiratory or renal insufficiency. Goodpasture syndrome often progresses rapidly, so it can be fatal if it's delayed with the diagnosis and the treatment. The aim of this case report is a clinical overview of this rare and severe syndrome.

CASE REPORT

The patient, 22-years-old was sent to the Center of Urgent Medicine of Clinical Center Kragujevac from General Hospital of Paraćin because of blood poisoning, fever, symptoms and signs of renal and respiratory weakness and suspected of Wegener's disease. After the examination in Internist Clinic, patient was immediately admitted to the Stationary Section of Urgent Medicine Center of Clinical Centre of Kragujevac due to the extremely low saturation values measured by the pulse oximeter in the room air. The patient's report had occurred suddenly, by coughing up blood and elevated body temperature. The auscultator findings of the lungs were dominated by inspiratory fractures, both in the middle and lower lungs. The computerized tomography of chest, with the protocol for pulmoangiography excluded the presence of pulmonary thromboembolism. The confluent murmur, alveolar infiltrates with larger consolidations in the lower lobe posterobasal was observed diffusely. Both sides of the lower part of lungs had the pleural effusion. The heart action was tachyarrhythmia and the sounds were good with no noise. The echocardiographic examination was a neat. The radiographic examination of the heart and lungs



Figure 1. Patient attached device for noninvasive mechanical ventilation and oxygen catheter

were record alveolar infiltrations in the middle and lower lung fields on both sides, and more on the left. The upper echo abdominal was tidy. The echo of urinary tract showed an unclear medullocortical boundary and brighter kidney parenchyma. The pANCA and cANCA antibodies were negative as well as other standard immunological analyzes, that were made due to suspicion of Wegner's disease. Goodpasture's syndrome was suspicion after the consultative review of pulmonologist, nephrologist, infectologist, clinical pharmacologist, ophthalmologist, etc. Antibodies were taken on the basement membrane of glomeruli. The result of the required antibodies was enormously high. Until the arrival of the immunological confirmation, patient with Goodpasture syndrome was treated with antibiotics and symptomatic therapy, as well as standard hemodialysis. After the arrival of high GBM-titer, and due to the clinical diagnosis of Goodpasture's syndrome, the plasma-treatment was initiated. The standard hemodialysis was continued. Following the standard protocols, patient received pulse dozed of cytostatics, corticosteroids, etc. At beginning of the illness, the diuresis was low at level of oliguria, and after two weeks of baking over 2000 ml. Due to respiratory weakness, the patient was attached to the device for non-invasive mechanical ventilation for five days, shortly afterwards on oxygen catheter (Figure 1). In biochemical analyzes, leucocytosis, lower hemoglobin levels, hypoproteinaemia, hypoalbuminemia, hyperasothemia and elevated parameters of inflammation were recorded (Table 1). The control antibody determined by ELISA was significantly reduced with 200 U/mL, 160 U/mL, 110 U/mL, 34 U/mL and 10 U/mL compared to the first analysis (Table 2). The computerized tomography of chest reveals the reticulonodular lung infiltrate and extensive bilateral consolidations (Figure 2). Echo of urinary tract showed the unclear medullocortical boundary and brighter kidney parenchyma in Figure 3.

Table 1. Biochemical analyzes (erythrocytes, leucocytosis, hemoglobin, hypoproteinaemia, hypoalbuminemia, hyperasothemia, parameters of inflammation, etc)

Biochemical analyzes	Results	References
Erythrocytes	2.91	$4.34 - 5.72 \times 10^{12}/L$
Hemoglobin	84	138 – 175 g/G
MCV	87.6	80 – 97.2 (fL)
Leucocytes	15.54	$3.7 - 10.0 \times 10^9/L$
Trombocytes	149	$135 - 450 \times 10^9/L$
Creatinine	261	49 -106 mol/L
Urea	20.1	3.0-8.0 mmol/L
CRP	25.8	0.0 – 5.0 mg/L
Total serum protein	31	64 - 83 g/L
Serum albumin	24	35 – 52 g/L
24-hour-proteinuria	15.4	0.04 - 0.15 g/24h

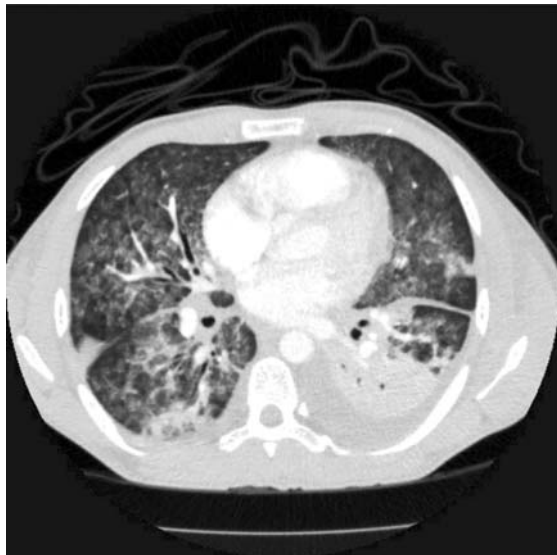
MCV - Mean Corpuscular Volume

CRP - C-Reactive Protein

Table 2. ELISA-control antibody reduced with compared to the first analysis

ELISA - Immunology	Results	Reference	Date
GBM antibody	200 U/mL	<20.0	5 th May 2019 (first analysis)
GBM antibody	163 U/mL	<20.0	11 th May 2019
GBM antibody	110 U/mL	<20.0	18 th May 2019
GBM antibody	34 U/mL	<20.0	28 th May 2019
GBM antibody	10 U/mL	<20.0	3 th June 2019

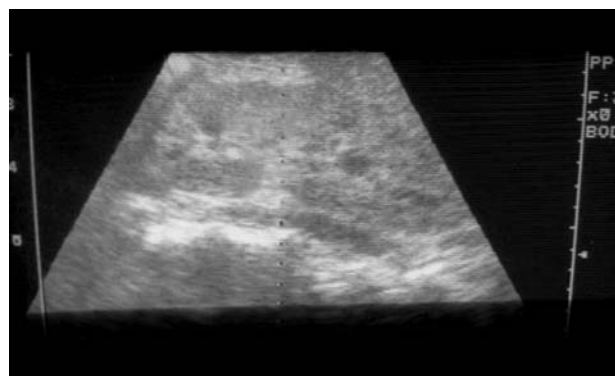
GBM antibody - antibodies against Glomerular-Basement-Membrane

**Figure 2.** Computerized tomography of chest revealed reticulonodular lung infiltrate and extensive bilateral consolidations

The Social history of our patient wasn't notable. The kidneys of young man were saved.

DISCUSSION

Our case report illustrates the complex nature of Goodpasture's syndrome. Antibodies from our patient were taken on the basal membrane of glomerulus, and

**Figure 3.** Echo of urinary tract showed unclear medullocortical boundary and brighter kidney parenchyma

desired antibody result was extremely high. Due to clinical and immunological diagnosis of Goodpasture syndrome, plasma treatment has begun and standard hemodialysis has been continued. By using follow-up clinical standard protocols, patient received pulse doses of cytostatics, corticosteroids, and other therapies. Timely diagnosis and adequate therapy saved the "lost kidney" of this young person, which the active life is preserved. The disease of the anti glomerular basal membrane is a rare, and an antibody-mediated disease. Consecutive severe changes are deposited which arise depending on the localization where these antibodies.

The most patients have joint pulmonary, kidney and other lesions. The renal system is the primary localization of damage with catastrophic exacerbation of acute glomerular inflammation of kidneys, from just a few days after diagnosis – Goodpasture's syndrome. Goodpasture syndrome refers to the condition characterized by pulmonary haemorrhagia and glomerulonephritis. Clinicians can use several terms, including the disease against the glomerular basement membrane, as Goodpasture syndrome and as Goodpasture disease. This last term is the most specific term and refers to the presence of kidney and lung infections, together with antibodies to glomerular basement membrane (2). Goodpasture's disease is an autoimmune disease that endangers life and can lead to kidney disease and death in the final phase. The diagnosis of anti-GBM-disease requires high clinical suspicion, necessary for early diagnosis and adequate treatment in order to improve survival rates (3). Antibodies initiate kidney glomeruli destruction, resulting in focal necrotizing glomerulitis, which can rapidly progress to renal failure. Damage to alveolar basal membranes mediated by autoantibodies leads to pulmonary hemorrhage, which causes respiratory failure. The immunofluorescence testing on anti-GBM antibodies on lung and kidney tissues confirms the diagnosis of Goodpasture syndrome. Tests can be falsely negative in 15% of patients with Goodpasture syndrome (4). The pathology is characterized by linear immunofluorescence coloring for immunoglobulin-G on glomerular base membrane, while bronchoscopy doesn't to show the obvious lesion. The kidney biopsy shows the fibrinoid necrosis. The research shows that early and aggressive therapy leads to improved disease forecasts (5). Patients may be twice as positive for anti-GBM and anti-proteinase-3 neutrophilic cytoplasmic antibodies (c-ANCA). Other patients may be twice as positive for anti-GBM and anti-myeloperoxidase cytoplasmic antibodies (p-ANCA). The antibodies are associated with serum ANCA in 10-40% of patients and indicate a poor prognosis of this disease. The function of auto reactive T cells is poorly defined, but it may involve a change from T_{H2} to T_{H1} cytokine regulation, thus improving the antigenic specificity of the antibody response. Timely diagnosis and triple therapeutic regimen involving plasmapheresis, corticosteroids and immunosuppressive drugs significantly improve patient outcomes, resulting in a survival rate of 70-90% for one year (6). The common immunodeficiency variable is the primary immunodeficiency that is manifested by hypogammaglobulinemia, the inability to create functional antibodies, and recurrent infections. The clinical course may be complicated by hypertensive encephalopathy, meningoencephalitis, status epilepticus, the change in the retina, the cutaneous-vasculitis, etc (7,

8). Autoantibody stimulates local capillaritis, which is manifested as progressive glomerulonephritis in 80-90% of patients, with concurrent alveolar bleeding in 50%. A small number of cases can be isolated from progressive pulmonary disease. Alveolar bleeding usually responds to treatment, and long-term respiratory complications are rare. Kidney prognosis is variable, although with aggressive treatment, an independent kidney function is maintained for one year in more than 80% of patients who do not require renal replacement therapy. In the case of unusual anti-GBM disease, unless there is the accompanying anti-neutrophilic cytoplasmic antibody (30-40%), maintenance of immunosuppression is also recommended (9). Hypertension may be present in 70% of cases, proteinuria (>3.5 g/24 h) in 42% of cases, nephrotic syndrome in 37%, microhematuria in 95%, renal insufficiency in 63%, lung abnormalities and anemia in 16% of patients. The electron microscopy can detect sparse electronic deposits in glomeruli or globally remove the sub-cell (10, 11). A small number of cases have been reported with eye symptoms and visual disturbances in the context of this rare syndrome. Ophthalmoscopic, bilateral cotton wool deposits were detected bilaterally along the blood vessels and bilateral retinal bleeding predominantly on the back half of the eye. By intensifying the existing antihypertensive therapy, vision is significantly improved. Although it is seen more often in Goodpasture syndrome, it is important to be aware of eye pathology because it can refer to diagnosis of this syndrome (12). The pathophysiology of this condition is understood by molecular analysis of the interactions of antibodies and antigens and the use of human leukocyte antigen-transgenic animals, while the association of anti-GBM antibodies with anti-neutrophilic antibodies to cytoplasm and their combined effect on the phenotype of the disease is increasingly recognized, providing some insights into the basis of glomerular damage and autoimmunity (13, 14). Tashiro et al points to pathological findings in autopsy with progressive glomerulonephritis, diffuse alveolar bleeding and fibroblast foci in the lungs. The cause of death is diagnosed as respiratory failure and the result of diffuse alveolar damage caused by a combination of diffuse alveolar bleeding and exacerbation of the interstitial pneumonia. Goodpasture syndrome with already existing chronic interstitial pneumonia and anti-neutrophil antibody against neutrophils is associated with poor prognosis (15).

