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DISCIPLINA ZA NAUKU I NASTAVU


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1894 - 2024
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Bosnia and Herzegovina was the fourth country in Europe that developed National version of HeartScore program !

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Novi Centralni medicinski blok - Klinički centar Univerziteta u Sarajevu
New Central Medical Building - Clinical Center University of Sarajevo

Novi Evropski vodič za prevenciju tromboembolizma kod A Fib

CHA_2DS_2-VASc skor za procjenu rizika od tromboembolizma kod A Fib!

Risk factor-based point-based scoring system - CHA_2DS_2 -VASc

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease*	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

*Prior myocardial infarction, peripheral artery disease, aortic plaque. Actual rates of stroke in contemporary cohorts may vary from these estimates.

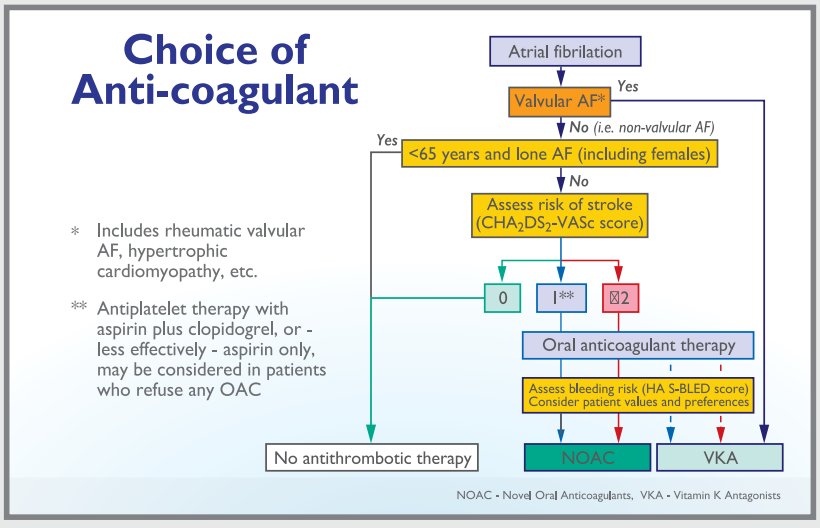
Major i non-major riziko fakori za procjenu tromboembolizma kod A Fib!

Risk factors for stroke and thrombo-embolism in non-valvular AF

Major risk factors	Clinically relevant non-major risk factors
Previous stroke	CHF or moderate to severe LV systolic dysfunction [e.g. LV EF ⊠ 40%]
TIA or systemic embolism	Hypertension
Age ⊠75 years	Diabetes mellitus
	Age 65-74 years
	Female sex
	Vascular disease

AF = atrial fibrilation; EF = ejection fraction (as documented by echocardiography, radio nudide ventriculography, cardiac catheterization, cardiac magnetic resonance imaging, etc.); LV = left venticular; TIA = trasient ischaemic attack.

Algoritam antikoagulantne terapije nakon procjene CHA_2DS_2VASc i major risk faktora!



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AIMS AND SCOPE

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Case reports

Myocarditis as Part of the COVID-19 Infection in Children Treated at the Pediatric Clinic of the Clinical Center University of Sarajevo - Correlation of Troponin and Pro BNP Biomarkers with Echocardiographic and Electrocardiographic Results, and the Impact on the Length of Hospital Treatment

Miokarditisi u sklopu COVID-19 infekcije kod djece tretirane na Pedijatrijskoj klinici Kliničkog centra Univerziteta u Sarajevu - Korelacija biomarkera troponina i pro BNP-a sa ehokardiograskim i elektrokardiografskim rezultatima, te uticaj na dužinu hospitalnog tretmana

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ABSTRACT

Introduction: the diagnosis of myocarditis is extremely complex. The incidence of this disease increased significantly after the COVID-19 pandemic. In a study published by the Center for Disease Control and Prevention (CDC), the overall risk of COVID-19 infection for children was relatively low, but children with proven infection had a 40% higher risk of developing myocarditis. Knowing the character of myocarditis, especially in children, adequate treatment is imperative. Aim: to determine the correlation of troponin biomarker and pro BNP with echocardiographic and electrocardiographic results, and the influence on the length of hospital treatment of the observed group. Materials and methods: this multicenter, retrospective study included patients aged 0-18, who in the period from 1 June 2020 to 1 June 2021 were hospitalized at the Pediatric Clinic of the CCUS due to severe clinical manifestations of the COVID-19 infection. The study was based on data available from medical records. Results: troponin and proBNP values were statistically significantly higher in the group of patients with tricuspid regurgitation - TR ($p=0.009$, $p=0.016$) and lower fractional shortening (FS) values ($p=0.023$, $p=0.016$). The length of hospitalization in children with elevated level of cardiac biomarkers was significantly higher in the group of patients with elevated values of troponin and proBNP, and FS < 27% ($p=0.001$). Conclusion: although endomyocardial biopsy is considered the gold standard in establishing a clear diagnosis of myocarditis, troponin and pro BNP values along with other laboratory-diagnostic procedures can significantly contribute to the early detection and evaluation of patients with myocarditis caused by COVID-19 infection.

Keywords: myocarditis, COVID-19, troponin, proBNP, pediatric population

SAŽETAK

Uvod: dijagnoza miokarditisa je izuzetno kompleksna. Incidenca ovog oboljenja se nakon COVID-19 pandemije značajno povečala. u studiji objavljenoj od strane Centra za kontrolu bolesti (CDC) ukupni rizik od COVID-19 infekcije za djecu je bio relativno nizak,

ali su djeca sa dokazanom infekcijom imala 40% veći rizik od razvoja miokarditisa. Poznavajući karakter miokarditisa, naročito dječije dobi adekvatan tretman je imperativ. Cilj: utvrditi korelaciju biomarkera troponina i pro BNP-a sa ehokardiograskim i elektrokardiografskim rezultatima, te uticaj na dužinu hospitalnog tretmana posmatrane grupe. Materijal i metode: provedena je multicentrična, retrospektivna studija u koju su bili uključeni pacijenti starosne dobi od 0-18 godina života, a koji su u periodu od 01.06.2020. do 01.06.2021. godine bili hospitalizirani na Pedijatrijskoj klinici Kliničkog centra Univerziteta u Sarajevu zbog teških kliničkih manifestacija infekcije COVID-19. Studija se zasnivala na upotrebi dostupnih podataka iz medicinske dokumentacije. Rezultati: vrijednost troponina i proBNP su bile statistički značajno više u skupini pacijenata s prisutnom trikuspidnom regurgitacijom- tr (p=0,009, p=0,016) i nižom vrijednosti frakcije skraćenja (FS) (p=0,023, p=0,016). Dužina hospitalnog tretmana kod djece sa višim vrijednostima markera oštećenja srčanog mišića bio je značajno viši u skupini pacijenata s većim vrijednostima troponina i proBNP-a i manjom FS od 27% (p=0,001). Zaključak: iako se endomiokardijalna biopsija smatra zlatnim standardom u postavljanju jasne dijagnoze miokarditisa, vrijednosti troponina i proBNP-a uz druge laboratorijsko-dijagnostičke postupke u značajnom mogu pridonijeti ranoj detekciji i evaluaciji pacijenata sa miokarditisom uzrokovanih COVID-19.

Ključne riječi: miokarditis, COVID-19, troponin, proBNP, pedijatrijska polupacija

INTRODUCTION

Statistical data before the pandemic indicate that the incidence of myocarditis is 1-10 per 100,000 people. This rate reaches its peak in healthy, active men aged 18 to 30 (1). The diagnosis of myocarditis is extremely complex and as the gold standard it also involves the use of endomyocardial biopsy (EMB), which is rarely performed in practice (2). An alternative to EMB is cardiac magnetic resonance (CMRI), which, given that it does not have high-energy radiation (for now unknown impact on genetic material or carcinogenic effect), makes this method extremely acceptable in the pediatric population. (3). In order to adequately carry out the mentioned procedure, it is necessary to meet certain conditions such as lower pulse values, which, given the specificity of the children's population, may sometimes imply the need for a significant lowering of these values. Although most cases of the COVID-19 infections are characterized by the respiratory system symptoms, infections of other organ systems have also been documented, with the cardiovascular system being at the top (4). The World Health Organization (WHO) states that the incidence of myocarditis has increased significantly after the pandemic caused by the COVID-19, reaching a value of up to 146 cases per 100,000 people (5). Myocarditis can be manifested by different severity of the clinical picture, and timely diagnosis is extremely important, especially of myocarditis characterized by fulminant forms, often accompanied by arrhythmias and signs of cardiac decompensation. 30-40% of myocarditis, even with an adequate treatment, can lead to dilated cardiomyopathy with an extremely uncertain outcome (6). Ali M, et al., in their study, presented facts related to the importance of early recognition, diagnosis and adequate treatment of myocarditis, suggesting the implementation of troponin, electrocardiogram and echocardiography, as simple and very important allies in the early detection of the disease (7). Sleem B, et al., state that severe forms of the COVID-19 infection have also been registered in children, with myocarditis accounting for a significant proportion (8). Literature data related to myocarditis in the pediatric population, especially the one caused by the COVID-19, are very poor. Consequently, further clinical studies are essential with the aim of obtaining clear and precise guidelines in the early detection, treatment and monitoring of pediatric patients with myocarditis.

Evaluating the period of the COVID 19 pandemic, we can rightly say that the special circumstances caused by the pandemic (significant influx of patients, redistribution of medical staff and equipment) dictated and influenced special working conditions, which was the reason why we relied on anamnestic data, available laboratory data when establishing a diagnosis of myocarditis - diagnostic procedures and the clinical course of the disease itself.

Witnessing repeated reports of new COVID-19 cases, in this study we will try to give our contribution in enlightening the role of certain laboratory-diagnostic procedures in the early detection of myocarditis in children, all with the aim of early diagnosing, adequate treatment and evaluation of sick children.

MATERIALAS AND METHODS

This multicenter, retrospective study included patients aged 0-18, who in the period from 1 June 2020 to 1 June 2021 were hospitalized at the Pediatric Clinic of the CCUS due to severe clinical manifestations of the COVID-19 infection and who until the moment of hospitalization had normal growth and development. The aforementioned respondents did not have previously verified heart diseases until the moment of hospitalization. The study did not include patients with congenital heart anomalies (CA), surgically treated CA, patients with chronic heart disease (cardiomyopathies) and patients with Kawasaki disease. As part of a multidisciplinary approach, patients were monitored by a cardiologist on a daily bases. Given the circumstances of work during the pandemic, the myocarditis was diagnosed based on detailed anamnestic data, clinical picture, physical findings, course of the disease, results of laboratory diagnostic procedures, electrocardiography and echocardiographic monitoring results.

The study used available data from medical records including anamnestic data, laboratory findings, which served as basis for COVID-19 diagnosis, laboratory values of cardiac markers, analysis of electrocardiographic records and echocardiographic findings.

Statistical analysis

The results were processed using standard statistical methods, the SPSS computer program for statistical analyzes (SPSS-Statistical Package for Social Sciences) version 21.0. The results were expressed as mean (X) and standard error of the arithmetic mean (SEM), and as median and interquartile range (25-75 percentiles). The Shapiro-Wilk test was used to test the significance of the difference in deviation from the normal distribution. The results were analyzed with the student t-test for variables which met the application conditions, specifically with the corresponding non-

parametric Mann-Whitney U test for variables with an irregular distribution. The degree of correlation was determined by the Pearson or Sperman method. The value of $p < 0.05$ was taken as statistically significant.

AIM

The aim of this study was to determine the correlation of troponin biomarker and pro BNP with echocardiographic and electrocardiographic results, and the influence on the length of hospital treatment of the observed group.

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RESULTS

In the period from 1 June 2020 to 1 June 2021, a total of 29 patients with a severe clinical picture of the COVID-19 infection were hospitalized at the Pediatric Clinic of the CCUS. The average age of the respondents was 6.34 ± 0.71. Out of the total of 29 respondents, 17 (58.6%) were boys.

Inflammatory parameters such as CRP, D dimer, fibrinogen, ferritin, procalcitonin were significantly elevated. The mean value of CRP in our sample was 177.87± 23.73; D dimer 182.02±143.43; fibrinogen 4.51± 0.32; ferritin 489.30±120.45, procalcitonin 3.07±1.11. 21 (72%) respondents had a positive radiographic finding related to the presence of changes in the lung parenchyma. Cardiac markers such as troponin and proBNP were also elevated, ranging from 50 to 90%. Troponin values in our sample were 37.72 ± 12.59 (reference values 0-14 mg/l), the lowest value being 3 mg/l, and the highest 364 mg/l. The mean value of proBNP ranged from 10,125.52 ± 2,270.98 (reference values 0-125 pg/ml), with the lowest value being 8 pg/ml and the highest 35,000 pg/ml.

Table 1 **Basic characteristic of the patients**.

Gender (male/female)	17 (58.6%) / 12 (41.4%)
Age	6.34±0.71
CRP	177.87±23.70
D-dimer	182.02±143.43
Fibrinogen (g/L)	4.51±0.32
Ferritin	489.30±120.45
Procalcitonin	3.07±1.11
Troponin	37.72±12.59
ProBNP	10125.52±2270.98
FS <27	6 (20.0 %)
Length of hospital stay	12.37±0.96

In 8 (28%) respondents, changes on the ECG were registered relating to lower voltage, and in two cases the presence of first-degree heart block was additionally noted. In our sample, 6 (20%) respondents had reduced left ventricular function values. Out of those six children, only two had a severe form of heart failure, and in the case of a 5-year-old boy, who also had the most severe clinical expression, FS amounted to 18%.