CONCLUSION

The case report of our young patient (Goodpasture's Syndrome) points to the necessity of a multidisciplinary approach in the treatment including medical team consisting of a nephrologist, pulmonologist, clinical

pharmacologist, ophthalmologist, and others. The prognosis is good, if treatment is started before irreversible pulmonary and/or renal changes, i.e. respiratory and/or renal insufficiency. Goodpasture syndrome often progresses rapidly, so it can be fatal if it's delayed with the diagnosis and the treatment. Patients with Goodpasture syndrome require adequate the socio-medical care of the society, as a rare and severe syndrome. The kidneys of young man were saved.

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Sažetak

IZGUBLJEN BUBREG U GOODPASTURE-OVOM SINDROMU - PRIKAZ SLUČAJA

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Uvod: Goodpasture sindrom je redak autoimuni sindrom s alveolarnim hemoragijama i glomerulonefritisom, uzrokovanim cirkulišućim antitelima na bazalne membrane glomerula. Antitela na bazalnu membranu glomerula usmerena su protiv nekolagenog dela (NC - 1) á3 lanca kolagena tipa IV, koji se nalazi u najvećoj koncentraciji u bazalnoj membrani bubrežnih i plućnih kapilara. Cilj prezentacije pacijenta je klinički osvrt na ovaj redak i težak sindrom.

Prikaz slučaja: 22-godišnji pacijent je zbog iskašljavanja krvi, groznice, simptoma i znakova bubrežne i respiratorne slabosti, a pod sumnjom na Wegener-ovu bolest, upućen je na Urgentnu medicinu Kliničkog centra Kragujevac iz Opšte bolnice Paraćin. Uzeta su antitela na bazalnu membranu glomerula, a rezultat traženih antitela bio je izuzetno visok. Zbog kliničke i imunološke dijagnoze Goodpasturovog sindroma, započeto je

lečenje plazmaferezom. Nastavljena je standardna hemodijaliza. Koristeći smernice protokola, pacijent je primio pulsne doze citostatika, kortikosteroida i dr.

Zaključak: Prikaz slučaja našeg pacijenta ukazuje na neophodnost multidisciplinarnog pristupa tima eksperata koji se sastoji od nefrologa, pulmologa, kliničkih farmakologa i drugih specijalista. Prognoza bolesti je dobra, ako se lečenje započne pre pojave ireverzibilnih plućnih i / ili bubrežnih promena, tj. respiratorne i/ili bubrežne insuficijencije. Goodpasture-ov sindrom često brzo napreduje i može biti fatalan ukoliko se sa dijagnozom i lečenjem zakasni. Pacijenti s Goodpastureovim sindromom zahtevaju adekvatnu društveno-medicinsku negu, kao redak i težak sindrom.

Ključne reči: Goodpasture-ov sindrom, autoimune bolesti, bolest glomerularne bazalne membrane i antitela, plućne hemoragije, glomerulonefritis.

REFERENCES

1. Nasrullah A, Fatima Z, Javed A, Tariq U, Saleem MS. A case of anti-glomerular basement disease without pulmonary involvement. *Cureus*. 2019; 11(2): e4130.
2. DeVrieze BW, Hurley JA. Goodpasture Syndrome (Anti-glomerular Basement Membrane Antibody Disease) [Updated 2020 Mar 25]. In: StatPearls [Internet]. Treasure Island (FL): Stat Pearls Publishing; 2020 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK459291/>
3. Kheiri B, Osman M, Elounais F, Alnimer Y, Owda AK, Modawi I, et al. A case report of double negative anti-GBM disease. *Oxf Med Case Reports*. 2019; (4): omy124.
4. Kussman A, Gohara A. Serum antibody-negative Goodpasture syndrome with delta granule pool storage deficiency and eosinophilia. *Clin Kidney J*. 2012; 5(6): 572-5.
5. Fernandes R, Freitas S, Cunha P, Alves G, Cotter J. Goodpasture's syndrome with absence of circulating anti-glomer-

ular basement membrane antibodies: a case report. *J Med Case Rep*. 2016; 10: 205.

6. Dammacco F, Battaglia S, Gesualdo L, Racanelli V. Goodpasture's disease: a report of ten cases and a review of the literature. *Autoimmun Rev*. 2013; 12(11): 1101-8.

7. Mannemuddhu SS, Clapp W, Modica R, Elder ME, Upadhyay K. End-stage renal disease secondary to anti-glomerular basement membrane disease in a child with common variable immunodeficiency. *Clin Nephrol Case Stud*. 2019; 7: 1-6.

8. Kluger N. Cutaneous vasculitis preceding the onset of anti-GBM disease (Goodpasture syndrome). *Presse Med*. 2019; 48(Pt 1): 79-80.

9. McAdoo SP, Pusey CD. Antiglomerular basement membrane disease. *Semin Respir Crit Care Med*. 2018; 39(4): 494-503.

10. Liang D, Liang S, Xu F, Zhang M, Li X, Tu Y, et al. Clinicopathological features and outcome of antibody-negative anti-glomerular basement membrane disease. *J Clin Pathol*. 2019; 72(1): 31-7.

11. Talash V, Bevzenko T, Yarmola T, Tkachenko L, Pustovoyt H. Goodpascher's syndrome – the challenges in a timely diagnosis and treatment in medical practice (clinical case). Georgian Med News. 2018; 278: 107-14.
12. Lommatzsch C, Lommatzsch A, Heinz C, Heiligenhaus A. Goodpasture syndrome: ocular manifestation in a young man. Ophthalmologe. 2018; 115(9): 761-4.
13. Lübbecke F. Particularities of Goodpasture Syndrome. Dtsch Arztebl Int. 2017; 114(39): 662.
14. Henderson SR, Salama AD. Diagnostic and management challenges in Goodpasture's (anti-glomerular basement membrane) disease. Nephrol Dial Transplant. 2018; 33(2): 196-202.
15. Tashiro H, Takahashi K, Ikeda Y, Uchiumi S, Fukuda M, Motoaki M, et al. Pre-existing chronic interstitial pneumonia is a poor prognostic factor of Goodpasture's syndrome: a case report and review of the literature. J Med Case Rep. 2017; 11(1): 102.

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PAIN MANAGEMENT OF NEWBORN WITH EPIDERMOLYSIS BULLOSA FOR WOUND DRESSING: A CASE REPORT

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Abstract: Epidermolysis bullosa (EB) is a genetic disease characterized by blisters on the skin and mucous membranes as a result of mechanical fragility. There are four types of EB: simplex (EBS), junctional (JEB), dystrophic forms (DEB), and Kindler syndrome. Simple analgesics such as paracetamol and ibuprofen in EB are also sufficient to reduce pain. Opioids and anxiolytics are necessary for severe pain during wound dressings. In this report, a case of JEB and its pain management at home during dressing by an anesthetist is presented.

Key words: Epidermolysis bullosa, chronic pain, home-care patients, wound dressing.

INTRODUCTION

Epidermolysis bullosa (EB) is a chronic, rare and heterogeneous group of diseases with blisters and erosions with minimal trauma in the deep and mucous membranes (1). EB has been classified into four categories according to the level of division in the dermal/epidermal compartment: EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB), and Kindler's syndrome (2).

Epidermolysis bullosa doesn't have a definitive treatment, but supportive treatment is applied. Cases should be protected from trauma, topical agent application should prevent infections and erosion, the skin should be moisturized, and infections must be treated. The most important goal during lesion treatment is to prevent pain during wound dressing; accordingly, atraumatic dressings should be applied (3). However, the availability of supplies and time required for patients, personal choice, and the carer's lifestyle also play important roles in preventing pain and bleeding (4). In this case report, we present the management of pain during wound dressings of patients with JEB at home in the neonatal period. Written consent was obtained from the patient's father for publication of this report.

CASE REPORT

A 41-weeks-old girl who was born weighing 3300 g via the normal spontaneous vaginal route. During labor, there were no complications. Ten days after birth, the patient was diagnosed as having junctional epidermolysis bullosa in a tertiary hospital, which was widespread over her body, but especially on the hands, feet, and in the gluteal region. Twenty five days after birth, the home health care unit began applying the patient's dressings at the family's home.

In her physical examination, body weight, height, and head circumference were normal and vital findings were stable. Widespread bullous lesions were found in the mouth mucosa, occipital region, ear bones, on both hands, arms, legs and feet, and in the lumbar and gluteal region (Figures 1, 2, and 3).

The Neonatal Facial Coding Scale (NFCS) was used during dressing changes (Table 1). Despite sensitive and careful handling by an anesthetist, the NFCS score was 9 points during the first dressing and the procedure lasted 90 minutes. The baby was constantly crying during the whole process. Bandages were wrapped around the arms, legs, chest and back, and was fixed. Two-way tubular bandages were used to strengthen the



Figure 1. Appearance of lesions in patient with newborn epidermolysis bullosa 1

Table 1. Neonatal Facial Coding Scale

Neonatal Facial Coding Scale(NFCS)	1st wound dressing without using analgesics		2nd wound dressing (paracetamol)		3rd wound dressing (paracetamol, tramadol and hydroxyzine dihydrochloride)	
	0 point	1 point	0 point	1 point	0 point	1 point
Brow bulge		√		√		√
Eye squeeze		√		√		√
Deepening of nasolabial furrow		√		√	√	
Open lips		√		√	√	
Mouth stretch (horizontal or vertical)		√		√	√	
Lip shrink		√		√	√	
Tongue tautening		√	√		√	
Chin quiver		√	√		√	
Tongue protrusion		√	√		√	
TOTAL	9		6		2	

**Figure 2.** Appearance of lesions in patient with newborn epidermolysis bullosa 2**Figure 3.** Appearance of lesions in patient with newborn epidermolysis bullosa 3

coil. After 3 days, the same wound care products were used for the reconstructed dressing. Six NFCS points were observed 1 hour after 15 mg/kg paracetamol oral administration and the dressing lasted for 45 minutes. The baby was crying only during the whole process. However, approximately 1 hour after the 2nd wound dressing, the patient's dressings were removed by the family because she was crying severely. After half an hour, the redness decreased and the baby settled; there was widespread redness throughout the body and the wound care products were removed. Allergic response was considered. After 3 days, 15 mg/kg paracetamol, 1 mg/kg tramadol drop, and 1 mg/kg hydroxyzine dihydrochloride were again orally administered one hour before the dressing. During the procedure, 2 NFCS points were measured and the baby never cried.

DISCUSSION AND CONCLUSION

Pain management is difficult in epidermolysis bullosa due to the variation in symptoms on any one day and

the multiple contributing factors (5). Pain is assessed using a recognized tool that includes behavioral and cultural characteristics (3). For newborns with EB, mild pain generally responds to simple analgesia such as paracetamol, combined with a nonsteroidal antiinflammatory drug or nitrous oxide at home (6). Newborns with EB who have severe pain require treatment with opioid analgesia, which can be combined with an anxiolytic such as midazolam and gabapentin at home (7). The family had not accepted the use of analgesics at the first dressing in our case. However, during the application of dressings she cried very much, as such, they allowed analgesic treatment for the other dressings. We treated the patient with oral paracetamol at the 2nd wound dressing but considered that paracetamol alone was not enough because she cried constantly. For the 3rd wound dressing, we treated the patient with hydroxyzine dihydrochloride to prevent allergy during dressing, and paracetamol and tramadol for analgesia. We did not want to combine benzodiazepine and an opioid because of the risk of complications dur-

ing home dressings. Newborns with JEB have never had their wounds dressed at home with a combination of hydroxyzine dihydrochloride, paracetamol, and tramadol. We calculated that hydroxyzine dihydrochloride, paracetamol, and tramadol had a Ramsey sedation score of 4. In the meantime, the dressings were made comfortable. Pain, anxiety, and itching are everyday companions for these patients and an anesthetist on the EB team contributes significantly to the successful management of these problems. Implementing measures to prevent damage to the skin and mucosa, and assuming a “no-touch” approach, ensures that anesthesia for children with EB may be undertaken with few untoward consequences.

This case report highlights the importance of analgesia and anesthesia for infants with EB. Children, especially newborn and infants with EB, and some more than others, pose a formidable challenge to an anesthetist. Although there is limited experience with hydroxyzine dihydrochloride during infancy, we feel that this compound should be considered when routine multimodal analgesia fails.

Whereas this is a dramatic case, it details only the first few dressings and we do not know how this difficult situation for baby, parents and health care providers, continued. Although tramadol may have been useful, we do not know how this drug would help in a longer time-perspective.

Abbreviations

EB — Epidermolysis bullosa

EBS — Epidermolysis bullosa simplex

JEB — Epidermolysis bullosa junctional

DEB — Epidermolysis bullosa dystrophic form

NFCS — The Neonatal Facial Coding Scale

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Licensing

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Sažetak

TERAPIJA BOLA TOKOM PREVIJANJA KOD NOVOROĐENČETA SA BULOZNOM EPIDERMOLIZOM: PRIKAZ SLUČAJA

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Epidermolysis bullosa (EB) je genetska bolest koju karakterišu plikovi po koži i mukoznim membranama kao rezultat mehaničke osetljivosti. Postoje četiri tipa EB: simplex (EBS), junkcijska (JEB), distrofična (DEB) i Kindlerov sindrom. Analgetici kao što su paracetamol ili ibuprofen kod EB su dovoljni da redukuju

bol. Opioidi i anksiolitici su potrebni kod jakih bolova tokom previjanja rana. U ovom radu je opisan slučaj JEB i terapija bola kod kuće tokom previjanja od strane anestetičara.

Ključne reči: Bulozna epidermoliza, hronični bol, pacijenti na kućnoj nezi, previjanje rane.

REFERENCES

1. Proding C, Reichelt J, Bauer JW, Laimer M. Epidermolysis bullosa: Advances in research and treatment. *Exp Dermatol.* 2019; 28(10): 1176-89.
2. Chan JM, Weisman A, King A, Maksomski S, Shotwell C, Bailie C, et al. Occupational therapy for epidermolysis bullosa: clinical practice guidelines. *Orphanet J Rare Dis.* 2019; 14(1): 129.
3. Denyer J, Gibson E. Use of fibre dressings in children with severe epidermolysis bullosa. *Br J Nurs.* 2015; 24(6): S38, S40-3.

4. Lynne V, Burns L, Handsaker J, Murdoch JM. Epidermolysis bullosa: Management complexities of pediatric patients. *BJ Nurs.* 2018; 27(Sup12): S20-5.
5. Togo CCG, Zidario APC, Gonçalves VSS, Hubbard L, de Carvalho KMB, Dutra ES. Quality of life in people with epidermolysis bullosa: a systematic review. *Quality of Life Research.* 2020; epub Apr 3.
6. Ingelmo P, Wei A, Rivera G. Nitrous oxide for procedural analgesia at home in a child with epidermolysis bullosa. *Paediatr Anaesth.* 2017; 27(7): 776-8.
7. Allegaert K, Naulaers G. Gabapentin as part of multimodal analgesia in a newborn with epidermolysis bullosa. *Paediatr Anaesth.* 2010; 20(10): 972-3.

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INTERVENTION OF RARELY SEEN CATHETER LOSS DURING PERMANENT TUNNELED HEMODIALYSIS CATHETERIZATION: A CASE REPORT

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Abstract: Introduction: In patients with end-stage renal disease (ESRD), permanent hemodialysis catheters are often used by performing percutaneous catheterization to create a permanent vascular access. To the best of our knowledge, no cases with accidental loss of catheter piece during hemodialysis catheter replacement or during its retrieval under scopy has been reported in the literature yet.

Case report: It was decided to retrieve the right permanent dialysis catheter of a 54-year-old woman, who had received a temporary dialysis catheter due to the development of catheter site infection in her 3rd permanent catheter (the first two were changed due to thrombosis). Due to excess adhesion in the region, the retrieval of the catheter was complicated, only half of it (proximal piece after cutting into two) was removed, while the distal section slipped and migrated to the right subclavian vein, up to the right atrium. The diagnosis was confirmed by chest radiographs showing that the distal piece of the catheter piece was in the right subclavian vein and right atrium. The catheter piece was retrieved through a minor invasive procedure made possible by scopy without any further complications.

Conclusion: Permanent dialysis catheters should ideally be placed under scopy. Also, when the retrieval of a catheter is planned, cutting from any part of the catheter should never be performed.

Key words: hemodialysis, replacement failure, catheter, complication.

INTRODUCTION

Hemodialysis is the basis of treatment in patients with end-stage renal disease (ESRD) that are on the waiting list for a kidney transplant. As noted in many hemodialysis guidelines, arteriovenous fistulas (AVF)

are very practical and have better success than any other vascular access route (1). While there are efforts to increase AVF in ESRD patients, there are also a great number of patients undergoing vascular surgery for the placement of tunneled catheters for hemodialysis. Some common complications, such as catheter infection and thrombosis, perforation, fragmentation and emboli into the main central vessels, and the rare complication of a catheter adhering to the superior vena cava (SVC) and right atrium are reported in the literature (2). Furthermore, aging and accompanying diseases in the population of ESRD patients may prevent creation of an AVF; thus, permanent catheter placement becomes the only alternative (3). As such, dialysis catheters remain as a vital option to continue renal-replacement therapy in patients that do not have a possibility for vascular access and also those with failure.

Hemodialysis catheters were originally developed for short- and medium- term hemodialysis access to provide permanent access during AVF maturation. Schwab et al. conducted the first study in the literature that demonstrated the effectiveness of hemodialysis catheters in 1988 (4). In the following two decades, the use of these catheters gained extreme popularity as semi-permanent catheters that enabled reliable access in patients with chronic hemodialysis (5). Reasons for this unprecedented increase in popularity included the ease of placement, increased numbers of elderly and diabetic patients whose veins were not suitable for AVF, and patients' preferences (4). With the widespread use of these catheters, significant experience was gained and the possible complications were identified and minimized. However, serious risks still exist and can be associated with patient-related characteristics (6) and other factors (2).

Here, we present a patient who suffered catheter loss in permanent tunneled hemodialysis catheterization and surgical retrieval of the catheter piece through the 2nd intercostal space under scopy.

CASE REPORT

The patient was a 54-year-old woman who was scheduled for semi-urgent catheter removal due to septicemia and non-response to broad-spectrum antibiotics.

In the patient history, a brachiocephalic AVF had been created on the left arm after dialysis for 3 years, two of which had been with hypertension. The patient had thrombosis 2 years later, and this time a radiocephalic AVF fistula was created in the right forearm which also had a similar fate within 6 months. Thus, a permanent dialysis catheter was placed into the right subclavian vein to enable dialysis. During follow-up, she had clinical findings suggestive of catheter infection; after consultation with the nephrology department, the catheter was removed due to a diagnosis of dialysis catheter infection that had been ongoing for 5 months. Meanwhile, a temporary dialysis catheter was placed into the patient's left internal jugular vein. The removal of the right subclavian permanent catheter of the patient was scheduled in two steps by performing a 1 cm incision from the old incision site under local anesthesia in the operating room and cutting from the middle, followed by retrieval of both pieces in rapid succession. After standard surgical approach, the middle part was reached under the skin; however, we encountered excessive adhesions throughout the region.

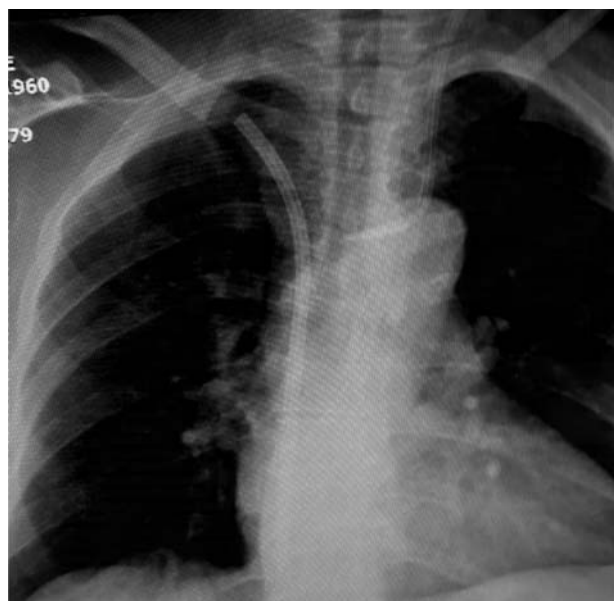


Figure 1. On the X-ray, the distal tip of the permanent catheter is seen in the inferior vena cava and right atrium, and on the other side, the tip of the left internal jugular vein catheter can be observed



Figure 2: Post-operative control X-ray, the temporary dialysis catheter is observed in the left internal jugular vein

The catheter was cut after clamping both pieces to separate clamps, while the proximal part of the catheter was easily retrieved, the distal part slipped from the second clamp and was lost; it was found that it had migrated towards the vena cava superior and right atrium (Figure 1).

There was no deterioration in the patient's vital signs or general condition. After ensuring that the patient remained stable, a fast council was held and a decision for emergency action was made. Firstly, the patient was put under general anesthesia and intubated. After surgical antisepsis the whole chest region of the patient, sterile covering was performed. A 5 cm incision was made through the 2nd intercostal space under the right infraclavicular region and subclavian vein was reached. Then, we managed to hold the distal tip of the distal piece using a long clamp in the subclavian vein, under scopy. The catheter piece was then carefully retrieved with the aid of scopy. The subclavian vein was repaired and the incisions were closed anatomically. A control X-ray was taken while the patient remained on the operating table (Figure 2).