Tricuspid regurgitation of various degrees was noted in 23 (79%) respondents.

Troponin and proBNP values were statistically significantly higher in the group of patients with tricuspid regurgitation - TR (p=0.009, p=0.016). The duration of hospitalization was significantly longer in the group of patients with present TR (p=0.012).

Table 2 **Comparative analysis of cardiac markers and length of hospital stay in patients with myocarditis stratified according to the presence of tricuspid regurgitation**.

	TR present	TR not present	p
CRP	199.45±26,77	151.30±41.41	0.321
D-dimer	3.73 (1,34-4,54)	2.91 (1.05-7.8)	0.792
Fibrinogen (g/L)	4.90±0.40	3.99±0.52	0.168
Ferritin	313.0 (198.0-995.0)	282,0 (47.0-528.0)	0.275
Interleukin-6	185.0 (28.0-813.75)	48.0 (2.90-114.0)	0.121
AST	29.50 (23.75-44.0)	32.0 (24.50-43.0)	0.880
Albumin (g/L)	24.0 (23.0-28.0)	27.0 (24.50-31.0)	0.121
Troponin	30.0 (16.0-45.50)	7.0 (4.0-201.0)	0.009
ProBNP	10800.0 (288.70-28221.0)	1150.0 (110.75-4166.0)	0.016
Length of hospital stay	14.50±1.23	9.76±1.22	0.012

Table 2 shows that troponin and proBNP values were statistically significantly higher in the group of patients with TR present (p=0.009, p=0.016). The length of hospital stay was significantly higher in the group of patients with present TR (p=0.012).

Comparative analysis of inflammatory parameters and duration of hospitalization in patients with myocarditis stratified based on the fractional shortening (FS) values, established that the value of troponin and proBNP were statistically significantly higher in the group of patients with FS < 27 (p=0.023, p=0.016). Accordingly, the duration of hospitalization was significantly longer in the group of patients with FS less than 27 (p=0.001) and elevated cardiac markers, such as troponin and pro BNP.

Table 3 **Comparative analysis of inflammatory parameters, cardiac markers and length of hospital stay in patients with myocarditis stratified according to ejection fraction values**.

	EF <27	FS ≥28	p
CRP	199.53±35.10	166.47±31.44	0.517
D-dimer	3.73 (1.04-4.18)	2.91 (1.30-7.27)	0.734
Fibrinogen (g/L)	4.55 (3.80-6.70)	4.35 (2.40-5.10)	0.245
Ferritin	313.0 (130.50-817.50)	282,0 (216,0-728,0)	0,941
Troponin	32.0 (22.75-74.25)	16.0 (6.0-36.0)	0.023
ProBNP	12881.0 (8581.50-32333.0)	2396.,0 (14350-8856.0)	0.016
Length of hospital stay	26.0±16.6	10.15±0.94	0.001

Troponin and proBNP values were statistically significantly higher in the group of patients with FS <27 (p=0.023, p=0.016). The length of hospital stay was significantly higher in the group of patients with FS <27 (p=0.001).

Pericardial effusion not behaving compressively was noted in 11 (37%) respondents.

Comparative analysis of inflammatory parameters and the duration of hospitalization in patients with myocarditis stratified based on the presence of pericardial effusion, established that the duration of hospitalization was significantly longer in the group of patients with pericardial effusion (p=0.012), compared to patients without it.

Table 4 **Comparative analyses of the mentioned parameters and length of hospital stay in patients with myocarditis stratified based on the presence of pericardial effusion (EP).**

	EP present	EP not present	p
CRP	209.52±40.13	155.52±28.63	0.270
D-dimer	3.73 (1.27-4.08)	2.75 (1.24-8.62)	0.790
Fibrinogen (g/L)	5.18±0.55	4.08±0.37	0.099
Ferritin	728.0 (298.50-995.0)	254.0 (125.0-405.0)	0.684
Troponin	11.0 (5.25-42.25)	22.0 (11.0-38.50)	0.303
ProBNP	11128,0 (417.75-29831.0)	2887.0 (598.50-11074.0)	0.286
Length of hospital stay	14.91±1.58	10.58±1.03	0.024

The length of hospital stay was significantly higher in the group of patients with EP (p=0.012).

In the total sample, a significant positive correlation was found between troponin values, proBNP and length of hospital stay (Rho=0.505**; p< 0.01).

DISCUSSION

Clinical picture of myocarditis is caused by the heart muscle malfunction manifested by dyspnea, orthopnea and chest pain. The intensity of symptoms can vary significantly, and occasionally lead the practitioner in the wrong direction to treat the respiratory system (9).

Güllü UU, et al., state that children can also have heart problems caused by COVID-19, which are clinically manifested by arrhythmias, myocarditis and cardiogenic shock (10). The mechanism of myocarditis caused by the COVID-19 virus is explained by direct cell damage or T lymphocytes-mediated cytotoxic effect in the cytokine storm (11). In a study published by the Center for Disease Control and Prevention (CDC), 0.133% of children with COVID-19 had myocarditis, while almost 0.0033% of children without COVID-19 had myocarditis, which is in favor of a higher incidence in the presence of COVID- 19 (12). The overall risk of COVID-19 for children was relatively low, but children with proven infection had 40% higher risk of developing myocarditis. Knowing the character of myocarditis, especially in children, adequate treatment is imperative.

According to data of the Federal Office of Statistics, from the beginning of the pandemic until June 2021 in the Federation of Bosnia and Herzegovina there were 139,368 laboratory-confirmed COVID-19 infections, with the pediatric population accounting for 6% (13). In the period from 1 June 2020 to 1 June 2021 a total of 29 patients with a severe clinical picture of COVID-19 infection were hospitalized at the Pediatric Clinic of the CCUS. The average age of hospitalized patients was 6.34 ± 0.71. Male respondents, 17 (58.6%) of them, were dominant in our sample.

As mentioned earlier, the gold standard for the diagnosis of myocarditis is EBM, rarely used in practice. CMRI significantly contributes to the assessment of the entire myocardium and the detection of inflammation signs. Given the circumstances of work during the pandemic, the myocarditis was diagnosed based on detailed anamnestic data, clinical picture, physical findings, course of the disease, results of laboratory diagnostic procedures, electrocardiography and echocardiographic monitoring results.

Fried JA, et al., state that inflammation parameters such as C reactive protein and others can be significantly elevated in the case of myocarditis caused by COVID-19 (14).

In their work, Okor I, et al., talk about the challenges faced by practitioners when diagnosing myocarditis as part of a COVID-19 infection, also registering elevated values of inflammatory parameters (15). Inflammatory parameters such as CRP, D dimer, fibrinogen, ferritin, procalcitonin were also significantly elevated in our study. Similar to other authors, we are also aware of the fact that these inflammatory parameters support the presence of infection, but not specifically the presence of myocarditis. Nevertheless, we still believe that, along with other laboratory diagnostic procedures, these inflammatory parameters can contribute to the early detection of myocarditis.

COVID-19 is primarily manifested by respiratory symptoms, although cases with domination of other organ system symptoms are not excluded. Among adult patients, there is a significant proportion of those treated for the heart muscle involvement (2-4). In our study, 21 (72%) respondents had a positive radiographic finding regarding the presence of changes of the lung parenchyma.

In their study, Fremed MA, et al., performed cardiology related treatment of pediatric patients with COVID-19, excluding those with chronic heart diseases. In 34% of cases, they noted elevated cardiac troponin and proBNP values, whereas elevated values were noted in 19% of respondents with accompanying comorbidities (16). Vukomanović VA, et al., evaluated children with proven myocarditis with and without COVID-19 infection. They concluded that respondents with myocarditis and COVID 19 infection had higher values of C reactive protein and higher levels of natriuretic peptide proBNP and troponin (17).

Sachdeva S, et al., state that troponin levels are more specific for the degree of myocardial damage, compared to CK and CK MB (18). Patients with acute myocardial infarction with left heart failure often had high troponin values. On the other hand, Wang Z, et al., believe that despite the increase in the values of CK, CK MB troponin, the mechanism of severe heart failure cannot be explained only by myocardial cell damage, but they believe that biomarkers of cardiac damage can play a significant role in the early detection of fulminant myocarditis (19). In our sample, cardiac markers troponin and proBNP were elevated in the range of 50-90%. At the same time, it was noted that inflammatory parameters were significantly elevated in all respondents. Comparative analysis of cardiac markers and duration of hospitalization in patients with myocarditis stratified based on fractional shortening (FS) values, established that troponin and proBNP values were statistically

significantly higher in the group of patients with FS < 27% (p=0.023; p= 0.016). The duration of hospitalization was significantly longer in the group of patients with elevated values of cardiac markers (troponin and pro BNP) and lower fractional shortening values.

Myocarditis can be accompanied by changes in ECG records. Ramoğlu MG, et al., evaluated 214 pediatric patients, with 15 (7%) of them having elevated troponin values. All patients with elevated troponin values had normal values for echocardiography, and in only two cases they noted ECG changes related to sinus tachycardia, which can be explained differently (20). In their study, Ozenen GG, et al., proved ECG changes in 3.5% of respondents related to negative T wave values in the precordial leads (21). In our work, 8 (28%) respondents had changes in the normal ECG pattern related to lower voltage values, and in two cases we recorded first-degree hart block.

The diagnosis of myocarditis is extremely complex and endomyocardial biopsy is cited as the gold standard, but is rarely performed compared to other procedures. We use EHO as an important source of data on the functional status of the heart muscle. Echo findings of the heart as part of myocarditis can vary significantly, depending on the moment of realization and the treatment nature (length of treatment, method of treatment, etc.) (22). The American College of Cardiology (ACC) recommends that all patients with suspected myocarditis undergo transthoracic echocardiography (TTE) as an initial diagnostic method (23). Fung G, et al., state that due to the nature of the procedure, echocardiography cannot provide direct evidence of the myocarditis presence, and therefore cannot independently serve as a final diagnostic tool (24). Similar to other authors, Ozenen GG, et al., in their study re-emphasize the role of TTE in the diagnosis of myocarditis and patients with COVID-19 (16). Changes on TTE can relate to pericardial effusion, tricuspid regurgitation, reduced value of fractional shortening, mitral valve malfunction, and all other changes that can be detected in the heart muscle relaxation (25). In our sample, 6 (20%) respondents had reduced left ventricular function values. The most severe form of cardiac decompensation was noted in a 5 years-old-boy, with FS of 18%. Tricuspid regurgitation of varying degrees was noted in 23 (79%) respondents. Troponin and proBNP values were statistically significantly higher in the group of patients with tricuspid regurgitation - TR (p=0.009, p=0.016) and lower FS values, FS < 27 (p=0.023, p=0.016). The duration of hospitalization was significantly longer in the group of patients with altered echocardiographic parameters.

CONCLUSION

The values of troponin and proBNP were statistically significantly higher in the group of patients with lower fractional shortening values. Troponin and pro BNP values were statistically significantly higher in respondents with tricuspid regurgitation. The duration of hospitalization was statistically longer in the group of patients with elevated cardiac markers (troponin and proBNP), fractional shortening < 27% and inherent tricuspid regurgitation. In our study, elevated troponin and pro BNP values showed a significant statistical correlation with deviations of echocardiographic findings from age-based reference values. Elevated values of troponin, pro BNP and deviations in the echocardiographic findings statistically significantly influence the length of hospital treatment of children with myocarditis as part of the COVID-19 infection.

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C-Reactive Protein as an Indicator of the Acute Phase of Inflammation and its Role in the Cause of Different Types of Glaucoma Through Parameters of Visual Acuity, Visual Field and Optical Coherence Tomography

C-reaktivni protein kao pokazatelj akutne faze inflamacije i njegova uloga u nastanku različitih vrsta glaukoma kroz parametre vidne oštrine, vidnog polja i optičke koherentne tomografije

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ABSTRACT

Introduction: glaucoma is a syndromic disease characterized by a triad of symptoms, namely: occasional or permanent increase in intraocular pressure, changes in the papilla nervi optici and damage to the visual field. Aim: to examine the role of elevated C reactive protein (CRP) values as a good indicator of the acute phase of inflammation in the serum of patients with different types of glaucoma, which can be linked to the pathogenesis and progression of glaucoma itself. Materials and methods: the study included 180 eyes of patients of both sexes, aged from 40 to 70 years old, who were diagnosed with glaucoma by diagnostic tests. Results: the concentration of CRP in the serum of the subjects was determined by laser nephelometry (BN II analyzer) at the Institute of Clinical Chemistry and Biochemistry of the CCUS. A statistically significant difference in serum CRP levels was observed between patients with NG and subjects of the control group (p=0.008), and between patients with NG and GA (p=0.043). Conclusion: no statistically significant correlation was observed between CRP concentration in serum and OCT parameters neither in patients with glaucoma nor in the control group of subjects (Table 1). Also, no statistically significant correlation was observed between serum CRP concentration and visual field parameters (LVD, LVS, MDD, MDS), nor statistically significant correlation between serum CRP and visual acuity in both eyes, nor statistically significant correlation between serum CRP and intraocular pressure in both eyes (results not shown!).