The patient was extubated and taken to the intensive care unit. The general condition of the patient during follow-up was good and no coagulopathy was detected in the patient. The patient's normal dialysis program was continued.

DISCUSSION

After loss of the distal piece of the dialysis catheter, the patient was successfully operated for the retrieval of the piece with a relatively less-invasive method, especially considering the possibility that more extensive approaches may have been required. The subclavian vein was accessed through a 5 cm incision in the right-side 2nd intercostal space. The use of a long clamp under scopy was critical to be able to grab the catheter

piece that was lodged within the subclavian vein. If this method was not successful, it was thought that the catheter piece would be removed from the right atrium by performing a right thoracotomy. Thanks to this method, a less invasive approach was used.

Although the best vascular access route for hemodialysis treatment is undoubtedly AVF formation, the prevalence hemodialysis catheter use is increasing in ESRD patients (7). The advantages of permanent central venous catheters are that they can be placed quickly and easily and allow immediate access to hemodialysis and missing cardiac volume load in non-traumatic, and therefore, painless way. The disadvantages of permanent central venous catheters are that they have a significantly higher complication rate than other vascular access options.

In our experience, the key factor in catheter function and survival is the expertise of the team performing catheter placement and catheter care in dialysis units. Careful evaluation of the access point prior to implantation with the use of ultrasound, appropriate choice of catheter length according to body size, as well as placement localization and strict compliance with asepsis rules during catheter placement, are critical for success. Additionally, regular maintenance of the hemodialysis connections and the catheter are the post-intervention cornerstones of sustained and safe use of these catheters.

Considering the increase in the average age of dialysis patients in developing countries and the increase of dialysis times required by these patients, it is concluded that vascular surgery facilities cannot continue to provide sufficient service in response to the increasing number of hemodialysis patients. Even though suggesting AVF whenever possible is a good approach to reduce this excessive workload burden, it is critical to note that they are, indeed, very reliable and must be used wisely to ensure the best possible results for patients. Forauer et al. have reported various catheter-induced histological venous wall changes (8). They found that short-term catheter use caused endothelial damage in the vascular wall adjacent to the catheter in focal areas; whereas, long-term catheter use caused wall

thickening and bridges between the catheter and the venous wall. The issue of managing catheters causing intravascular adhesions has not been adequately discussed in the medical literature. Traction of the catheter, which is the first method used to remove the catheter from the central vein, can cause severe vascular, atrial and tricuspid valve damage. When removing the catheters, it is a reasonable method to cut them from the venous area where they are placed (9). However, various complications, including inability to retrieve the catheter piece, have been reported while applying this method (10, 11, 12). Thoracotomy might be considered as the last option for treatment. Ideally, thoracotomy with cardiopulmonary bypass should be avoided to retrieve catheters, because this operation is associated with severe morbidity and possible mortality. Among the various recommended techniques to retrieve an adherent catheter, interventional venocavagram exploration of the catheter seems to be a worthwhile option because this method might result in fewer complications than other procedures.

As a result, **we conclude** that permanent dialysis catheters should ideally be placed under scopy. Also, when the retrieval of a catheter is planned, cutting from any part of the catheter should never be performed. Since this procedure has a risk for mortal complications, the patient must be informed about this before the procedure and the procedure must be carried out in the operating room.

Abbreviations

ESRD — end-stage renal disease

AVF — arteriovenous fistulas

SVC — superior vena cava

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Sažetak

REŠAVANJE RETKO VIĐENOG GUBITKA HEMODIJALIZNOG KATETERA TOKOM NJEGOVE ZAMENE: PRIKAZ SLUČAJA

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Sažetak: Kod pacijenata sa terminalnom bubrežnom insuficijencijom, dijalizni kateter se često koristi

kao trajni vaskularni pristup za sprovođenje hemodijalize perkutanom kateterizacijom. Koliko je nama po-

znato, u literaturi do sada nije zabeležen ni jedan slučaj slučajnog gubitka dela katetera tokom njegove zamene ili vadenja pod kontrolom skopije.

Prikaz slučaja: Odlučeno je da se zameni desni trajni dijalizni kateter kod pacijentkinje stare 54 godine, kojoj je prethodno plasiran privremeni dijalizni kateter zbog razvoja infekcije trećeg trajnog dijaliznog katetera (prethodna dva su zamenjena zbog tromboze). Zbog izraženih okolnih priraslica, zamena trajnog dijaliznog katetera je bila praćena komplikacijama, samo polovina (gornji kraj nakon presecanja na pola) je izvučena, dok je donji kraj katetera skliznuo i migrirao

u desnu subklavijalnu venu, sve do desne pretkomore. Dijagnoza je potvrđena radiografijom grudnog koša koja je pokazala da je distalni deo dijaliznog katetera u desnoj subklavijalnoj veni i desnoj pretkomori. Deo katetera je izvučen manjom invazivnom procedurom uz pomoć skopije, bez daljih komplikacija.

Zaključak: Stalni dijalizni kateteri u idealnom slučaju trebaju biti postavljeni pod kontrolom skopije. Takođe, kada se planira ukljanjanje katetera, presecanje bilo kojeg dela katetera se nikad ne sme uraditi.

Ključne reči: hemodijaliza, neuspešna zamena, kateter, komplikacija.

REFERENCES

1. Sequeira A, Sachdeva B, Abreo K. Uncommon complications of long-term hemodialysis catheters: adhesion, migration, and perforation by the catheter tip. *Semin Dial.* 2010; 23(1): 100-4.
2. Banerjee S. Dialysis catheters and their common complications: an update. *Scientific World Journal.* 2009; 9: 1294-9.
3. Gianotti MR, da Silva NM. Dialysis in the elderly patient: a challenge of the XXI century-narrative review. *J Bras Nefrol.* 2013; 35(2): 132-41.
4. Little MA, O'Riordan A, Lucey B, Farrell M, Lee M, Conlon PJ, et al. A prospective study of complications associated with cuffed, tunneled haemodialysis catheters. *Nephrol Dial Transplant.* 2001; 16(11): 2194-200.
5. Kumwenda MJ, Wright FK, Haybittle KJ. Survey of permanent central venous catheters for haemodialysis in the UK. *Nephrol Dial Transplant.* 1996; 11(5): 830-2.
6. Wang K, Wang P, Liang X, Lu X, Liu Z. Epidemiology of haemodialysis catheter complications: a survey of 865 dialysis patients from 14 haemodialysis centres in Henan province in China. *BMJ Open.* 2015; 5(11): e007136.
7. Malas MB, Canner JK, Hicks CW, Arhuidese IJ, Zarkowsky DS, Qazi U, et al. Trends in incident hemodialysis access and mortality. *JAMA Surg.* 2015; 150(5): 441-8.
8. Forauer AR, Theoharis C. Histologic changes in the human vein wall adjacent to indwelling central venous catheters. *J Vasc Interv Radiol.* 2003; 14(9 Pt 1): 1163-8.
9. Jones SA, Giacomantonio M. A complication associated with central line removal in the pediatric population: retained fixed catheter fragments. *J Pediatr Surg.* 2003; 38(4): 594-6.
10. Thein H, Ratanjee SK. Tethered hemodialysis catheter with retained portions in central vein and right atrium on attempted removal. *Am J Kidney Dis.* 2005; 46(3): e35-9.
11. Field M, Pugh J, Asquith J, Davies S, Pherwani AD. A stuck hemodialysis central venous catheter. *J Vasc Access.* 2008; 9(4): 301-3.
12. Ndzengue A, Kessaris N, Dosani T, Mustafa N, Papalois V, Hakim NS. Mechanical complications of long-term Tesio catheters. *J Vasc Access.* 2009; 10(1): 50-4.

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SUICIDALITY IN HEALTHS CRISIS - CASE REPORTS

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Abstract: Introduction: Suicide represent a major health problem of great importance for public health in Serbia. In the whole world in last decades, the number of committed suicides is constantly increasing. The most dramatic increase is the number of committed suicides among adolescents, but also among the elderly, over 65 years of age. Serbia ranks 13th in Europe in terms of the number of suicide (13.6/100.000 inhabitants) and Vojvodina is at the top place as region in Serbia (15.3/100.000 inhabitants). It is alarming that suicide attempts are 10-15 times more frequent, as well as that a large number of people who have committed suicide in the last month have reported in medical institutions with various problems. Situations and conditions that increase suicide risk are mental disorders and chronic physical illness, as well as life crises, which include pandemic. Also of great importance is positive heredity, as well as previous suicide attempts. Usually, during crisis, number of suicide attempts and committed suicides decline, but after crisis there is lot of evidence that symptoms of anxious and depressive disorders increase and number of suicide attempts and committed suicides is growing up.

Cases reports: In presented case reports the trigger for a suicide attempt was the current situation during the covid-19 epidemic. One of the leading reasons for the increase in number of attempted and committed suicides is the unrecognition and lack of treatment of mental disorder symptoms. Most frequently symptoms of depression and severe anxiety result in a suicide attempt. Early recognition and treatment either with psycho and/or pharmacotherapy in a significant percentage can reduce the number of attempted and committed suicides.

Conclusion: In currently pandemic and in next period, it is necessary for medical staff to look after various, but mostly depressive and anxious symptoms in patients, that frequently result in suicide attempt, if

stay unrecognized and untreated. That is the best way to prevent suicide and to improve mental health, as it is very important for national interests.

Keywords: suicidality, pandemic, prevention.

INTRODUCTION

The definition of suicidal behavior is numerous, but one of the most general claims: suicide represents active or passive self-destructive act in which a person consciously and intentionally takes his own life because of various motives." (1, 2, 3). Certainly, these motives may be psychopathological genesis, which is the case with most patients who suffer from mental disorder. In addition to suicide, self-destructive behavior includes attempted suicide, planning or contemplating suicide, as well as a self-harm behaviour.

Parasuicide is a deliberate self-harm behavior that does not end up lethal, as opposed to suicidal intent. A parasuicidal break is by definition a procedure with no suicidal intention, for example, when a person takes a higher dose of sedatives or hypnotics, without suicidal intention at mind but with the intention of falling asleep. About 50-75% people who commit suicide have contact with medical services within a month before committing suicide (4, 5, 6).

Suicide is considered as multidimensional phenomena, while its genesis is interpreted by interplay of biological, psychological and socio-cultural factors. Numerous religions, primarily Christianity, condemn suicide and just until recently there was an explicit prohibition on suicides being buried in Christian rites (1, 3, 4).

As a phenomenon, suicide is disengaged from social, gender, cultural and age boundaries. It manifests itself in all climates, but records of the number of suicides executed and attempted vary significantly from country to country, thus making the existing statistics relatable (60 country in the world has statistics about sui-

cide). A particular problem is the high number of fatal accidents in which, retrospectively, the cause of the accident cannot be determined, as well as the number of casualties in occupational accidents (7, 8).

Each year, approximately 800.000 persons commit suicide, other wise, every 40 second someone on the planet die from suicide (2, 3, 9). Epidemiology data becomes alarming as during last decade suicide present leading cause of premature mortality in individuals between 15 to 29 years (2, 3, 10). In the reality, suicide attempts are 15-20 times more frequent than committed suicide. Statistical evidence indicate that 86% of all suicides are registered in underdeveloped and middle-developed countries, mainly in Eastern Europe. In elderly category (more than 65 years), suicide rate accounts for 14% of the world's total mortality. In world statistics the rate of suicide is 11.6 per 100,000 inhabitants. Sex ratio (male: female) is the largest in Europe, with the smallest difference in the Mediterranean region. The highest number of suicides perpetrated in the male population was recorded in Ukraine (61.1) and in the female population in South Korea, where the number of suicidal young women in the large population is growing (2, 3, 11, 12).

Due to WHO (World Health Organization) statistics, in 2016 suicidal rate in lot of community increased.

The highest rates of more than 15/100.000 inhabitants were recorded in Switzerland, Sierra Leone, Sweden, Republic of Korea, North, Bulgaria, Serbia, Belgian, Finland, Slovenia (Table 1).

In terms of the percentage of committed suicide, Lithuania, Russia and Belarus have reached the first place in recent decades. Compared to the countries of Western Europe, this data are inconsistent. It is interesting that suicide rate is very high in Switzerland and it is also surprising that Bhutan, in which the level of community satisfaction is extremely high, also has significance number of committed suicide (11 per 100,000 inhabitants). According to the suicide rate, Serbia is in the 13th place in Europe. The suicide rate is 13.6 per 100,000 inhabitants according to the latest statistics (2016), but within the Republic the rates are significantly different.

Vojvodina is still in the first place in the number of suicides, as in previous decades, with a rate of 15.3 In past few decades, the number of suicides in Serbia has increased significantly, with the largest increase being recorded in adolescence and late life.

This is alarming data indeed, giving that the number of attempted suicides is at least ten times higher. The largest number of suicides in the period 2010-2019 was carried out in the cities with the majority Hungarian population (Subotica), unlike the southern part, where the number of suicides is significantly reduced.

Table 1. Suicide rate in the world (2016, WHO)

Region	Total Suicide Rate per year	Male	Female
Lithuania 894	31.9	58.1	9.5
Russia 45178	31	55.9	9.4
Ukraine 9911	22.4	41.1	6.3
Belgium 2377	20.7	27.8	13.8
Hungary 1854	19.1	29.7	9.6
Slovenia 386	18.6	30.4	6.9
Japan 23532	18.5	26.0	11.4
France 11503	17.7	23.9	11.7
Switzerland 1466	17.2	22.0	12.4
Croatia 686	16.5	25.6	7.9
India 220481	16.3	17.8	14.7
Poland 6143	16.2	28.9	4.3
Finland 878	15.9	23.9	8.1
Serbia 1373	13.6	23.5	8.1
Germany 11305	13.6	19.7	7.7
Bulgaria 811	11.5	18.2	5.1
Bhutan 86	11.4	14.0	8.5

At greater risk for suicidal thoughts and behavior are patients with chronic somatic or psychiatric problems, personality disorders, especially if there occur life crisis or if they are in low socio-economic situation. At greater risk are persons with positive heredity, or persons who have already attempted suicide.

Environmental factors that enhance the occurrence of suicidal thoughts, attempts, suicide planning: broken home, loss of a close person or social support, loss of business or bankruptcy, easy availability of me-

ans of committing suicide (firearms, poisons), frequent suicides in the local community.

Socio-cultural factors that promote suicidal ideation / behavior: stigmatization of help-seeking services, unavailability of mental health and psycho-psychiatric services; cultural or religious prejudices that "call" for suicide; exposure to suicidal ideation (networks, groups).

Crisis of various type present frequently a trigger in predisposed people. One is up-to date, health crisis in form of covid-19 pandemic. In desperate to save people's life, lot of rules were pronounced, like police hour, work from home, reducing social contacts. Therefore, life became worldwide harder, especially for people with mental disorders.

Here are presenting cases of patient with suicidal attempts during health crisis.

Case report No1

Patient, female, 60 years old, never came to see psychiatrist, single, no children. Patient came in urgent ambulance in last 4 months for her mother and her best friend has died. She was living alone and she was employed, but during pandemic she lost her job and from that period she felt lonely, she had insomnia, she could not eat, whole day she was just sitting, without energy and motivation, she could not concentrate and was frightening about disease and finally she decided to make a suicide. One evening patient went to the bridge, planning to jump and dive in the river. Some people saw her, called ambulance and police who took her in the hospital. During examination patient was depressive, bradypsychic, with ideas of less worth, hopeless, reluctant, failed, with strong suicidal ideation. She was admitted in hospital. Psychopharmacs (antidepressants and anxiolytics) were administered, in combination to cognitive-behavioral therapy. After 40 days patient was dismissed from hospital, in satisfied condition, euthymic and without symptoms of mental disorder. The plan was that in next few months she will be with two friends and she will work in family business one of the friends. In the next six months patient regularly came to psychiatric control examination, remission persist and she took psychopharmacs and came to visit psychologist too.

Case report No1

Patient, female, 20 years old, student. She was living in flat alone and her family lived in another city. During pandemic she decided not to go home, but in flat she felt lonely, frighten, anxious, all the time she was watching television and information about covid-19. Last three weeks, while police hour was dis-

missed, she was frightened to go out, feeling that something terrible will happened and she experienced 4-5 panic attacks every day. Patient felt exhausted, could not sleep or eat any more. Then she decided to make suicide as she didn't see another way out from this situation. She took 30 tablets (analgetics) with half bottle of liquor, then she changed her mind and call ambulance for help. After monitoring in urgent centre for 6 hours, patient was admitted at psychiatric Clinic. She was in satisfied condition but depressive and anxious, she was crying and call for help. In next period, support and CBT was administered in combination with antidepressants. After three weeks patient was dismissed, she went home to live with her family during summer holiday. She had no longer anxiety or panic attacks, and became euthymic. Control examination was fixed in a week.

DISCUSSION

There are numerous interpretations trying to explain why the number of suicides in young people is rising. Among the most important is the breakup from the traditional family, the fast way of living, the lack of quality communication within family which should allow better recognition of problems in the young person (eg. depressive disorder, substance abuse), peer violence, changing value systems, excessive expectations of the environment from the child, etc.

In elderly, one of the leading causes of suicide is evidently the loss of social support, loneliness, very often the comorbidity of many chronic physical illnesses and worsening financial status. National Healthcare system should amplify efforts to help predisposed people, especially during actual health crisis, for better prevention of suicide.

During various crisis, number of suicidal attempts and committed suicide usually decline, but after crisis suicidality has trend of increase (2, 3, 7). During actual pandemic people spend lot of time with family but problems appears in singles or molested. It is very important to recognize those people on time and support them. Psychotherapy can be beneficial for clients in various type of crisis. Usually CBT (Cognitive-Behavior Therapy), REBT (Rational Emotive Behavior Therapy), TA (Transactional analysis) are used by therapist, accompanying with progressive muscle relaxation techniques, usually when depression or severe anxiety lies in the background of suicidal ideas (12, 13). Cognitive restructuring, social skills, checking negative thoughts, writing diary of daily activities are some of useful psychotherapeutic technique. When it is indicated, psychopharmacs should be prescribed during and for some period after crisis, in combination with psy-

chotherapy. The best suicide prevention presents adequate and timely recognition and treatment of community mental disorders, the availability of medical, especially psychiatric-psychological services as well as education of healthcare professionals.

In all parts of the community persists necessity for continuous screening programs to reach as many members as possible (students, adolescents, the unemployed, employees of different qualifications).

CONCLUSION

The interpretation of the high percentage of suicide attempts and execution is based on the assumption that the main problem is the non-recognition of psychological problems which result in inappropriate treatment since most suicide is attempted and executed by patients who have mental disorders. In order to prevent

suicide it is necessary to activate and educate medical staff of all profiles with the aim of better and timely recognition of mental disorders at any age, neglect of children, insufficient social support, identification of problems and investing additional efforts and resources in overcoming them, but emphasizing also the education of family members, school staff and the wider community as well as organizing free psychological assistance (type "Heart").

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Sažetak

SUICIDALNOST TOKOM ZDRAVSTVENE KRIZE - PRIKAZI SLUČAJEVA

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Uvod: Samoubistvo predstavlja veliki zdravstveni problem od velikog značaja za javno zdravlje u Srbiji. U celom svetu poslednjih decenija broj izvršenih suicida je u stalnom porastu. Najdramatičniji je porast broja izvršenih suicida među adolescentima, ali i osobama starijeg životnog doba, iznad 65 godina starosti. Srbija zauzima 13-to mesto u Evropi prema broju izvršenih suicida (13,6/100.000 stanovnika), a od regiona u Srbiji, na prvom mestu je Vojvodina (15,3/100.000 stanovnika). Alarmantan je podatak da su pokušaji suicida 10-15 puta češći od izvršenih suicida, kao i da se veliki broj ljudi koji su izvršili suicide u poslednjih mesec dana javljao u zdravstvene ustanove sa različitim tegobama. Situacije i stanja koja povećavaju suicidalni rizik su mentalni poremećaji, hronična oboljenja, kao i životne krize u koje spadaju i epidemije. Takođe je značajan faktor rizika pozitivno hereditarno opterećenje, kao i prethodni pokušaji suicida. Obično, tokom trajanja krize, broj pokušanih i izvršenih suicida opada, međutim, postoji dosta dokaza da nakon njenog okončanja dolazi do pojačane pojave simptoma anksioznih i depresivnih poremećaja, kao i do porasta broja pokušanih i izvršenih suicida.

Prikaz slučaja: Kod prikazanih slučajeva je kada za pokušaj samoubistva bila aktuelna situacija tokom epidemije Covid-19. Jedan od vodećih razloga povećanja broja pokušanih i izvršenih suicida je neprepoznavanje i izostanak lečenja simptoma mentalnih poremećaja. Često simptomi depresije i intenzivne anksioznosti rezultiraju pokušajem samoubistva. U radu su opisani pacijenti kod kojih su se tokom perioda epidemije, ispoljili simptomi depresivnosti i izrazite anksioznosti, a rezultirali pokušajem suicida. Rano prepoznavanje kao i pravovremena primena psiho i farmakoterapijskih mera u značajnom procentu može da smanji broj pokušanih i izvršenih suicida.

Zaključak: Tokom aktuelne pandemije i u periodu nakon nje, neophodno je da medicinski stručnjaci prepoznaju i prate razne, posebno depresivne i anksiozne simptome kod pacijenata koji često rezultiraju pokušajem samoubistva ukoliko ostanu neprepoznati i nelečeni. To je najbolji način da se prevenira samoubistvo i unapredi mentalno zdravlje, što je od velikog nacionalnog značaja.

Ključne reči: suicidalnost, pandemija, prevencija.

REFERENCES

1. Dendup T, Zhao Y, Dorji T, Phuntsho S (2020) Risk factors associated with suicidal ideation and suicide attempts in Bhutan: An analysis of the 2014 Bhutan STEPS Survey data.