Keywords: CRP, inflammation, glaucoma, optical coherence tomography

SAŽETAK

Uvod: glaukom je sindromska bolest koju karakteriziraju tri simptoma, a to su: povremeno ili trajno povišenje očnog tlaka, promjene na papilla nervi optici i oštećenje vidnog polja. Cilj: ispitati ulogu povišenih vrijednosti C reaktivnog proteina (CRP) kao dobrog pokazatelja akutne faze inflamacije u serumu pacijenata sa različitim tipovima glaukoma, koji se mogu dovesti u vezu sa samom patogenezom i progresijom glaukoma. Materijali i metode: u istraživanje je uključeno 180 očiju pacijenata oba spola, starosne dobi od 40 do 70 godina kod kojih je dijagnostičkim pretragama ustanovljeno da boluju od glaukoma Rezultati : u istraživanje je uključeno 180 očiju pacijenata oba spola, starosne dobi od 40 do 70 godina kod kojih je dijagnostičkim pretragama ustanovljeno da boluju od glaukoma. Rezultati: koncentracija CRP u serumu ispitanika određivana je laser nefelometrijom (aparat BN II analizator) na Institutu za kliničku hemiju i biohemiju KCUS-a. Statistički značajna razlika u nivou CRP u serumu uočena je između pacijenata sa NG i ispitanika kontrolne grupe (p=0,008), te između pacijenata sa NG i GA (p=0,043). Zaključak: nije uočena statistički značajna korelacija između koncentracije CRP u serumu i parametara OCT-a ni kod pacijenata sa glaukomom, kao ni u kontrolnoj skupini ispitanika (Tabela 1). Također nije uočena statistički značajna korelacija između koncentracije CRP u serumu i parametara vidnog polja (LVD, LVS, MDD, MDS), niti statistički značajna korelacija između CRP u serumu i vidne oštrine na oba oka, kao ni statistički značajna korelacija između CRP u serumu i intraokularnog pritiska kod oba oka (rezultati nisu prikazani!).

Ključne riječi: CRP, inflamacija, glaukom, optička koherentna tomografija

INTRODUCTION

Glaucoma is a syndromic disease characterized by a triad of symptoms, namely: occasional or permanent increase in intraocular pressure, changes in the papilla nervi optici and damage to the visual field. It is a progressive optic neuropathy with irreversible loss of retinal ganglion cells leading to blindness (1,2). Previous research has shown that numerous risk factors contribute to the development of glaucoma, such as age, gender, race, genetics, increased eye pressure, refractive errors, etc. (3). Recent studies have shown that oxidative stress and inflammation contribute to the development of this disease (4,5).

According to the cause of glaucoma, we distinguish primary, secondary and congenital forms of this disease:

Primary glaucoma is the most common and accounts for over 80% of all glaucomas. It occurs, as the name suggests, without a previous eye disease (1-3).

We divide it according to the finding of the chamber angle into:

a) open-angle glaucoma - simplex glaucoma
b) glaucoma due to angle closure - angular glaucoma
c) mixed forms with characteristics of one and the other group - glaucoma mixtum

C-reactive protein (CRP)

Structure, synthesis and biochemical characteristics of CRP

CRP belongs to a family of pentameric proteins known as pentraxins. It is composed of five identical, non-covalently bound subunits, arranged around a central pore. A single subunit is made up of 206 amino acid residues whose molecular mass is 23,017 kiloDaltons (kDa), so the total molecular mass of CRP is approximately 118,000 kDa (Figure 1).

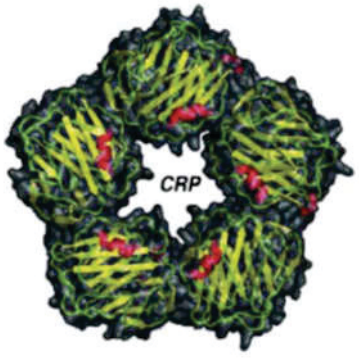


Figure 1 **Scheme of the molecular structure of C-reactive protein**
(from http://www.pace-cme.org/images/Molecular-structure-of-C-reactive-protein-C-reactive-576x482px.png)

The gene encoding CRP is located on the proximal long arm of chromosome 1, as are the inflammation-related genes for serum amyloid P component and Fc receptor. There is a significant association between CRP genotypes and serum concentrations (6).

Primarily, CRP is synthesized in hepatocytes, and its activity is stimulated by cytokines. Inflammation caused by infection or tissue damage causes the release of circulating cytokines including interleukin-6 (IL-6), interleukin-1b (IL-1b), and tumor necrosis factor-alpha (TNF-α). These cytokines stimulate the liver to increase the synthesis and release of acute phase proteins, including CRP. Interleukin-6 has the most potent stimulatory effect on increased CRP production (6).

Factors affecting the value of CRP concentration in the serum

The value of CRP in serum is influenced by numerous factors such as: gender, race, age, height, increased physical exertion, pregnancy, smoking, etc. (6). The interdependence of CRP levels and some drugs such as acetylsalicylic acid and statins has also been investigated. It has been observed that daily use of acetylsalicylic acid is directly related to CRP levels. The higher the CRP values, the greater the benefits of using acetylsalicylic acid. Statins have been observed to lower CRP levels in addition to lowering cholesterol levels (6,7).

CRP – marker and mediator of inflammatory processes

The concentration of CRP in the serum is an indicator of the degree of the inflammatory process in the body. It is important in assessing disease progression and treatment effectiveness.

Like numerous mediators of the inflammatory process, CRP has pleiotropic effects. In vivo and in vitro studies have shown that CRP has proinflammatory and antiinflammatory effects. CRP achieves its anti-inflammatory effects by stimulating the expression of the interleukin-1 (IL-1) receptor antagonist, increasing the release of the anti-inflammatory cytokine IL-10 and suppressing the synthesis of -interferon. The protective role of CRP is reflected in its ability to bind to FcgR present on phagocytes, resulting in opsonization and phagocytosis of apoptotic and necrotic cells (6,7,15).

Many other functions of CRP can be explained as proinflammatory, because CRP stimulates the expression of adhesive molecules in endothelial cells, inhibits the expression of endothelial nitric oxide synthase (eNOS) in aortic endothelial cells. CRP also stimulates the release of interleukin-8 (IL-8) from several cell types by increasing the expression and activity of plasminogen activator inhibitor-1 (PAI-1), and increases the release of IL-1, IL-6, IL-18, and TNF-α (6,7,15).

CRP and glaucoma

In the introduction, we mentioned that the basic characteristic of glaucoma is elevated intraocular pressure, which depends on the comparative rate between production and drainage of aqueous humor. Both of these processes, as well as the circulation of the aqueous humor itself, can be altered in inflammatory conditions. It is known that the obstruction of the trabecular meshwork is the biggest reason for the increase in IOP, and its obstruction correlates with inflammation in such a way that the intensity of inflammation, the recurrence of inflammation and inflammatory chronic conditions disturb and overwhelm the phagocytic potential and the process of trabecular endothelial cell cleaning pathways. As the level of C-reactive protein in the serum is the best indicator of all inflammatory conditions in the body, by monitoring its level in the serum of glaucoma patients, we can prove this correlation (1, 6-7, 34-35).

Leibovich I, et al. (2) in their study found elevated CRP values in patients with NTG, while Stefan C, et al. (18) found a direct connection between elevated CRP values in open-angle glaucoma and vascular inflammatory factors that directly affect trabecular

meshwork obstruction to an increase in intraocular pressure. While de Voogd S. in his research and follow-up of patients with OAG glaucoma for 6.5 years older than 55 years with atherosclerotic changes did not prove that elevated CRP is an important risk factor for the development of glaucoma.

Definition of the problem

Previous research has shown that inflammatory processes can be associated with optic neuropathy and glaucoma. An association between certain cytokines and glaucoma has been observed. It was shown that interleukin-6 (IL-6), along with correlation with inflammatory processes in optic neuropathy, was also involved in apoptotic processes in the retina (20,21).

Research has shown that inflammatory processes in the eye can cause a characteristic glaucomatous optic disc with damage to the visual field and an increase in intraocular pressure (IOP). Also, it has been shown that inflammation causes ischemia and infiltration of the optic nerve head, and more recent studies also pseudoexfoliative syndrome (20).

It has been shown that inflammation and endothelial dysfunction can persist in a causal relationship (36). It has been observed that a large number of relevant factors leading to endothelial dysfunction or activation, for example, oxidized low-density lipoprotein (ox-LDL), lipopolysaccharides, interleukin1 (IL1), tumor necrosis factor (TNF-alpha), C-reactive protein (CRP), free radicals caused by smoking, hypertension, diabetes, genetic alterations, elevated plasma homocysteine concentrations, infectious microorganisms and other factors stimulate endothelial expression of adhesive molecules, monocyte chemotactic factor1, tissue factor, plasminogen activator inhibitor1, cyclooxygenase (COX2) and other contributing factors inflammation in the vascular wall (22). Caused by the mentioned factors, endothelial vascular dysfunction is manifested by disturbed permeability of blood vessels, disturbed coagulation, and triggers inflammatory and immune responses. Consequently, all of the above contributes to the development of glaucoma, as well as to the progression of existing glaucoma.

The main characteristic of glaucoma is elevated intraocular pressure, which depends on the comparative rate between production and drainage of aqueous humor. Both of these processes, as well as the circulation of the aqueous humor itself, can be altered in inflammatory conditions (1-3, 20). The connection between inflammation and changes in eye pressure is very complex but not clear enough. It is known that the obstruction of the trabecular meshwork is the biggest reason for the increase in IOP and correlates with inflammation in such a way that the intensity of inflammation, recurrence of inflammation and inflammatory chronic conditions disturb and overcome the phagocytic potential and the process of cleaning trabecular endothelial cells. Inflammatory parameters disturb the cytoskeletal organization of phagocytic cells.

It has been shown that the accumulation of white blood cells (especially macrophages and activated T lymphocytes) consequently leads to angle-closure glaucoma (20).

It has been shown that inflammatory debris, which includes proteins, fibrin and high-molecular compounds, can even in normal concentrations lead to disturbances in the blood-aqueous barrier. In addition to the physical obstruction of the pathways that drain the aqueous humor, it can cause an increase in IOP, in a way that increases aqueous viscosity. It has been observed that inflammatory disease of the eye leaves behind a trace on the vascular network, in a way that it changes the vascular permeability, which can persist in the long term. Such conditions make the eye more susceptible to recurrence of inflammation, and at the same time lead to changes in the content, primarily by an increase in the concentration of prostaglandins (20).

Acute phase proteins are very good indicators of the degree of inflammation. The level of these proteins correlates with the degree of inflammation affecting the human body (23).

Previous studies have shown that there are statistically significant differences in the levels of acute phase proteins in patients with glaucoma compared to the control group of subjects. Certain studies have shown differences in the levels of these proteins between different types of glaucoma, and that their effects differ from one type of glaucoma to another (24-26).

Studies examining the association between CRP levels and glaucoma have shown contradictory results. One part of the study found differences in the level of CRP concentrations in patients with glaucoma compared to the control group, while another part of the study showed that there are no differences in the levels of CRP between patients with glaucoma and subjects of the control group (2,7,27-31).

Leibovitch I, et al. (2) showed that CRP was statistically significantly higher in patients with normotension glaucoma compared to the control group of subjects. The authors believe that vascular inflammatory processes play an important role in the pathogenesis of this type of glaucoma.

Choi J, et al. (7) did not find a statistically significant difference in the level of CRP in the blood between patients with normotensive glaucoma and subjects of the control group. Their study did not include patients suffering from diabetes mellitus, hypertension, hypercholesterolemia, as well as other diagnoses known to be accompanied by an increase in CRP levels. The authors suggest that CRP is not a direct risk factor for the development of normotensive glaucoma in patients who do not have systemic vascular disease.

Su WW, et al. (27) showed that there is no statistically significant difference in CRP concentration between control subjects and patients with normotension glaucoma and open-angle glaucoma.

De Voogd S, et al. (28) found no significant association between serum CRP levels and the incidence of open-angle glaucoma.

MATERIALS AND METHODS

The study was designed as a clinical, retrospective, prospective, controlled study. 120 patients of both sexes, aged from 40 to 70 years old, who were diagnosed with glaucoma by diagnostic tests, were included in the research. The values in both eyes were considered. The patients were selected at the Clinic of Eye Diseases of the Clinical Center University of Sarajevo (CCUS) in the Department for Glaucoma and Intraocular Hypertension.

Based on the type of glaucoma, patients are divided into four groups:

- 60 eyes with simplex glaucoma
- 60 eyes with normotensive glaucoma
- 60 eyes with angular glaucoma
- 60 eyes with senile cataract without glaucoma

1. The group of patients with a diagnosis of glaucoma simplex included 60 ophthalmological examinations with a diagnosis of glaucoma simplex
2. The group of patients with a diagnosis of normotensive glaucoma included 60 ophthalmological examinations with a diagnosis of normotensive glaucoma
3. The group of patients with a diagnosis of angular glaucoma included 60 ophthalmological examinations with a diagnosis of angular glaucoma
4. The group of patients with a diagnosis of cataract included 60 ophthalmological examinations and without a diagnosis of glaucoma - the control group

Criteria for inclusion in the study:

The study included patients diagnosed with simplex glaucoma, normotensive glaucoma and angular glaucoma in the last 3, 5 or more years. Patients without glaucoma with senile cataract - control group.

Criteria for exclusion from the study:

The study did not include patients whose subjective and objective data indicated signs of:

- acute or chronic inflammatory conditions
- asthma
- cirrhosis of the liver
- Crohn's disease and ulcerative colitis
- malignant neoplasms
- diabetes mellitus
- non-glaucoma eye diseases
- myocardial infarction and cardiovascular diseases due to the possible influence on the acute phase protein values in the serum.

All patients were informed in detail about the research plan and procedure, after which written consent was requested for participation in the project.

Work methods

Taking blood samples

Blood for laboratory tests was taken from all subjects in the early morning on an empty stomach, due to possible influence on the tested humoral markers. Blood was taken by venipuncture of the cubital vein at the Clinic of Eye Diseases of the Clinical Center University of Sarajevo (CCUS) as well as at the Central Laboratory for Clinical Biochemistry of the CCUS. After centrifugation (5 minutes at 2000 g), serum and plasma were separated from which acute phase proteins were determined.

Procedures for diagnosing primary glaucoma

Visual acuity

The best corrected visual acuity was determined at a distance of 6 m without correction or with appropriate correction using the Snellen optotype.

Applanation tonometry

Applanation tonometry according to Goldman is the method of choice for measuring the subject's intraocular pressure. Intraocular pressure was measured with a calibrated applanation Goldmann tonometer (Haag-Streit, mod. 900.4.2.130621) and is expressed in mmHg.

Gonioscopy

Gonioscopy was performed with the help of a Haag-Streit prism for gonioscopy with one mirror, which, after instillation of local anesthetic, rests on the cornea, and then the chamber angle is observed in 360 degrees starting from the lower pole upwards.

Ophthalmoscopy

Direct ophthalmoscopy was performed with the help of a hand-held ophthalmoscope (Heine Ophtalmoscop, Germany) on dilated pupils and the subjective appearance of the optic nerve head, its excavation (indentation), which is marked E/D from 0.1 to 0.9, i.e. marginal when the diameter of the healthy edge of the optic nerve was determined the nerve is completely lost, in which case we speak of optic nerve atrophy.

Field of view

Visual fields were measured by computerized static perimetry (Octopus perimeter 101, Interzeag AG, Schlieren, Switzerland). Computerized static perimetry is performed with the G2 program, seven in one test, with Goldman III stimulus size, exposure time of 100 milliseconds, background illumination of 4 apostils, maximum stimulus intensity of 1000 apostils and the so-called 4-2-1 dB method, which determines retinal sensitivity with accuracy of 1 dB.

Retinal Coherence Tomography (OCT)

Retinal coherence tomography (OCT) was performed in all subjects (Stratus OCT. Model 3000. Carl Zeiss MEDITEC, Jena, Germany). Numerical values of the excavation of the optic nerve will be taken, as well as the ratio of horizontal and vertical depression (excavation).

Individual forms/questionnaires are specially designed for this research, and will contain general data (name and surname, year of birth, gender), data on the current disease, socio-epidemiological data (smoking, alcohol consumption, etc.), and data on earlier diseases.

Statistical data processing

The results were processed using standard statistical methods using the computer program Excel (Microsoft Office Excel 2003) and the SPSS computer program for statistical analysis (SPSS-Statistical Package for Social Sciences) version 12.0. Results are expressed as mean (X) and standard error of the arithmetic mean (SEM). To test the significance of the difference in deviation from the normal distribution, we used the Shapiro–Wilk test. We analyzed the results with the ANOVA test, where the conditions for application are met, that is, with appropriate non-parametric tests (Mann-Whitney test), if an irregular distribution of variables is determined. Values of $p < 0.05$ were taken as statistically significant. The degree of correlation was determined by the Pearson or

Sperman method. A statistical technique whose goal is to determine the threshold value of a text that gives the best ratio of specificity and sensitivity was done by analyzing the ROC curve (Receiver Operating Characteristic Curve).

RESULTS

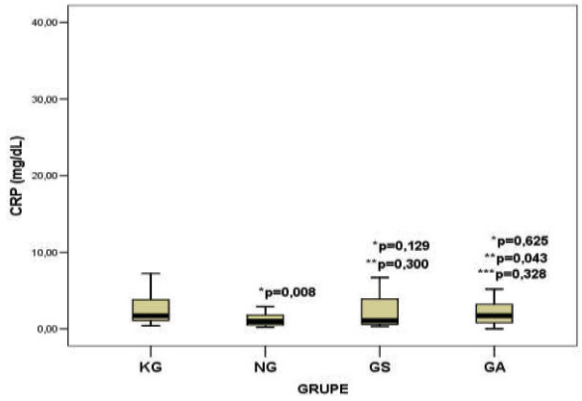


Figure 1 **Concentration of CRP in the serum of subjects of the control group and patients with glaucoma**.

Results are presented as median and interquartile range (25-75 percentiles).
p – probability
KG - control group (n=30)
NG - patients with normotensive glaucoma (n=30)
GS - patients with glaucoma simplex (n=30)
GA - patients with angular glaucoma (n=30)
* compared to the control group
** compared to the group of patients with normotensive glaucoma
*** in relation to the group of patients with simplex glaucoma

The concentration of CRP in the serum of the control group was 1.70 (1.05-3.82), while in the group of patients with NG it was 0.95 (0.47-1.82). In the group of patients with GS, the concentration of CRP was 1.10 (0.60-4.00), and in the group of patients with GA it was 1.75 (0.77-3.37). A statistically significant difference in serum CRP levels was observed between patients with NG and subjects of the control group (p=0.008), and between patients with NG and GA (p=0.043). No statistically significant difference was observed in the level of CRP in the serum between the other groups (Figure 1).

Table 1 **Correlation of C-reactive protein in serum and OCT parameters.**

Varijabla	CRP KG (n=30)	CRP NG (n=30)	CRP GS (n=30)	CRP GA (n=30)
OCT1D	rho= -0.150	rho= -0.137	rho= 0.248	rho= -0.146
OCT2D	rho= -0.060	rho= -0,144	rho= 0.159	rho= 0.026
OCT3D	rho= -0,051	rho= -0.045	rho= 0.251	rho= -0.037
OCT1S	rho= 0.055	rho= -0.180	rho= 0.018	rho= -0.105
OCT2S	rho= -0.093	rho= -0.145	rho= -0.064	rho= 0.074
OCT3S	rho= -0.092	rho= -0.120	rho= 0.198	rho= 0.122

rho – correlation coefficient
KG - control group (n=30)
NG - patients with normotensive glaucoma (n=30)
GS - patients with glaucoma simplex (n=30)
GA - patients with angular glaucoma (n=30)
CRP – C-reactive protein

No statistically significant correlation was observed between CRP concentration in serum and OCT parameters neither in patients with glaucoma nor in the control group of subjects (Table 1).

Also, no statistically significant correlation was observed between serum CRP concentration and visual field parameters (LVD, LVS, MDD, MDS), nor statistically significant correlation between serum CRP and visual acuity in both eyes, nor statistically significant correlation between serum CRP and intraocular pressure in both eyes (results not shown!).

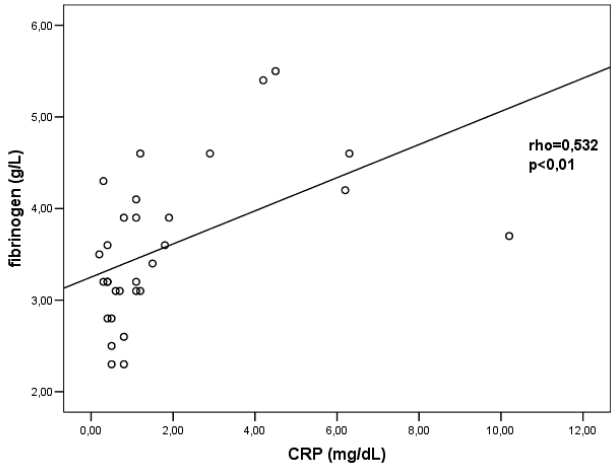


Figure 2 **Relationship between CRP and fibrinogen concentration in patients with NG**
rho - correlation coefficient
p - probability
CRP – C-reactive protein

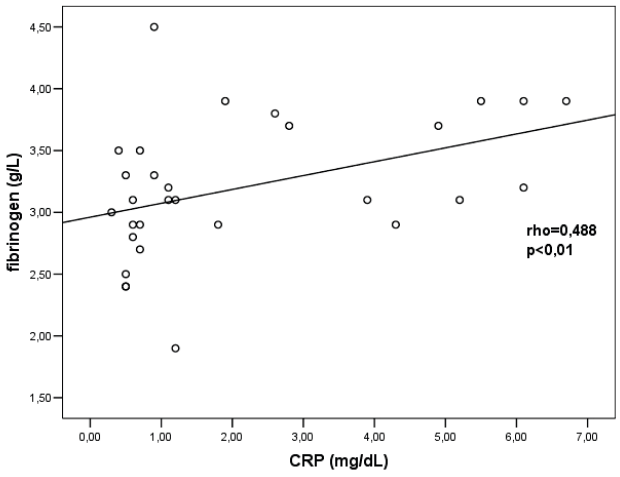
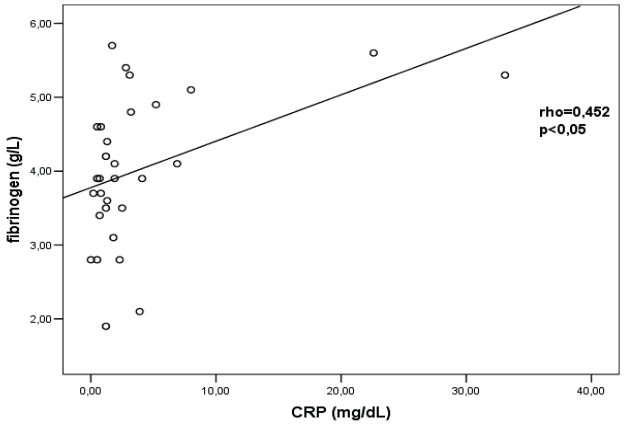


Figure 3 **Relationship between CRP and fibrinogen concentration in patients with GS**

rho - correlation coefficient
p - probability



CRP – C-reactive protein

Figure 4 **Relationship between CRP and fibrinogen concentration in patients with GA**

DISCUSSION

CRP is an indicator of the degree of the inflammatory process in the body and is important in monitoring the progression of the disease and the effectiveness of treatment.

The results of our research showed that there is a statistically significant difference in the level of CRP in the serum between patients with NG and subjects of the control group (p=0.008), and between patients with NG and GA (p=0.043), while no statistically significant difference was observed between the other examined groups significant difference in the level of CRP in the serum (20).

Contrary to our results, Choi J, et al. (7) did not find a statistically significant difference in the level of CRP in the blood between patients with normotension glaucoma and subjects of the control group.

Interesting results were presented by de Voogd S, et al. (28) who found no significant association between serum CRP levels and the incidence of open-angle glaucoma.

When it comes to the connection between serum CRP concentration and ophthalmological findings, the results of our study did not show a statistically significant correlation between serum CRP concentration and OCT parameters neither in patients with glaucoma nor in the control group of subjects. There was also no statistically significant correlation between serum CRP concentration and visual field parameters (LV OD, LV OS, MD OD, MD OS), nor a statistically significant correlation between serum CRP and visual acuity in both eyes, nor a statistically significant correlation between CRP in serum and intraocular pressure in both eyes.

Given that a large number of previous results have shown an insignificant increase in the level of the same in patients with glaucoma, and an insignificant association of CRP with parameters of ophthalmological findings, it is considered that the systemic level of CRP does not reflect its local influences (27).

CONCLUSION

There is a statistically significant difference in the level of CRP in the serum between patients with NG and subjects of the control group, and between patients with NG and GA, while no statistically significant difference in the level of CRP in the serum was observed between the other examined groups. There is no statistically significant correlation between the concentration of CRP in the serum and parameters of ophthalmological findings in any group of subjects. The results of this research made a significant contribution to a better understanding of the role of endothelial vascular dysfunction and inflammation monitored through the parameters of markers of inflammation and cell damage. The results of this study could contribute to the application of acute phase proteins as potential biomarkers for the differen tial diagnosis of different types of glaucoma.

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Clinical Efficacy of Midazolam Syrup (1mg/ml) Made in the Deparment for Clinical Pharmacy, Clinical Center University of Sarajevo

Klinička efikasnost upotrebe midazolam sirupa, koncentracije 1mg/ml, napravljene u Galenskom laboratoriju, Kliničke apoteke UKCS

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ABSTRACT

Introduction: Midazolam is a benzodiazepine differs from other drugs in the benzodiazepine class because of its rapid absorption and short duration of action. It is an effective option for premedication before surgical procedures, introduction and maintenance of anesthesia, long-term sedation in intensive care units, moderate sedation before therapeutic and diagnostic procedures in infants, children and adolescents, as well as in convulsion therapy. Aim: The aim of this study is to evaluate the clinical efficacy of midazolam syrup (1mg/ml) using parameters of the behavioral rating scale for pediatric patients. Midazolam syrup (1mg/ml) was prepared in the Galenic Laboratory of Clinical pharmacy, Clinical Hospital Sarajevo, according to the standard prescription of the production of midazolam syrup (1mg/ml). Patients and study design: Pediatric patients in three UKCS clinics, over a period of 3 months. The study was conducted on 62 pediatric patients of different gender, ages and weight. Materials and methods: to assess the degree of sedation, the Houpt Categorical Rating Scale was used to determine the level of sleep, crying, movement and overall behavior of the child during each period of sedation. Before sedation, an adequate assessment of the patient's status is required. Results: the degree of sedation of a child from awake and calm, distressed and crying to wide awake and brawl are significantly influenced by: weight of the child - at greater weights, the child is more likely to be awake and calm or wide awake and brawl; longer time since administration – more likely that the child will be awake and calm or wide awake and brawl; measured pH - at higher pH of the solution, there is a higher probability that the child will be awake and calm whilst at lower pH, the child will be distressed and crying, and wide awake and brawl. Conclusion: our results suggest that midazolam syrup (1 mg/ml) is effective at a dose of 0.5 mg/kg and 1 mg/kg for pre-medication in children aged 1-3 years. The first symptoms of sedation appear 10-15 minutes after use. The pH value of the midazolam syrup when most effective is 5.11-5.16. The findings of this study align with those reported in the literature.