PLoS ONE.2020; 15(1): e0225888. doi.org/10.1371/journal.pone.0225888.

2. World Health Organization. Global Health Observatory data repository. Suicide rates crude data by WHO region 2016. Available from <https://apps.who.int/gho/data/view/main/MH.SUICIDER6Y?lang=en>.

3. Borges G, Haro JM, Chiu Wt H, de Giorlamo G, Medina-Mora ME et al. Prevalence and identification of groups at risk for 12-month suicidal behavior in the WHO World Mental Health Surveys in: Nock MK, Borges G, Ono Y, edit. *Suicidality in the WHO World Mental Health Surveys*. New York. Cambridge University Press; 2012: 185-98.
4. Niederkrotenthaler T, Fu KW, Yip PS, Fong DY, Stack S, Cheng Q, et al. Changes in suicide rates following media reports on celebrity suicide: a meta analysis. *J. Epidemiol. Community Health*. 2012. 66(11): 1037-42.
5. Bernert RA, Turvey CL, Conwell Y, Joiner TE Jr. Association of poor subjective sleep quality with risk for death by suicide during a 10-year period: A longitudinal, population-based study of late life. *JAMA Psychiatry*, 2014; 71(10): 1129-7.
6. Sharma B, Nam K, Kim HY, Kim JR. Factors associated with suicidal ideation and suicide attempt among school-going urban adolescents in Peru. *Int J Environ Res. Public Health*. 2015; 12(11): 1482-66.
7. Klopsky ED, May AM, Satter BY. Suicide, suicide attempts and suicide ideation. *Annu Rev Clin Psychol*. 2016; 12: 307-30.
8. Pandey AR, Bista B, Dhungana RR, Aryal KK, Chalise B, Dhimal M. Factors associated with suicidal ideation and suicidal attempts among adolescent students in Nepal. Findings from Global Scholl-based Students Health Survey *PloS One*. 2019; 14(49): e0210383.
9. Darvishi N, Farhadi M, Haghtalal T, Poorogabaj J. Alcohol-related risk of suicidal ideation, suicide attempt and completed suicide: a meta analysis *PLoS One*. 2015; 10(5): e012680-e.
10. Barzillay S, Feldman D, Snir A, Agiter A, Carli V et al. The interpersonal theory of suicide and adolescent suicidal behavior. *J Affect Disord*. 2015; 183: 68-74.
11. Clifford AC, Doran CM, Tsey K. A systematic review of suicide prevention interventions targeting indigenous peoples in Australia, United States, Canada and New Zealand. *BMC publish health*. 2013; 13(1): 463.
12. Blumenthal S, Bell V, Neumann NU, Schuttler R, Vogel R. Mortality and rate of suicide of first admission psychiatric patients. A 5-year follow-up of a prospective longitudinal study. *Psychopathology*. 1989; 22(1): 50.
13. Melartin, T. K. Isomets E. T. Differences in incidence of suicide attempts between bipolar I and II disorders and major depressive disorder. *Bipolar Disorders*. 2014; 16(6): 652-1.

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ASTHMA AMONG ELITE ATHLETES, MECHANISM OF OCCURENCE AND IMPACT ON RESPIRATORY PARAMETERS: A REVIEW OF LITERATURE

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Abstract: Introduction: It is generally accepted that physical activity benefits every person but athletes diagnosed with asthma face various challenges during their training to keep the symptoms of the disease under control. Prolonged exposure to agents in the environment in which athletes train favors the development of permanent changes in the airways. Their action leads to permanent hyper reactivity with development of an inflammatory response and the release of mediators (IL-8, leucotriens, eicosanoids) that lead to damage epithelial cells with breaking connection between them and consequent dysfunction of the respiratory system. This condition is called exercise-induced asthma (EIA). This fact is especially important for athletes who have long endurance training. The best way to check the condition of breathing system is with a diagnostic method which is the „gold“ standard- spirometry.

Aim: The point of this systematic review is to get closer the mechanism occurrence of EIA/(exercise induced bronchoconstriction)-EIB, prevalence and incidence of EIA/EIB, changes of pulmonary function and quality of life in elite athletes. We searched papers from PubMed and Cochrane database using keywords: 'exercise-induced asthma', 'athletes', 'spirometry', 'bronchoconstriction', 'bronchospasm', 'physical activity', 'physical training', 'prevalence', 'incidence'. We have studied 48 scientific papers in total. **Conclusion:** The prevalence of asthma among elite athletes, especially endurance athletes is higher than in general population. The explanation of this phenomenon is related to the whole mechanism of occurrence, it is still insufficiently clarified, but one thing is for sure that

with good disease control athletes can play and compete undisturbed for many years.

Keywords: exercise-induced asthma, elite athletes, mechanism of occurrence, spirometry, prevalence.

INTRODUCTION

Over the years, the definition of asthma has changed and supplemented with new knowledge. Nowadays, The National Institute of Health Guidelines of Asthma defined asthma like chronic inflammatory disturbance of the airways where macrophages, T-lymphocytes, mast cells, neutrophils, eosinophils and their elements have notable role in the occurrence of this disease (1). According to data WHO around 235 million people have diagnosed of asthma. Daily physical activity is recommended for all individuals but athletes with asthma confront special challenges in managing their disease while exercise (2). According to some data, top athletes had 17% prevalence of asthma, 10% of them used asthma drugs, which is almost three times higher than in general population which took participation in the research (3). When we talk about asthma among athletes, the most researchers think about exercise-induced asthma (EIA) or exercise-induced bronchoconstriction (EIB). Exercise-induced bronchoconstriction is manifestation of airway hyper responsiveness (AHR) and is defined like temporarily airway obstruction and fall forced expiratory volume in first second (FEV1) after training for at least 10% of baseline (4). The clinical picture of EIA/ EIB is presented by coughing, wheezing, shortness of breath or chest tightness for an average of 5-30 minutes after exercise (5). According to

some Swiss guidelines the diagnosis of asthma is based on: history of respiratory system, confirmed variable expiratory airflow limitation, positive bronchodilator reversibility test, excessive variability in twice daily PEF over two weeks, significant increase in lung function after four weeks of anti-inflammatory treatment, positive exercise challenge test and positive bronchial challenge test.

The objective of this handwriting is to ensure a concise overview of the effects of exercise on development of EIA/EIB, prevalence and incidence, their effects on lung function and quality of life at elite athletes.

MATERIAL AND METHODS

We selected substantial studies from databases of PubMed and Cochrane. The next keywords/ Mesh terms were used: 'exercise-induced asthma', 'athletes', 'spirometry', 'bronchoconstriction', 'physical activity', 'physical training', 'prevalence', 'incidence'. Headline, abstracts and full-text articles of possibility useful studies were independently checked by three researches. The reference lists of articles were scrutinized for detecting studies which were not grabbed by the electronic search. The study was conducted used literature published up to February, 2020. We searched, in detail, 48 scientific research papers.

Effects of exercise on development of asthma

How the literature explained the onset of EIA/EIB? The literature provides data for two type of mechanism of emergence EIA/EIB, *osmolar* and *vascular* hypothesis. Common to these two hypotheses is that they lead to increased ventilation throughout physical activity which leads to lose of water and heat during breathing. During water loss there is an increase in extracellular fluid osmolarity, that covers bronchial mucose, which leads to stimulation of cells to secrete fluid in extracellular environment leading to their shrinkage. This process is crucial in relishing the mediators of inflammation and consequently causing the contraction of the smooth muscles of the bronchial wall (6). The vascular hypothesis involves reheating the airways after cooling them. Throughout normal tidal volume the nose functions like rebreathing organ which warming up to 37,8° C and humidifying inspired air. By intensifying physical activities, it intensifies and ventilates, whereby nasal breathing stops and ventilation through the mouth rises, which leads to the loss of the heat and water through the expiration, also intensive physical activity induced releasing of growth hormone (GH) especially in water polo players (7, 8). Airway cooling causes the vagal parasympathetic reflex to

be triggered thereby causing the airway narrow (9). Toward to neural theories, sensory nerves can be stimulated by osmotic stress and dry air causing hyperpnea releasing eicosanoids which activate sensory nerves (10). Prostaglandin D2 (PDG2) release from mast cells also stimulate sensory nerves across DP1 receptors (11). Increase in CysLTs and neurokin A is linked to bronchoconstriction. Also production of MUC5AC enclose the airway obstruction after exercise in patients with EIB (12). According to one study which scrutinized parasympathetic activity in athletes, correlation between parasympathetic activity and PD_{20met} depends on the type of sports (especially endurance sports, like swimming) and may be influenced by the training environment or specificity of training. In addition to osmotic and vascular theory, today's researches believe that oxidative stress is key to the development of bronchoconstriction because it can make cellular damage by oxidize membrane lipids, nuclear acid and proteins which cause the release of inflammatory cells (13). According to some authors, in the USA, ozone, particulate matter (PM) and trichloramines in swimming pools are the biggest pollutions to witch athletes are exposed during training. These pollutions increase the oxidative stress provokes airway inflammation and decrease lung function, especially in cold weather endurance athletes, swimmers and ice rink athletes (14). Expose to different allergens, PM, pollutants, cold and dry air, their inhalation leads to damage epithelial cells breaking the connections between them and making inflammation (15). This process resulting by relief markers of inflammation: Clara Cell protein 16 (marker of epithelial damage) and in sputum rising of: leukotriens and IL-8 after exercise (16). Some studies found that athletes like skiers and swimmers have bigger chance to develop some respiratory diseases, including asthma. Swimmers are exposed to chlorine, skiers train in dry air environment conditions. Exposing to this type of conditions, long time, it can cause epithelial damage, inflammation and finally remodeling airways like in asthma conditions (17).

Incidence and prevalence of EIA/EIB

The prevalence of EIA/EIB among elite athletes is high especially among durability athletes. Incidence testing is less prevalent among researches. One Swedish research showed that incidence of asthma diagnosed by physician was 61.2 per 1000 person-years, more common to the female population, in those with a familial predisposition to asthma and in all those whom wheezing is the most common symptom (18). With a prevalence of about 8%, asthma is the most represented chronic disorder that occurs in Olympians, especially those who play endurance sport (19). Some data

have shown that intense physical activity in Olympians leads to an increase in the number of asthma suffers, rises bronchial hyperactivity, leads to an increase in respiratory infections and impaired immune response. A large study conducted on 659 Italian Olympians who participated in the Summer and Winter Olympics in the period from 2000. to 2012. showed the following data: the number of asthma athletes who participated in the Olympic games in Sidney in 2000. was 11.3%, and in Beijing in 2008. it was 17.2%. The total prevalence for the examined period was 14.7% (20). There is also a higher prevalence of cross country skiers compared to general population, 23% of them have been diagnosed with asthma and 25% use asthma medications. This is almost twice as much as in the examined, general population (21). In relation to athletes who train endurance, some elite athletes evolved asthma or air-hyper responsive (AHR) late in their sports careers. A key factor was the quality of the inhaled air, which may be detrimental but not observed in athletes in every Olympic discipline eg. the use of β_2 adrenoceptor agonists has been reported in 10% of rowers (19).