Keywords: Midazolam, premedication, pediatrics

SAŽETAK

Uvod: midazolam je benzodiazepin i razlikuje se od drugih lijekova u klasi benzodiazepina zbog svoje brze apsorpcije i kratkog trajanja djelovanja. Efikasna je opcija za premedikaciju prije hirurških zahvata, kao i za uvođenje i održavanje anestezije, za dugotrajnu sedaciju prije terapijskih i dijagnostičkih procedura kod dojenčadi, djece i adolescenata, u terapiji konvulzija. Cilj: procjena kliničke efikasnosti sirupa midazolam (1mg/ml), za oralnu upotrebu, korištenjem parametara skale ocjenjivanja ponašanja za pedijatrijske pacijente. Midazolam sirup (1mg/ml) je napravljen u obliku magistralnog preparata u Galenskom laboratoriju, Kliničke apoteke, Kliničkog centra Univerziteta u Sarajevu (KCUS). Proskripcija za izradu midazolam sirupa (1mg/ml) je standardna. Materijali i metoda: istraživanje je vršeno na 62 pedijatrijska pacijenta, različite starosne dobi (od 0 do 1 godine, od 1-3, od 3 do 5 godine i od 5 do 8 godine). Ispitivanje kliničke efikasnosti midazola sirupa (1mg/ml je) je urađeno u periodu od 3 mjeseca. Ispitivanje kliničke efikasnosti midazolam sirupa (1mg/ml) je bazirano na procjeni Houpt Categorical Rating Scale za određivanje nivoa sna, plača, kretanja i cjelokupnog ponašanja djeteta tokom termina sedacije. Kao dio protokola sedacije, svi pacijenti moraju proći pregled anesteziologa. Doza midazolam sirupa je prilagođena individualno prema starosnoj dobi i tjelesnoj težini djeteta, stepenu uznemirenosti, kao i potrebnom nivou sedacije. Mjerenje pH vrijednosti midazolam sirupa (1mg/ml) vršeno je na aparatu Easy pH titrator, proizvođača Mettler Toledo. Rezultati: ako analiziramo sve varijabile putem koeficjenta korelacije onda na stepen sedacije budan i miran, preko uznemiren i uplakan do potpuno budan i svadljiv statistički signifikantan uticaj pokazuju: težina djeteta - sa povećanjem težine postoji veća vjerovatnoća da će dijete biti budno i mirno ili uznemireno i uplakano; duži vremenski period od uzimanja - veća vjerovatnoća da će dijete biti budno i mirno do potpuno budno i svadljivo; izmjereni pH - viši pH - veća vjerovatnoća da će dijete biti budno i mirno, a kod nižih izmjerenih pH vrijednosti dijete će biti uznemireno i uplakano, te potpuno budno i svadljivo. Zaključak: ukratko, naši rezultati sugeriraju da midazolam sirup (1mg/ml) je efikasan u dozi 0.5 mg i 1mg/kg za premedikaciju za upotrebu za djecu od 1-3 godine. Prvi simptomi

sedacije se javljaju 10-15 minuta nakon upotrebe. pH vrijednost sirupa midazolama je 5.11-5.16, kada je midazolam sirup najefikasniji. Dobiveni podaci odgovaraju podacima u literaturi.

Ključne riječi: Midazolam, premedikacija, pedijatrija

INTRODUCTION

Midazolam is a benzodiazepine (1). Benzodiazepines belong to the group of drugs called central nervous system (CNS) depressants. Midazolam differs from other drugs in the benzodiazepine class due to its rapid absorption and short duration of action (1). Midazolam is rapidly excreted, with a half-life of only about 2 hours (1). It is generally well tolerated (1). It was synthesized in 1976 and introduced into wide use as the first water-soluble benzodiazepine for parenteral administration (2). This drug was initially approved by the FDA (USA) in 1985, and has been approved for various indications since (2). It is an effective option for premedication before surgical procedures, introduction and maintenance of anesthesia, long-term sedation in intensive care units, moderate sedation before therapeutic and diagnostic procedures in infants, children and adolescents, and for convulsion therapy (3,4).

AIM

The aim of this study is to evaluate the clinical efficacy of midazolam syrup (1mg/ml) using parameters of the behavioral rating scale for pediatric patients. Midazolam syrup (1mg/ml) was made in the Galenic Laboratory of Clinical pharmacy, Clinical Hospital Sarajevo, according to the standard proscription of the production of midazolam syrup (1mg/ml). The work is carried out with the principles of medical deontology (5).

MATERIALS AND METHODS

The study included 62 pediatric patients treated in three clinics of the Clinical Center University of Sarajevo (CCUS) over a period of 3 months.

Table 1 **Sociodemographic data of the studied children.**

		N	%
Gender	Male	45	72,6
	Female	17	27,4
Weight	10-20 kg	28	45,2
	20-30 kg	20	32,3
	30-40 kg	5	8,1
	40-50 kg	6	9,7
	> 50 kg	3	4,8
Age	0-1	11	17,7
	1-3	25	40,3
	3-5	12	19,4
	5-8	12	19,4
Total		62	100,0

Among 62 pediatric patients who were given midazolam syrup orally (1 mg/ml), 45 (72.6%) were male and 17 (27.4%) patients were female.

The weights of children were measured and recorded. The children's weights varied significantly. The largest number of children (28) weighted between 10-20kg (inclusive), which was 45.2%. According to the collected data, the smallest number of children (3) weighted more than 50kg, which was 4.8%.

According to age the children are divided into four groups (from 0 to 1 year, from 1 to 3 years, from 3 to 5, from 5 to 8 years). The largest number of children (25) were (1-3 year of age), which was 40.3%. The smallest number (11) were (0-1 year of age), which was (17.7%).

The examination of clinical effectiveness of midazolam syrup (1mg/ml) is based on the assessment of the degree of sedation. Before sedation, an adequate assessment of the patient's status (the diseases from which he suffers, as well as the kind and duration of the examination – whether the examination is more or less painful or painless) is required (6). All patients who undergo anesthesia must have a preanesthesia evaluation by an anesthesia clinician to assess the patient's medical conditions. Exclusion criteria (according to literature data) were severe dysfunction of the CNS, pressure, malformations of the cardiovascular system, hyperthyroidism, and long - term therapy with theophylline. The Houpt Categorical Rating Scale was applied to evaluate levels of sleep, crying, movement and overall behavior during each sedation period (7).

Table 2 **The Houpt Categorial Rating Scale.**

Results:	Sedation	Emotinal status	N	%
1.	Wide awake	Brawl	11	27.5
2.	Distressed	Crying	4	10,0
3.	Awake	Calm	25	62.5
Total			40	100,0

Out of the total of 62 pediatric patients included in the study, clinical efficacy data were collected for only 40 of them. Data from clinic were not provided for the remaining 22 pediatric patients. The relatively small number of subjects on whom the level of sedation was assessed is a limiting factor of this research. To assess the level of sleep, crying, movement and overall behavior of the child, the Houpt Categorical Rating Scale was used through a questionnaire, which was filled out by the clinic staff, during the use of midazolam syrup, concentration 1mg/ml by examinee. Despite this limitation, the author believes that the result of research could be useful as a practical result of the clinical use of midazolam syrup (1mg/ml), as well as directly affect the standardization of the midazolam syrup application protocol. The future studies should allow the presence of hospital pharmacist before, during and after oral administration of midazolam syrup, (1mg/ml) by pediatric patients. In the author's opinion, the data of this paper would then be more complete and complex.

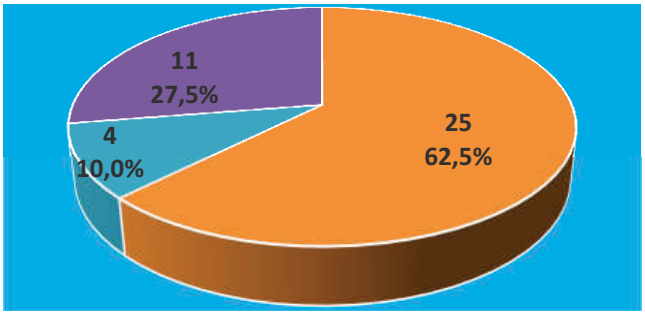

Figure 1 **Graphical representation of the Houpt Categorial Rating Scale**

Twenty minutes after oral premedication, the final assessment of the degree sedation and emotional status of children were performed (10). The following results were obtained: The largest number of children (25) were awake and calm, which was 62.5%. The smallest number of children (4) was distressed and crying, which was 10%.There were no significant differences between the children during the study. Hysterical crying, violent movements and interrupted treatment have not been observed in any child.

Statistical analysis

The data was analyzed using the Kruskal-Wallis's test. The comparison was made using the arithmetic mean and the non-parametric Kruskal-Wallis's test. The value of chi-squared distribution was high.

RESULTS

Midazolam syrup (1mg/ml) was freshly made as extemporaneous preparation in the Galenic Laboratory of Clinical Pharmacy, Clinical Hospital Sarajevo according to the standard proscription of production midazolam syrup. Long-term stability of ready to use midazolam syrup was 30 days (8). The most frequently dose of midazolam syrup (1mg/ml) was used for sedation of children was 0.5 mg/kg of body weight (8).

Table 3 **The doses of midazolam syrup (1mg/ml), used for sedation of pediatric in three clinics over a period of three months.**

		N	%
Doze	2,5 ml	2	3.2
	5 ml	33	53.2
	7,5 ml	6	9.7
	10 ml	18	29.0
	15 ml	3	4.8
Total		62	100.0

The dose of midazolam syrup (1mg/ml) was individually adjusted and based on the children's age, body weight, degree of anxiety, and the required sedation level. Among 62 pediatric patients who received midazolam syrup orally (1 mg/ml), the largest number of children (33) received a dose of 5 ml midazolam syrup, which was 53%. The smallest number of children (2) received a dose of 2.5 ml midazolam syrup, which was 3.2%. The most frequently reported effective doses of midazolam syrup (1mg/ml) ranged from 0.25 mg/kg to 1.5 mg/kg (for a child aged 0 to 8 years). The single, most frequently effective dose is 0.5 mg/kg of the child's body weight.

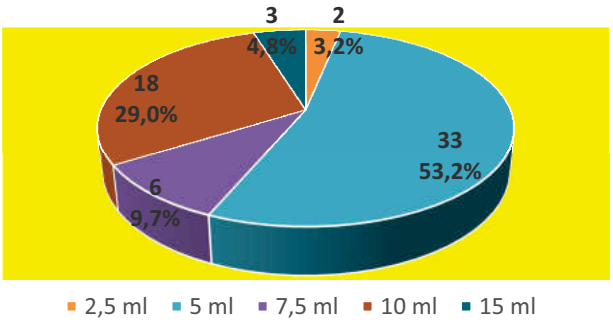

Figure 2 **Graphical representation of the doses of midazolam syrup (1mg/ml), used for sedation of pediatric patients in three clinics, over a period of three months.**

The time from administration of midazolam syrup (1mg/ml) to the onset of sedation symptoms ranged from 5 minutes to more than 15 minutes.

Table 4 **The time from ingestion of midazolam syrup (1mg/ml) to the appearance of the first symptoms.**

		N	%
Time frame from ingestion of midazolam (1mg/ml) to the appearance of the first symptoms	0-5 minuta	0	0.0
	5-10 minuta	14	22.6
	10-15 minuta	30	48.4
	>15 minuta	18	29.0
Total		62	100.0

The largest number of children (30) displayed the first sedation's symptoms from 10 to 15 minutes after taking a dose of midazolam syrup (1mg/ml), which was 48.4%. The smallest number of children (14) displayed the first sedation's symptoms from 5 to 10 minutes, which was 22.6%. The most frequently reported time of the appearance of the first sedation's symptoms from 10 to 15 minutes.

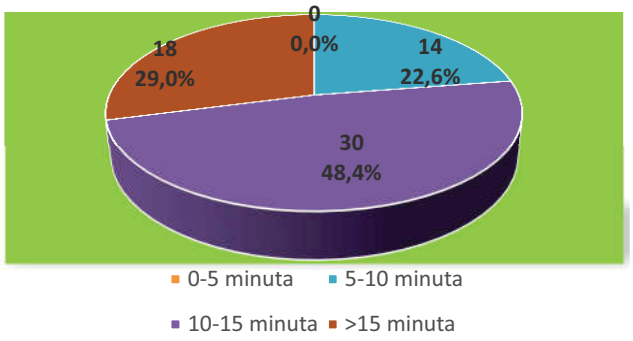

Figure 3 **Graphical representation of the time from ingestion of midazolam syrup (1mg/ml) to the appearance of the first symptoms.**

The pH value of freshly prepared, midazolam syrup (1mg/ml) was measured over a period of one month. The measuring of the pH value of the midazolam syrup (1mg/ml), was performed on the Easy pH titrator, manufactured by Mettler Toledo. Before measuring the pH value of midazolam syrup (1mg/ml), the Easy pH titrator was calibrated with pH calibration solutions meters: solution for calibration: 4±0.02, 250 ml, batch number: 51350004, deadline: 05.01.2026 and solution for calibration: 7.00±0.02, 250 ml, batch number: 51350006, deadline: 18.12.2026.

Table 5 **The measured pH value of midazolam syrup (1mg/ml), immediately after a period of one month.**

		N	%
pH value	4,75-4,80	5	8,1
	4,81-4,86	3	4,8
	4,87-4,92	4	6,5
	4,93-4,98	0	0,0
	4,99-5,04	8	12,9
	5,05-5,10	12	19,4
	5,11-5,16	22	35,5
	5,17-5,22	5	8,1
	5,22-5,30	3	4,8
Total		62	100,0

The measured pH value of midazolam syrup (1mg/ml) was ranged from 4.75 to 5.30 in a period of one month. The most frequently measured pH value of midazolam syrup (1mg/ml) was ranged from 5.11 to 5.16. This pH value was measured in 22 midazolam syrup (1mg/ml), after preparation, which was 35.5%.

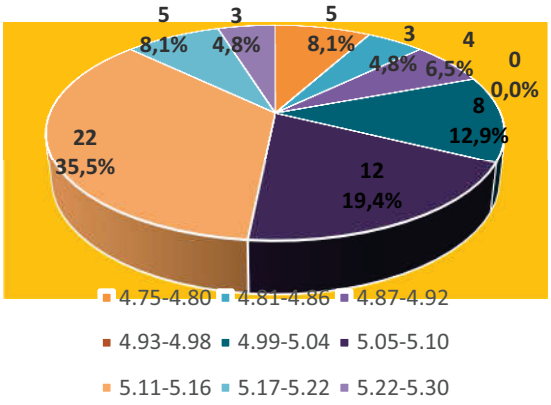

Figure 4 **Graphic representation of the measured pH values of midazolam syrup (1mg/ml), after making it, for a period of one month.**

DISCUSSION

Midazolam is a 1.4 benzodiazepine derivative (11). Midazolam is a white to light yellow crystalline compound (12). It has no solubility in water (12,13). It can be dissolved in aqueous solutions forming the hydrochloride salt in situ under acid conditions (12,13). Midazolam syrup is made from ampoules of midazolam, with a concentration of 15 mg/3ml, so that the solubility of midazolam in solution was achieved using ampoules.

Midazolam is distinctly different from the other benzodiazepines (Figure 5). Under acid condition (pH<4), the diazepine ring of midazolam undergoes a ring-opening reaction that leads to improving its water solubility (14). Stable derivative of primary amine was formed (14). At pH higher than 4, the diazepine ring was closed, resulting in increased lipophilicity (15). At the physiologic conditions under which the product is absorbed (pH of 5 to 8) into the systemic circulation, any open-ring form present reverts to physiologically active, lipophilic, closed-ring form and is absorbed as such (15).

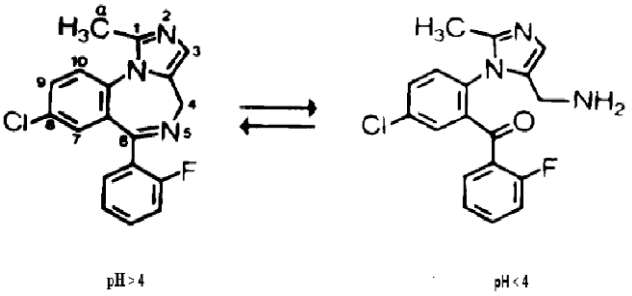

Figure 5 **Chemical structure of midazolam.**

The dependence of mucosal absorption on pH is suggested by the dependence of the opening or closing of the ring in the molecular structure of midazolam (15). A significant amount of orally administered midazolam can be absorbed in the mucosa of the oral cavity, oesophagus and stomach. This contributes to the rapid onset of action and good clinical tolerance.

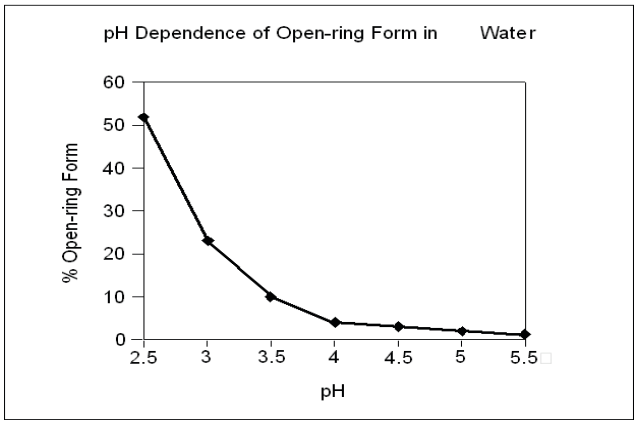

Figure 6 **The percentage of midazolam present as the open-ring form as a function of pH in aqueous solutions.**

The amount of open-ring compound present in solution is sensitive to change in pH over the pH range specified for the product: from 3.0 to 4.0. Above pH 5, at least 99% of the mixture is present in the closed- ring form.

The acceptability of the preparation to the child is largely dependent on its taste (16). Pharmaceutical preparations who taste better were easier to give to infants and young children, which reduce the possibility of loss of the preparation due to spillage during oral use. The general perception of taste includes the initial taste, the taste after the appearance and texture of the product itself (17). Midazolam syrup (1 mg/ml) has a bitter taste, so it is necessary to add a flavor corrector. The bitter taste of midazolam syrup can be improved with cherry, peppermint, and anise.

It is recommended to take midazolam syrup with juice. Grapefruit juice is contraindicated for this purpose. It inhibits cytochrome P450 (CYP) 3A4.CYP 3A4 is located in intestine and liver. Inhibition of cytochroma results in delayed absorption and reduced first pass effect on midazolam. This results in increased blood plasma levels of midazolam of 56% and increased midazolam biovailability of 35%. This can result in excessive levels of sedation for pediatric patient (18).

If we analyze all variables through the correlation coefficient on the degree of sedation, the data are presented in table and graphically:

Table 6 **The correlation between the weight of child and the degree of sedation.**

			The degree of sedation			Total
			Awake and calm	Distressed and crying	Wide awake and brawl	
The weight of child	10-20kg	N	11	1	4	16
		%	44.0	25	36.4	40
	20-30 kg	N	14	0	1	15
		%	56	0.0	9.1	37.5
	30-40kg	N	0	1	2	3
		%	0.0	25.0	18.2	7.5
	40-50kg	N	0	2	4	6
		%	0.0	50	36.4	15
Total		N	25	4	11	40
		%	100	100	100	100

Table 7 **The correlation between time frame from ingestion of midazolam (1mg/ml) to the appearance of the first sedation's symptom and the degree of sedation.**

			The degree of sedation			Total
The time frame from ingestion of midazolam (1mg/ml) to the appearance of the first sedation's symptom	5-10 minuta		Awake and calm	Distressed and crying	Wide awake and brawl	
		N	14	0	0	14
		%	56	0.0	0.0	35.0
	10-15 minuta	N	10	0	2	12
		%	40	0.0	18.2	30.0
	15 minuta	N	1	4	9	14
		%	4.0	100	81.8	35.0
Total		N	25	4	11	40
		%	100	100	100	100

Table 8 **The correlation between the measured pH value of midazolam syrup (1mg/ml) immediately after a period of one month and the degree of sedation.**

			The degree of sedation			Total
			Awake and calm	Distressed and crying	Wide awake and brawl	
The measured pH value of midazolam syrup (1mg/ml) immediately after a period of one month	4.75-4.80	N	0	0	5	5
		%	0.0	0.0	45.5	12.5
	4.81-4.86	N	0	3	0	3
		%	0.0	75.0	0.0	7.5
	4.87-4.92	N	0	0	4	4
		%	0.0	0.0	36.4	10.0
	4.99-5.04	N	0	0	1	1
		%	0.0	0.0	9.1	2.5
	5.05-5.10	N	3	1	1	5
		%	12.0	25.0	9.1	12.5
	5.11-5.16	N	14	0	0	14
		%	56.0	0.0	0.0	35 .0
	5.17-5.22	N	5	0	0	5
		%	20.0	0.0	0.0	12.5
	5.22-5.23	N	3	0	0	3
		%	12.0	0.0	0.0	7.5
Total		N	25	4	11	40
		%	100.0	100.0	100.0	100.0

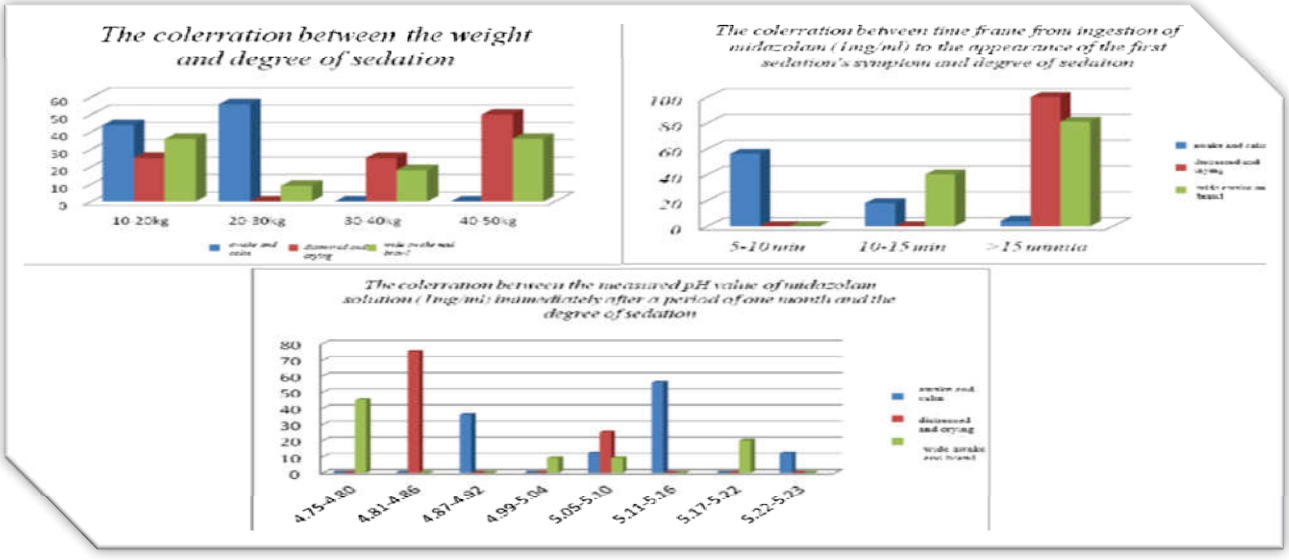

Figure 7 **The clinical efficacy of the use of midazolam syrup (1mg/ml), in pediatric patients in three clinics over a period of three months.**

If we analyze all the variables using the correlation coefficient, the degree of sedation of a child from active and calm, distressed and crying to wide awake and brawl are significantly influenced by:

- Weight of the child - at greater weights, the child is more likely to be awake and calm or wide awake and brawl
- Longer time since administration – more likely that the child will be awake and calm or wide awake and brawl
- Measured pH - at higher pH of the solution, there is a higher probability that the child will be awake and calm whilst at lower pH, the child will be distressed and crying, and wide awake and brawl.

Several studies have documented the clinical efficacy of midazolam syrup (1 mg/ml), as a premedication compared to placebo or other premedication. Earlier studies have stated that a

child can be separated as early as 10 minutes after oral midazolam (0.5 mg/kg) from the parents. Significant anxiolytic effects of oral Midazolam were observed after 15 ± 4 minutes of administration. According to the literature, this is a common practice in pediatric anesthesia. In dental practice, according to literature data, the rate of sedation for pediatric patients is also lower (50%). 80 to 90% of children who received midazolam showed minimal sedation (anxiolytic) 30 minutes after administration of midazolam syrup for oral use.

CONCLUSION

Our results suggest that midazolam syrup (1 mg/ml) is effective at a dose of 0.5 mg/kg and 1 mg/kg for pre-medication in children aged 1-3 years. The first symptoms of sedation appear 10-15 minutes after use. The pH value of the midazolam syrup when most effective is 5.11-5.16.

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The Radiological Findings and the Results of Sputum Microbiological Analysis in Patients with Chronic Obstructive Lung Disease Using Two D ifferent Modes of Non-Invasive Ventilation

Radiološki nalazi i rezultati mikrobiološke analize sputuma bolesnika s hroničnom opstruktivnom bolesti pluća primjenom dva različita načina neinvazivne ventilacije

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ABSTRACT

Introduction: exacerbation of chronic obstructive pulmonary disease (COPD) requiring use of noninvasive ventilation (NIV) is a manifestation of airway inflammation which is most often triggered by a bacterial or viral infection. Primary workup of a patient with suspected COPD exacerbation should among all include chest X-ray findings as well as microbiological analysis of sputum. Previous studies have not evaluated the radiological findings and results of sputum microbiological analysis in COPD patients treated with two different modes of NIV. Aim: to evaluate the results of radiological findings on admission and sputum microbiological analysis in patients with COPD requiring the application of two modes of NIV (CPAP-continuous positive air pressure and BiPAP-positive air pressure on two level). Materials and methods: the prospective study included 80 subjects, divided into two groups of 40 patients according to the prescribed mode of NIV- CPAP and BiPAP. The selection of patients for the application of the ventilation mode was performed by randomization 1:1. The research was conducted in the General Hospital "Prim. dr. Abdulah Nakaš" in Sarajevo and included patients hospitalized in the Non-Surgical Intensive Care Unit who have chronic respiratory failure that has one of the three COPD phenotypes. Upon admission, the COPD severity degree was verified for all patients according to the spirometry testing. A standard chest radiograph and chest CT scan were also performed and sputum samples were taken for microbiological analysis. Results: no statistically significant difference was found between the groups of patients on both NIV modes according to the spirometric testing performed upon admission. Patients on BiPAP mode had a more prominent appearance of hilar blood structures (p=0.014) and more frequently verified panlobular emphysema (p=0.026). Patients on CPAP mode more often had verified pleural effusions (p=0.005), basally visible pathologic changes in the lungs consistent with stasis (p=0.005), thickening of the bronchial walls (p=0.013) and pneumonia (p=0.042). A slightly higher percentage of sputum isolates positivity for bacteria was recorded in the group with CPAP mode (15%) in comparison with BiPAP (5%), but the mentioned difference did not reach statistical significance. Conclusion: the evaluation of microbiological analysis of sputum samples taken upon admission did not identify statistical significance between groups treated with two different NIV modes. According to the radiological findings of the examined patients the group with CPAP mode use had more often basally visible pathologic changes in the lungs consistent with stasis while patients on BiPAP mode had more frequently verified panlobular emphysema.