Lung function

Spiro metric examination of lung function provides an insight into the differences in the examined parameters in athletes who compete in different disciplines. Spirometry results, in athletes who examine, are most often described by comparing the following parameters: vital capacity (VC), forced expiratory volume in 1s (FEV1), forced vital capacity (FVC), relationship FEV1/FVC, peak expiratory flow (PEF) and maximum voluntary ventilation (MVV) (22,23). FEV1 is considered to be a priority indicator of pulmonary function while PEF is less reproducible and refined (24). One study confirmed that fact, measuring FEV1 and PEF among athletes and control group and made conclusion that FEV1 are changeable in exercise training while the values of PEF did not have significant role in both of testing group (25). Constant physical activity during which endurance exercises are emphasized leads to permanent changes in spirometry parameters. This emphasizes the need to consider the development of different breathing patterns in different sports (26). According one study the elite athletes showed the significance in spirometry results. They discovered that the values of FVC, FEV1, MVV and VC were higher in water polo players than the other sports, the value of PEF was higher in basketball player than in handball player (27). That athletes who play endurance sports have significant changes in spirometry parameters is also shown by a study where swimmers recorded higher values of VC, FEV1, FVC, FEV1/FVC when compared to the parameters of football players and control group

(28). Contrary to the above, by searching the literature, data can be obtained that there was no significant difference in spirometric evaluation between aerobic, anaerobic and control group. Diffusing capacity for carbon monoxide (DLCO) like the most valuable clinical test for the pulmonary function comparing with transfer coefficient for carbon monoxide (KCO) did not showed the statistical difference between mentioned groups (29). In one study, they compared respiratory parameters of aerobic and anaerobic athletes and control group with values of maxima oxygen consumption (VO_{2max}) and made conclusion that there were no statistical difference between compared groups. Their conclusion was that physical activity improves respiratory function and VO_{2max} , especially the aerobic type of training (30). Since it is hypertension the most common disorders of cardiovascular system, some authors have examined the effect of high blood pressure on exercise capacity. Their results showed that during the exercise there is a decrease in maximal oxygen consumption (VO_{2max}), heart rate reserve (HRR) and ventilatory anaerobic threshold (VAT) in groups of sportsmen with high normal blood pressure (HNBP) and in hypertensives after adjustment of ages, body fat lining and type of sports activity (31).

Quality of life

Researchers believe in fact that asthmatics tolerate physical activity well and no study has shown otherwise, which could be proven in reached enormous success and playing elite sports (32). The quality of life at elite and endurance athletes depends on marginal performance benefits to reach the highest possible competitive positions. With certain pharmacological and non-pharmacological treatments, symptoms that would interfere with the performance of athletes can be prevented and treated, as well as reduced mortality and morbidity rates (15).

CONCLUSION

The prevalence of asthma among elite athletes, and especially those involved in endurance sports (water polo, swimming) is significantly higher than in the general population. Constant exposure to agents in environments where athletes exercise throughout frequent training and their inhalation leads to hyper reactivity of the respiratory mucosa which is accompanied by frequent inflammation and disruption of the structure of the bronchial tree. The entire pathophysiological mechanism is reflected in changes in spirometry parameters that are significantly higher among endurance athletes. The mechanism of EIA is significantly more complex and still insufficiently clarified. In the future, more researches should be conducted related to the

mechanism of occurrence, monitoring of spirometry parameters and quality of life of athletes during their careers and after that, in retirement.

Abbreviations

EIA — exercise-induced asthma

EIB — exercise induced bronchoconstriction

AHR — airway hyper responsiveness

FEV1 — forced expiratory volume in first second

PEF — peak expiratory flow

VC — vital capacity

FVC — forced vital capacity

MVV — maximum voluntary ventilation

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Sažetak

ASTMA KOD VRHUNSKIH SPORTISTA; MEHANIZAM NASTANKA I UTICAJ NA DISAJNU FUNKCIJU - PREGLED LITERATURE

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Uvod: Opšte je prihvaćen stav da je fizička aktivnost korisna svakom pojedincu, ali sportisti sa dijagnostikovanom astmom se suočavaju sa raznim izazovima tokom treniranja da bi održali simptome pod kontrolom. Dugotrajno izlaganje faktorima iz okruženja u kom treniraju dovodi do trajnih promena na disajnim putevima. Njihovim dugotrajnim delovanjem dolazi do hiperreaktivnosti disajnih puteva sa posledičnim izazivanjem zapaljenskog odgovora i oslobađanjem medijatora zapaljenja (IL-8, leukotrieni, eikosanoidi) koji dovode do oštećenja epitelnih ćelija, izazivajući prekid konekcija među njima, sa posledičnim razvojem disfunkcije respiratornog sistema. Ovo stanje se naziva naporom izazvana astma. Ova činjenica je posebno važna kod sportista koji se bave sportovima izdržljivosti. Spirometrija, kao suverena metoda, predstavlja „zlatni standard“ za procenu funkcije respiratornog sistema. Cilj naše studije je bio da razjasnimo

mehanizam nastanka vežbama izazvane astme, njenu prevalencu i incidencu kod sportista, posledice tih vežbi na respiratorni sistem i kvalitet života sportista sa astmom. Pretražili smo radove na Pubmed-u i Kohranovoj bazi koristeći sledeće reči: 'naporom izazvana astma', 'sportisti', 'spirometrija', 'bronhokonstrikcija', 'fizička aktivnost', 'trening', 'prevalenca', 'incidenca'. Detaljno smo proučili 48 naučno-istraživačkih radova. **Zaključak:** Prevalenca astme među sportistima, posebno onima koji se bave sportovima izdržljivosti, značajno je viša nego u opštoj populaciji. Objašnjenje ove pojave se vezuje za mehanizam nastanka, koji je još uvek nedovoljno razjašnjen, ali je zasigurno da dobrom kontrolom bolesti sportisti mogu neometano da treniraju i da se takmiče dugi niz godina.

Cljučne reči: astma izazvana naporom, vrhunski sportisti, mehanizam nastanka, spirometrija, prevalenca.

REFERENCES

1. National Heart, Lung and Blood Institute. Guidelines for the Diagnosis and Management of Asthma (EPR-3). 2007. <http://www.nhlbi.nih.gov/guidelines/asthma/index.htm>.
2. Couto M, Moreira A, Delgado L. Diagnosis and treatment of asthma in elite athletes. *Breathe*. 2012;8: 286-96.
3. Thomas S, Wolfarth B, Wittner C, Nowak D, Radon K, GA2LEN-Olympic study-Team. Self-reported asthma and allergies in top athletes compared to the general population- results of the German part of the GA2 LEN- Olympic study 2008. *Allergy Asthma Clin Immunol*. 2010; 6(1): 31.

4. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, et al. Guidelines for metacholine end exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med*. 2000; 161(1): 309-29.

5. Weiler JM, Bonini S, Coifman R, Craig T, Delgado L, Capao-Filipe M, et al. American Academy of Allergy, Asthma & Immunology Work Group report: exercise-induced asthma. *J Allergy Clin Immunol*. 2007; 119(6): 1349-58.

6. Anderson SD, Daviskas E. The mechanism of exercise-induced asthma is. *J Allergy Clin Immunol*. 2000; 106(3): 453-9.

7. Djelic M, Mazic S, Tepsic J, Nesic D, Lazovic B, Radovanovic D, et al. Effect of acute exercise on serum growth hormone and fatty acid levels in elite male water polo players. *Arch Biol. Sci.* 2014; 66(1): 355-61.
8. Carlsen KH. Sports in extreme conditions: the impact of exercise in cold temperatures of asthma and bronchial hyper-responsiveness in athletes. *Br J Sports Med.* 2012; 46(11): 796-9.
9. Deal EC Jr, MacFadden ER Jr, Ingram RH Jr, Strauss RH, Jaeger JJ. Role of respiratory heat exchange in production of exercise-induced asthma. *J Appl Physiol Respir Environ Exerc Physiol.* 1979; 46(3): 467-75.
10. Kippelen P, Anderson SD, Hallstrand TS. Mechanisms and biomarkers of exercise-induced bronchoconstriction. *Immunol Allergy Clin North Am.* 2018; 38(2): 165-82.
11. Maher SA, Birrell MA, Adcock JJ, Wortley AM, Dubuis DE, Bonvini JS, et al. Prostaglandin D2 and the role of the DP1, DP2 and the TP receptors in the control of airway reflex events. *Eur Respir J.* 2015; 45(4): 1108-18.
12. Hallstrand TS, Debley JS, Farin FM, Henderson WR Jr. Role of MUC5AC in the pathogenesis of exercise-induced bronchoconstriction. *J Allergy Clin Immunol.* 2007; 119(5): 1092-8.
13. Ciencewicz J, Trivedi S, Kleeberger SR. Oxidants and the pathogenesis of lung diseases. *J Allergy Clin Immunol.* 2008; 122(3): 456-68.
14. Rundell KW, Smoliga JM, Bougault V. Exercise-induced bronchoconstriction and the air we breathe. *Immunol Allergy Clin North Am.* 2018; 38(2): 183-204.
15. Atchley TJ, Smith DM. Exercise-induced bronchoconstriction in elite or endurance athletes: Pathogenesis and diagnostic considerations. *Ann Allergy Asthma Immunol.* 2020; 125(1): 47-54.
16. Chimenti L, Morrici G, Paterno A, Santagata R, Bonanno A, Profita M, et al. Bronchial epithelial damage after a half-marathon in nonasthmatic amateur runners. *Am J Physiol Lung Cell Mol Physiol.* 2010; 298(6): L857-62.
17. Boulet L, O'Byrne PM. Asthma and exercise-induced bronchoconstriction in athletes. *N Engl J Med.* 2015; 372(7): 641-8.
18. Irewall T, Söderström L, Lindberg A, Stenfors N. High incidence rate of asthma among elite endurance athletes; a prospective 4-year survey. *J Asthma.* 2020; 20: 1-7.
19. Fitch KD. An overview of asthma and airway hyper-responsiveness in Olympic athletes. *Br J Sports Med.* 2012; 46(6): 413-6.
20. Bonini M, Gramiccioni C, Fioretti D, Ruckert B, Rinaldi M, Cezmi Akdis C, et al. Asthma, allergy and the Olympics: a 12-year survey in elite athletes. *Curr Opin Allergy Clin Immunol.* 2015; 15(2): 184-92.
21. Lennelov E, Irewall T, Naumburg E, Lindberg A, Stenfors N. The prevalence of asthma and respiratory symptoms among cross-country skiers in early adolescence. *Can Respir J.* 2019; 2019: 1514353.
22. Lazovic B, Mazic S, Suzic-Lazic J, Djelic M, Djordjevic-Saranovic S, T Durmic, et al. Respiratory adaptations in different types of sports. *Eur Rev Med Pharmacol Sci.* 2015; 19(12): 2269-74.
23. Mazic S, Lazovic B, Djelic M, Suzic-Lazic J, Djordjevic-Saranovic S, Durmic T, et al. Respiratory parameters in elite athletes—does sport have an influence? *Rev Port Pneumol.* 2015; 21(4): 192-7.
24. Parsons JP, Hallstrand TS, Mastronarde JG, Kaminsky DA, Rundell KW, Hull JH, et al. An official American Thoracic Society clinical practice guideline: exercise-induced bronchoconstriction. *Am J Respir Crit Care Med.* 2013; 187(9): 1016-27.
25. Eichenberger PA, Diener SN, Kofmehl R, Spengler CM. Effects of exercise training on airway hyperreactivity in asthma: a systematic review and meta-analysis. *Sports Med.* 2013; 43(11): 1157-70.
26. Durmic T, Lazovic Popovic B, Zlatkovic Svenda M, Djelic M, Zugic V, Gavrilovic T, et al. The training type influence on male elite athletes' ventilatory function. *BMJ Open Sport Exerc Med.* 2017; 3(1): e000240.
27. Durmic T, Lazovic B, Djelic M, Suzic Lazic J, Zikic D, Zugic V, et al. Sport-specific influences on respiratory patterns in elite athletes. *J Bras Pneumol.* 2015; 41(6): 516-22.
28. Lazovic-Popovic B, Zlatkovic-Svenda M, Durmic T, Djelic M, Djordjevic-Saranovic S, Zugic V. Superior lung capacity in swimmers: some questions, more answers! *Rev Port Pneumol* (2006). 2016; 22(3): 151-6.
29. Lazovic B, Zlatkovic-Svenda M, Grbovic J, Milenkovic B, Sipetic Grujicic S, Kopitovic I, et al. Comparison of lung diffusing capacity in young elite athletes and their counterparts. *Rev Port Pneumol* (2006). 2017; S2173-5115(17)30150-1.
30. Lazovic-Popovic B, Zlatkovic-Svenda M, Djelic M, Durmic T, Zikic D, Zugic V. Is there relationship between dynamic volumes of pulmonary function and cardiac workload (maximal oxygen uptake) in young athletes? *Rev Port Pneumol* (2006). 2016; 22(4): 237-40.
31. Mazic S, Suzic Lazic J, Dekleva M, Antic M, Soldatovic I, Djelic M, et al. The impact of elevated blood pressure on exercise capacity in elite athletes. *Int J Cardiol.* 2015; 180: 171-7.
32. Carson KV, Chandratilleke MG, Picot J, Brinn MP, Esterman AJ, Smith BJ. Physical training for asthma. *Cochrane Database Syst Rev.* 2013; 30(9): CD00116.