Keywords: COPD, chest radiological findings, sputum microbiological analysis, non-invasive ventilation

SAŽETAK

Uvod: egzacerbacija hronične opstruktivne plućne bolesti (HOPB) koja zahtijeva upotrebu neinvazivne ventilacije (NIV) je manifestacija upale disajnih puteva najčešće uzrokovane bakterijskom ili virusnom infekcijom. Primarni pristup pacijentu sa sumnjom na HOPB egzacerbaciju uključuje, između ostalog, snimak grudnog radiograma kao i mikrobiološku analizu sputuma. Prethodne studije nisu evaluirale radiološke pretrage i rezultate mikrobioloških analiza kod pacijenata sa HOPB-om koji su tretirani

sa dva različita moda NIV. Cilj: evaluirati rezultate radioloških nalaza pri prijemu, kao i mikrobiološke analize sputuma pacijenata sa HOPB koji zahtijevaju primjenu jednog od dva modaliteta NIV (CPAP- kontinuirani pozitivni pritisak zraka i BiPAP- pozitivni pritisak zraka na dva nivoa). Materijal i metode: prospektivnim istraživanjem je obuhvaćeno 80 ispitanika, podijeljenih u dvije skupine od po 40 pacijenata prema ordiniranom modu NIV- CPAP i BiPAP. Selekcija pacijenata za primjenu moda ventilacije izvršena je randomizacijom 1:1. Istraživanje je sprovedeno u Općoj bolnici „Prim. Dr. Abdulah Nakaš" u Sarajevu i obuhvatilo je pacijente hospitalizirane u Jedinici nehirurške intenzivne terapije koji imaju hroničnu respiratornu insuficijenciju (HRI) koja u podlozi ima neki od tri fenotipa HOPB. Svim pacijentima pri prijemu verificiran je stupanj težine HOPB prema rezultatima spirometrijskog testiranja. Takođe su učinjeni standardni grudni radiogram i CT torakalnih organa i uzeti sputumi za mikrobiološku analizu. Rezultati: nije utvrđeno postojanje statistički značajne razlike među grupama pacijenata na oba modaliteta NIV prema urađenom spirometrijskom testiranju na prijemu. Pacijenti na BiPAP modu su imali izraženiji prominentan izgled hilarnih krvnih struktura (p=0.014) i češće verificiran panlobularni emfizem (p=0.026). Pacijenti na CPAP modu su češće imali verificirane pleuralne izljeve (p=0,005), stazne promjene bazalno (p=0.005), zadebljanje bronhalnih zidova (p=0.013) i nalaz pneumonija (p=0,042). Nešto veći procenat pozitivnosti izolata sputuma na bakterije evidentiran je u grupi sa CPAP modom (15%) u komparaciji sa BiPAP (5%), ali navedena razlika nije dostigla statističku signifikantnost. Zaključak: evaluacija mikrobioloških analiza uzoraka sputuma uzetih pri prijemu nije evidentirala statistički signifikantnu razliku između grupa tretiranih sa dva različita modaliteta NIV. Prema radiološkim nalazima ispitivanih pacijenata grupa, grupa sa upotrebom CPAP moda je češće imala bazalno vidljive patološke promjene na plućima koje su odgovarale staz, dok su pacijenti na BiPAP modu češće imali panlobularni emfizem.

Ključne riječi: HOPB, radiološki nalazi na plućima, mikrobiološka analiza sputuma, neinvazivna ventilacija

INTRODUCTION

COPD is characterized by persistent respiratory symptoms and airflow limitation caused by airway disorders and alveolar abnormalities, and due to significant exposure to harmful particles and gases (1).

Exacerbation of COPD is a manifestation of airway inflammation, which is most often triggered by an infection. Bacterial and viral infections are responsible for more than half of the causes of exacerbations, and their recognition is important for the selection of adequate antimicrobial therapy and the implementation of preventive measures in the form of immunization. The incidence of exacerbations is twice as high in the winter months due to frequent infections of the upper respir atory tract, but also because lung function in people with COPD decreases slightly, but significantly, with a decrease in external temperature (2).

The clinical manifestation of an acute exacerbation of COPD varies from mild worsening of productive cough and shortness of breath to respiratory failure accompanied by acidosis and hypoxemia (3). Acute exacerbations of COPD have a negative effect on the course of the disease, which is why their recognition and adequate treatment are key to slowing down progress ion and ensuring the patient's quality of life. They often remain unrecognized and untreated (4).

Taking phenotype as a subgroup, the initial division of the American Thoracic Society in 1995 recorded three COPD phenotypes: chronic bronchitis, emphysema, and asthma (5). Chronic bronchitis is characterized by chronic productive cough, as well as airway inflammation colonized by neutrophils, macrophages and cytotoxic CD8 lymphocytes, in response to the presence of a pathogenic microorganism. The basic clinical characteristics are a higher degree of dyspnea and airway obstruction, more frequent exacerbations and increased thickness of the airway wall with frequent association with cardiovascular comorbidities and sleep apnea (6).

Primary workup of a patient with suspected COPD exacerbation should include pulse oximetry, arterial blood gas analysis to determine the need for ventilation, either noninvasive or mechanical; chest X-ray, complete laboratory analyses, including blood count and biochemical analyses, as well as microbiological analysis of sputum (5). The clinical features and physical examination are important, and the diagnosis is usually confirmed by a chest x-ray (7).

A chest X-ray can help differentiate heart failure from a COPD exacerbation, as it can show vascular pulmonary edema, pleural effusion, and cardiomegaly. Additionally, the best laboratory marker of heart failure is a significant increase in natriuretic peptides, BNP and NT-proBNP (8).

GOLD guidelines do not recommend routine collection of sputum for bacteriological analysis because false-negative results are very common. Cultures of sputum or other materials from the lungs are recommended only for patients with frequent exacerbations, severe broncho obstruction and/or exacerbations requiring mechanical ventilation (9).

AIM

The aim of this study was to evaluate the results of radiological findings on admission and sputum microbiological analysis of patients with COPD requiring the application of two modes of NIV (CPAP-continuous positive air pressure and BiPAP-positive air pressure on two level).

MATERIALS AND METHODS

The prospective study included 80 subjects, divided into two groups of 40 patients according to the prescribed mode of NIV-CPAP and BiPAP. The selection of patients for the application of the ventilation mode was performed by randomization 1:1. The research was conducted in the General Hospital "Prim. dr. Abdulah Nakaš" in Sarajevo and included patients hospitalized in the Non-Surgical Intensive Care Unit who have chronic respiratory failure that has one of the three COPD phenotypes. Upon admission, the degree COPD severity was verified for all patients according to the spirometry testing, a standard chest radiograph was performed as well as chest CT scan and sputum samples were taken for microbiological analysis.

Spirometry testing was performed on a calibrated device model BTL-08 Spiro produced in 2016 by BTL Industries LTD from Great Britain. Post-bronchodilator parameters were recorded: forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), FEV1/FVC ratio. If the patient has not already taken a bronchodilator, the bronchodilator test was performed by applying 400 mcg of a short-acting beta-2 agonist (salbutamol), with FEV1 recorded 10-15 minutes after application. The interpretation of the spirometry results was done by recording age, body height, gender and race, and by evaluating one of the three obtained curves, whereby the FVC and FEV1 values obtained for each of them must not vary by a percentage greater than 5%. The severity of airflow obstruction based on the post-bronchodilator FEV1 value was assessed according to the Global Initiative for Chronic Obstructive Lung Diseases (GOLD) 2023. Guidelines (9) implying mild FEV1≥80%, moderate 50%≤FEV1<80%, severe 30%≤FEV1<50%, very severe FEV1<30% airflow obstruction.

Statistical analysis

Statistical analysis was performed by two different programs, MS Excel (Microsoft Office Excel 2010) and SPSS (SPSS-Statistical Package for 27 Social Sciences) version 22.0. The Shapiro-Wilk tests were used to assess the normality of variable distribution. The mean value (X) and standard deviation (SD) for continuous independent variables that followed the normal distribution were determined, and the median and interquartile range for independent continuous variables did not follow the normal distribution. The Student t-test tested the significance of the difference for the independent variables that followed the normal distribution. In contrast, the Mann - Whitney U- test tested the significance of the difference for the independent variables that did not follow the normal distribution. A $p<0.05$ was considered statistically significant.

RESULTS

No statistically significant difference was found between the groups of patients on both NIV modes according to the spirometry testing performed on admission (Table 1). The group of patients on BiPAP mode had the highest percentage of patients with severe ventilatory insufficiency of mixed, predominantly obstructive type (62.5%), and the group on CPAP mode had a significant number of patients (20%) with moderately severe ventilatory insufficiency of mixed, predominantly obstructive type.

Table 1 **Severity of the patients' clinical feature on admission evaluated by spirometry testing.**

Post-bronchodilator spirometry finding	BiPAP (n = 40)	CPAP (n = 40)	(p)*
Unknown/not done	8 (20%)	6 (15%)	0.062
Severe ventilatory insufficiency, predominantly obstructive type	25 (62.5%)	17 (42.5%)	
Severe ventilatory insufficiency of obstructive type	3 (7.5%)	2 (5%)	
Moderate ventilatory insufficiency, predominantly obstructive type	3 (7.5%)	8 (20%)	
Mild ventilatory insufficiency, predominantly obstructive type	1 (2.5%)	7 (17.5%)	

* The significance of the difference

As it can be seen from Table 2, regarding the radiological findings upon admission to the hospital, there was a statistically significant difference between the observed groups regarding the prominent appearance of hilar blood structures, basally visible pathologic changes in the lungs consistent with stasis, then thickening of the bronchial walls, registration of pleural effusions, panlobular emphysema and pneumonia. Patients on BiPAP mode had a more prominent appearance of hilar blood structures ($p=0.014$) and more frequently verified panlobular emphysema ($p=0.026$). Patients on CPAP mode more often had verified pleural effusions ($p=0.005$), basally visible pathologic changes in the lungs consistent with stasis ($p=0.005$), thickening of the bronchial walls ($p=0.013$) and pneumonia ($p=0.042$). Other radiological findings were generally similarly distributed by study group.

Table 2 **Radiological findings on admission.**

Parameter		BiPAP (n = 40)	CPAP (n = 40)	(p)*
Aligned diaphragms	No	20 (50%)	22 (55%)	0.654
	Yes	20 (50%)	18 (45%)	
Reduced peripheral bronchovascular pattern	No	30 (75%)	24 (60%)	0.152
	Yes	10 (25%)	16 (40%)	
Lumps on the lungs (bullae)	No	37 (92.5%)	35 (87.5%)	0.712
	Yes	3 (7.5%)	5 (12.5%)	
Prominent appearance of hilar blood structures	No	15 (37.5%)	26 (65%)	*0.014*
	Yes	25 (62.5%)	14 (35%)	
Cranial distribution of blood flow	No	34 (85%)	34 (85%)	1.000
	Yes	6 (15%)	6 (15%)	
Enlarged heart shadow	No	22 (55%)	28 (70%)	0.166
	Yes	18 (45%)	12 (30%)	
Emphasized basal vascular shadow	No	18 (45%)	20 (50%)	0.654
	Yes	22 (55%)	20 (50%)	
Pleural effusion	No	35 (87.5%)	24 (60%)	*0.005*
	Yes	5 (12.5%)	16 (40%)	
Basally pathologic changes consistent with stasis	No	40 (100%)	32 (80%)	*0.005*
Centrolobular emphysema	No	37 (92.5%)	38 (95%)	0.644
	Yes	3 (7.5%)	2 (5%)	
Panlobular emphysema	No	24 (60%)	33 (82.5%)	*0.026*
	Yes	16 (40%)	7 (17.5%)	
Paraseptal emphysema	No	40 (100%)	35 (87.5%)	0.055
	Yes	0 (0%)	5 (12.5%)	
Thickening of the bronchial walls	No	28 (70%)	17 (42.5%)	*0.013*
	Yes	12 (30%)	23 (57.5%)	
Enlargement of the pulmonary artery	No	36 (90%)	38 (5%)	0.675
	Yes	4 (10%)	2 (5%)	
Lung neoplasm	No	39 (97.5%)	39 (97.5%)	1.000
	Yes	0 (0%)	1 (2.5%)	
Pneumonia	No	32 (80%)	24 (60%)	*0.042*
	Yes	8 (20%)	16 (40%)	
Bronchiectasis	No	40 (100%)	39 (97.5%)	1.000
	Yes	0 (0%)	2 (5.0%)	

* The significance of the difference

Evaluation of microbiological analysis of sputum taken on admission did not record a statistically significant difference between the groups treated with CPAP and BiPAP mode, and no microbiological agent was isolated in most patients (Table 3).