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IODINE-INDUCED HYPERTHYROIDISM: DO YOU MIND?

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Abstract: Iodine can be obtained by consumption of the foods that include it or to which it is added. Iodine-induced hyperthyroidism, also known as Jod-Basedow Syndrome, usually rise in the cases of an underlying thyroid disease, such as autoimmune thyroid disease, latent Graves disease, non toxic diffuse or nodular goiter or previous thyroid surgery. Iodine-induced hyperthyroidism is frequently self-limited with a period of 1-18 months after the discontinuance of iodine supply/repletion. The prognosis is frequently favorable, the majority returns to the baseline hormonal status. The long term outcomes of Jod-Basedow effects remain unknown due to the scarcity of phenomenon. Nonetheless, it is remarkable that treatment, devoted to the underlying thyroid diseases, should be addressed after resolution of the acute episode. Furthermore, an interprofessional health care team must serve and officiate not only to treat iodine-induced hyperthyroidism, but also to concern themselves actively in prophylaxis.

Key words: Iodine; Hyperthyroidism; Jod-Basedow; Thyroid; Endocrine Surgery; Thyroidology.

IODINE-INDUCED HYPERTHYROIDISM

Iodine can be obtained by consumption of the foods that involve it or to which it is annexed. Dietary iodine is absorbed from stomach and duodenum in the rate of > 90% as iodide and rapidly distributed in the extracellular fluid, transported to the thyroid gland by sodium/iodide symporter with a gradient of 25-50 times of plasma. The recommended minimum daily intake of iodine is 150 µg for nonpregnant adults, > 12

years; 220 to 250 µg for pregnant; 290 µg for lactating women, and 90 µg to 120 µg for children, 0-59 months and 6-12 years, respectively (1).

The prevalence of hyperthyroidism that has been reported subsequent to the iodine administration is 1-20%, while the higher frequency, 10-20%, appears in the individuals with nodular goiter living in the areas of iodine deficiency (2, 3). Iodine-induced hyperthyroidism, also known as Jod-Basedow Syndrome, scarcely occurs in cases in the absence of an underlying thyroid disease like autoimmune thyroid disease, previous thyroid surgery, latent Graves disease, and non-toxic diffuse or nodular goiter (4-8). The autonomy of underlying areas within the thyroid gland leads to thyrotoxicosis and the autonomous areas generate the thyroid hormones independently of normal regulatory mechanisms as exogenous iodine supply is augmented usually by iodinated contrast media used in conjunction with computed tomography scans, angiography, and various other imaging studies, or by intake of iodinated antiseptic solutions, and oral supplements (5, 9). A subclinical hyperthyroidism before iodine supply may exist in such cases (3).

In general, iodine-induced hyperthyroidism is self-limited with a period of 1-18 months after cessation of iodine administration. The preliminary treatment modality of iodine-induced hyperthyroidism is i) discontinuation of iodine administration, ii) abstaining from further exposure and iii) administration of a beta-adrenergic antagonists, such as atenolol 25-50 mg/day, as an initial dose, to diminish the symptoms of hyperthyroidism (10). Administration of a thionamide may expedite the recovery (11). Methimazole, possessing long duration of action, allowing for once-daily do-

sing, quicker efficacy and lower incidence of side effects, is recommended while the relevant symptoms are severe or prolonged (> 1 month) as starting dose of 10-20 mg/day. Corticosteroid therapy is suggested to accelerate the return of thyroid hormones to their normal ranges. In case, anti-thyroid drugs fail to attenuate thyroid hormone production, providers may regard to prescribe lithium, owing to its inhibitory impacts on the thyroid gland (5).

The prognosis is frequently affirmative, the majority of the cases returns to the baseline thyroid status. The complications of iodine-induced hyperthyroidism are consist permanent hyperthyroidism, thyroid storm, and atrial fibrillation (5). The longterm outcomes of iodine-induced hyperthyroidism, Jod-Basedow Effect, remain unknown because the phenomenon is rare. However, appropriate treatment leads to good outcomes in Thyroidology. Nevertheless, some cases may require the longterm treatment with antithyroid drugs and beta-blockers. Against all odds it is noteworthy that treatment of the underlying thyroid diseases should be addressed after resolution of the acute episode of Jod-Basedow Syndrome. In addition, the interprofessional health care team must serve and officiate not only to treat iodine-induced hyperthyroidism but also to

concern themselves, actively in the relevant prophylaxis (5).

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Authors' contribution

IS, originating the idea, constituting the notion, intellectual planning, design, co-writing, editing, and the final approval, agreement to be accountable for all aspects of the work; DS, originating the idea, constituting the notion, intellectual planning, design, and co-writing, editing, supervision, and the final approval, agreement to be accountable for all aspects of the work; AP, design, co-writing, editing, and final approval, agreement to be accountable for all aspects of the work.

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Sažetak

JODOM-IZAZVAN HIPERTIREOIDIZAM: DA LI STE?

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Jod se može uneti hranom koja ga sadrži ili kojoj je dodat. Jodom izazvan hipertireoidizam, također poznat i kao Jod-Basedow Sindrom, obično se javlja u slučajevima već prisutne bolesti štitaste žlezde, kao što su autoimuna bolest štitaste žlezde, latentna Graves-ova bolest, netoksična difuzna ili nodularna gušavost ili prethodna operacija štitaste žlezde. Jodom izazvan hipertireoidizam je često samolimitirajući tokom perioda 1-18 meseci nakon prekida unosa joda. Prognoza je često povoljna, veći-

na se vrati na početni hormonalni status. Dugoročni ishodi Jod-Basedow Sindroma ostaju nepoznati zbog retkosti i ograničenosti fenomena. Bez obzira na to, bitno je da lečenje postojeće bolesti štitaste žlezde bi trebalo nastaviti nakon akutne epizode. Multidisciplinarni tim medicinskih radnika mora ne samo lečiti jodom izazvan hipertireoidizam, već i aktivno se baviti profilaksom.

Ključne reči: Jod, Hipertireoidizam, Jod-Basedow, Štitasta žlezda, Endokrina hirurgija, Štitnjača.

REFERENCES

1. WHO, UNICEF, ICCIDD. Assessment of iodine deficiency disorders and monitoring their elimination: a guide for programme managers, third edition (updated 1st September 2008). Geneva, World Health Organization, 2001. Available at: www.who.int/nutrition/publications/micronutrients/iodine_deficiency/9789241595827/en/. Accessed June 10, 2020.

2. Martins MC, Lima N, Knobel M, Medeiros-Neto G. Natural course of iodine-induced thyrotoxicosis (Jodbasedow) in endemic goiter area: a 5 year follow-up. *J Endocrinol Invest*. 1989; 12(4): 239-44.

3. Roti E, Uberti ED. Iodine excess and hyperthyroidism. *Thyroid*. 2001; 11(5): 493-500.

4. Skare S, Frey HM. Iodine induced thyrotoxicosis in apparently normal thyroid glands. *Acta Endocrinol (Copenh)*. 1980; 94(3): 332-6.

5. Rose HR, Zulfiqar H. Jod Basedow Syndrome. In: Stat Pearls [Internet]. Treasure Island (FL): Stat Pearls Publishing, 2020.
6. Al-Yaarubi S, Farhan H, Al-Futaisi A, Al-Qassabi S, Al-Rasadi K, Al-Riyami S, et al. Accuracy of ultrasound-guided fine-needle aspiration cytology for diagnosis of carcinoma in patients with multinodular goiter. *Indian J Endocrinol Metab.* 2011; 15(Suppl 2): S132-5.
7. Sengul D, Sengul I. Is there any link between a kind of thyrocyte dysfunction, hypothyroidism, and inflammatory hematologic parameters in the cases having the benign thyroid nodules? A 5-year single-centre experience. *Sanamed.* 2018; 13(1): 35-40.
8. Sengul D, Sengul I, Van Slycke S. Risk stratification of the thyroid nodule with Bethesda indeterminate cytology, category III, IV, V on the one surgeon-performed US-guided fine-needle aspiration with 27-gauge needle, verified by histopathology of thyroidectomy: The additional value of one surgeon-performed elastography. *Acta Chir Belg.* 2019; 119(1): 38-46.
9. Stanbury JB, Ermans AE, Bourdoux P, Todd C, Oken E, Tonglet R, et al. Iodine-induced hyperthyroidism: occurrence and epidemiology. *Thyroid.* 1998; 8(1): 83-100.
10. Bahn Chair RS, Burch HB, Cooper DS, Garber JR, Greenlee MC, Klein I, et al. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Thyroid.* 2011; 21(6): 593-646.
11. Burman KD, Wartofsky L. Iodine effects on the thyroid gland: biochemical and clinical aspects. *Rev Endocr Metab Disord.* 2000; 1(1-2): 19-25.

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