A slightly higher percentage of sputum isolates positivity for bacteria was recorded in the group with CPAP mode (15%) in comparison with BiPAP (5%), but the mentioned difference did not reach statistical significance.

Table 3 **Microbiological sputum analysis of patients upon admission.**

Parametar		BiPAP (n = 40)	CPAP (n = 40)	(p)*
Sputum positivity for bacterial isolates	No	38 (95%)	34 (85%)	0.263
	Yes	2 (5%)	6 (15%)	
Types of bacteria isolated from sputum	Negative	38 (95%)	34 (85%)	0.388
	Klebsiella pneumoniae	1 (2.5%)	1 (2.5%)	
	Acinetobacter species	0 (0%)	1 (2.5%)	
	Pseudomonas aeruginosa	0 (0%)	2 (5%)	
	Escherichia coli	1 (2.5%)	0 (0%)	
	Enterobacter species	0 (0%)	1 (2.5%)	
	Citrobacter species	0 (0%)	1 (2.5%)	
Types of bacteria isolated from sputum	Negative	40 (100%)	40 (100%)	-
	Positive	0 (0%)	0 (0%)	
Skin swab	Negative	39 (97.5%)	40 (100%)	1.000
	Positive	1 (2.5%)	0 (0%)	

* The significance of the difference

DISCUSSION

Regarding the data of this research, no statistically significant difference was found between the groups of patients on both NIV modes according to the spirometry testing performed upon admission.

According to a study by Fernandez-Villar A, et al., the number of patients with COPD exacerbation who were able to perform spirometry testing with validity and reproducibility was 69-90%. Also, more than a third of patients are not able to perform spirometry testing within 8-12 weeks after remission of an exacerbation, either due to the occurrence of a new exacerbation or due to the poor evolution of the disease (10). Thus, in the study by Cushen B, et al., where a functional test was performed on patients during hospitalization and after discharge, a new exacerbation was recorded in 52% of patients (11).

Parker CM, et al. did not record changes in FEV1 between admission and the seventh day after admission in patients with acute exacerbation of COPD, but its increase was recorded from 14-30 days, by 120-130ml reaching 240ml, on the 60th day from admission (12).

In the literature review Wageck B, et al. included data from a cohort study of 73 patients with moderate to severe COPD and a drop in FEV1 by 5.1% (IQR-15.0 to 6.2%) with the onset of exacerbation. The authors report that recovery of 88% of lung function occurs on average in the first week after the onset of exacerbation, with the duration of improved recovery during the first 30 days (13,14).

However, in patients with COPD, the relationship of FEV1 with symptoms and outcomes such as exacerbations is weak, and FEV1 does not take into account the heterogeneity of COPD or its different phenotypes. Thoracic imaging provides a way to quantify airway remodeling, emphysematous destruction, regional ventilation abnormalities (ventilation defects), and gas trapping in ex-smokers in whom FEV1 may be normal and in patients with COPD with very modest lung function deterioration (15).

According to the results of this study, patients on BiPAP mode had more prominent hilar blood vessels (p=0.014) and more frequently verified panlobular emphysema (p=0.026). Patients on CPAP mode more often had verified pleural effusions (p=0.005), basal pathologic changes consistent with stasis (p=0.005), thickening of the bronchial walls (p=0.013) and pneumonia (p=0.042). The effect of these two modes of NIV should be observed in the framework of verified dominantly hypercapnic or hypoxemic acute respiratory failure during acute exacerbation of COPD, which occurs with recorded radiological characteristics.

The future of radiographic evaluation of COPD exacerbation stands in dynamic chest radiography which allows collecting sequential chest radiographs with lower costs and radiation exposure while subjects are standing or sitting. Diaphragm and thoracic cage movements, lung ventilation and perfusion can be evaluated and are positively associated with the percentage of predicted FEV_1 (16).

Moghoofei M, et al., identified that bacterial infection is the cause of about 50% of exacerbations, and in 20% of cases it occurs together with viral infection (17). Research of Monso E, et al. has confirmed the existence of potentially pathogenic bacteria in approximately 30% of sputum cultures and in 50% of bronchial secretion cultures. In severe exacerbations that require ventilatory support, this number is even higher, over 70% (18). Soler N, et al., identified that the most commonly isolated bacteria in ICU environment are H. influenzae, M. catarrhalis and S. pneumoniae. In a patient with severe COPD, Pseudomonas aeruginosa and Enterobacteriaceae are still frequently found. Atypical bacteria Chlamydophila pn., Mycoplasma pn. and Legionella sp. they are rarely the cause of exacerbations (19). According to the results of our study a higher percentage of sputum isolates positivity for bacteria was recorded in the group with CPAP mode (15%), predominantly with Pseudomonas aeruginosa, in comparison with BiPAP mode (5%).

It is believed that most infectious acute exacerbation of chronic obstructive pulmonary disease (AECOPD) begins with a viral infection, which is subsequently followed by a bacterial infection. Viral infection of airway epithelial cells promotes an inflammatory process that damages the epithelium, allowing easier bacterial invasion. In addition, many patients with moderate and severe

COPD are chronically infected with multiple pathogenic bacteria, which significantly contribute to the possibility of developing an acute bacterial infection after a viral one (20). Coinfection with a virus and bacteria increases the severity of exacerbation and is associated with a greater degree of pulmonary function impairment and longer hospitalization (21).

CONCLUSION

No statistically significant difference was found between the groups of COPD patients on both NIV modes according to the spirometry testing upon admission. The evaluation of microbiological analysis of sputum samples taken upon admission did not identify statistical significance between two groups of COPD patients treated with two different NIV modes. According to the radiological findings the group with CPAP mode use had more often basally visible pathologic changes in the lungs consistent with stasis, verified pleural effusions and pneumonia, while patients on BiPAP mode had more frequently verified panlobular emphysema. Other radiological findings were generally similarly distributed by study group.

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Evaluation of the Success of the Treatment of Unstable Intertrochanteric Femur Fractures with DHS Fixation and Hemiarthroplasty in People of the Third Age

Procjena uspješnosti liječenja nestabilnih intertrohanternih prijeloma femura DHS-om i parcijalnom endoprotezom kod osoba treće životne dobi

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ABSTRACT

Introduction: the incidence of patients with fractures of the proximal end of the femur increases every year. Intertrochanteric fractures account for about 50% of all hip fractures, and the one-year mortality of patients with this type of injury is about 15-20%. Because hip fractures in elderly patients are usually accompanied by comorbidities such as hypertension, osteoporosis, or diabetes, such patients are usually of poorer general condition and poorer operative tolerance. One of the biggest challenges is functional recovery after hip surgery of these fractures specially regarding the problems of the poor bone density and quality, weakend muscular-tendon apparatus and accompanied comorbidities. Aim: evaluation of functional recovery with these two surgical methods in people of the third age through these parameters: length of the surgical incision, VAS pain scale, Harris Hip Score, Barthel index. The study is designed as an observational, average, prospective, clinically controlled study. Materials and methods: the research was conducted at the Clinic of Orthopedics and Traumatology of the Clinical Center University of Sarajevo. Patients with unstable intertrochanteric fractures of the femur will be included in the study while pathological fractures are excluded. The study includes 96 elderly patients, operated on at the Clinic of Orthopedics and Traumatology. 60 female patients (62.5%) and 36 male patients (37.5%) were included in the study. The average age of all patients was 77.38±5.20 years; the average age of female patients was 77.42±5.41 years, and the average age of male subjects was 77.31±4.90. Results: it was found that in Group I patients, the average value of the Harris Hip score after 6 months postoperatively was 84.06±4.787, while the value in Group II was 88.94±3.43. Six months after the operation, the average VAS score was 2.21±0.68 in Group I and 2.10±0.66 in Group II. The average value of the Barthel index in Group I was 74.92, while in Group II it was 88.65. Conclusion: partial endoprosthesis can very quickly restore the function of the hip itself, it is mainly used for the treatment of femoral neck fractures in the elderly, including unstable intertrochanteric fractures and failed osteosynthesis of intertrochanteric fractures. The same is recommended as the method of choice for fractures of weak stability, severe osteoporosis, poor prognosis after internal fixation and expected short life expectancy of the patient. We expect that the operative treatment of unstable introchanteric fractures with a biarticular endoprosthesis will be the standard due to fewer complications, more successful functional status and thus an improvement in the quality of life.

Keywords: intertrochanteric fracture, surgical procedure, hemiarthroplasty, functional outcome

SAŽETAK

Uvod: intertrohanterni prijelomi podrazumijevaju oko 50% svih prijeloma kuka, a jednogodišnji mortalitet pacijenata sa ovakvom vrstom povrede iznosi oko 15-20%. Obzirom da su prijelomi kuka kod pacijenata treće životne dobi obično praćeni komorbiditetima kao što je hipertenzija, osteoporoza ili dijabetes, ovakvi pacijenti su obično slabijeg općeg stanja i slabije operativne tolerancije. Jedan od najvećih izazova jeste funkcionalni oporavak pacijenata nakon operativnog zbrinjavanja ovih prijeloma a naročito zbog problema vezanih sa smanjenjem gustine i lošeg kvaliteta kostiju, oslabljenog mišićno-tetivnog aparate te pratećih komorbiditeta. Cilj: evaluacija funkcionalnog oporavka kod intertrohanternih prijeloma kuka kod pacijenata treće životne dobi kroz sljedeće parametre: dužina operativnog reza, VAS skala boli, Harris Hip Score, Barthel Index. Materijali i metode: studija je dizajnirana kao retrospektivna, klinički kontrolisana studija. Istraživanje je provedeno na Klinici za ortopediju i traumatologiju Kliničkog centra Univerziteta u Sarajevu. U studiju je uključeno 96 pacijenata treće životne dobi sa rtg verificiranim intertrohanternim prijelomima femura, operisanih na

Klinici za ortopediju i traumatologiju. U studiju su uključeni pacijenti sa nestabilnim intertrohanternim prijelomima femura, isključujući patološke prijelome navedene regije. U istraživanje je uključeno 60 pacijentica ženskog spola (62,5%) i 36 pacijenata muškog spola (37,5%). Prosječna starost svih pacijenata iznosila 77,38±5,20 godina; prosječna starost pacijenata ženskog spola je iznosila 77,42±5,41 godina, a ispitanika muškog spola 77,31±4,90. Rezultati: utvrđeno je da je kod pacijenata iz grupe I prosječna vrijednost Harris Hip scora nakon 6 mjeseci postoperativno iznosila 84,06±4,787, dok je vrijednost od 88,94±3,43 bila u grupi II. Šest mjeseci nakon operativnog zahvata, prosječna vrijednost VAS scora iznosila 2,21±0,68 u grupi I i 2,10±0,66 u grupi II. Prosječna vrijednost Barthel indeksa u grupi I je iznosila 74.92, dok je u grupi II iznostila 88.65. Zaključak: intramedularna osteosinteza i dalje predstavlja zlatni standard za liječenje zbog rane mobilizacije, oslonca punom težinom, boljeg obima pokreta i manje boli. Parcijalna endoproteza može vrlo brzo vratiti funkciju samog kuka, uglavnom se koristi za liječenje prijeloma vrata femura kod starijih osoba, uključujući nestabilne intertrohanterne frakture i neuspjele osteosinteze intertrohanternih prijeloma. Ista se preporučuje kao metoda izbora kod prijeloma slabe stabilnosti, teške osteoporoze, loše prognoze nakon unutrašnje fiksacije i očekivanog kratkog životnog vijeka pacijenta. Očekujemo da operativni tretman nestabilnih inertrohanternih prijeloma biartikularnom endoprotezom bude standard zbog manje komplikacija, uspješnijeg funkcionalnog statusa a time i poboljšanjem kvaliteta života.

Ključne riječi: intertrohanterni prijelom, operativni zahvat, parcijana endoproteza, funkcionalni ishod

INTRODUCTION

The incidence of patients with fractures of the proximal end of the femur increases every year and is constantly increasing. Hip fractures in the third age represent an increasing preventive problem worldwide (1,2). In contrast to femoral neck fractures, the fracture line in intertrochanteric fractures involves both trochanters, and due to the grip of large muscles, the region is abundantly vascularised, so complications such as pseudoarthrosis or avascular necrosis of the femoral head are extremely rare and can most often be caused by the action of indirect force (3). Treatment is operative, unless there are general or local contraindications for surgery. Replacement of the hip joint with an endoprosthesis is today a routine procedure that is considered the highest quality endoprosthetic orthopedic procedure in general (4). The complexity of intertrochanteric fractures in elderly patients presents a challenge due to the increased risk for morbidity and mortality (5). Risk factors include: age (over 65 years account for the majority of cases), gender (women account for 75% of hip fracture patients), lifestyle (people who live a sedentary lifestyle have a higher risk of hip fracture), osteoporosis (which makes bones weaker and more fragile which increases the risk of fractures, women have osteoporosis four times more often than men), the overall condition of the organism (deficiency of vitamin D, calcium and other minerals increases the risk of fractures), other diseases such as dementia or Parkinson's disease which increase the risk of falls and consequently fractures (6). Muller and his colleagues published the first alphanumeric classification supported by the Orthopedic and Traumatological Association (OTA) and the AO School, according to which the femur was given the numerical designation 3, the proximal end of the said bone was designated with the number 1, and the type of fracture (intertrochanteric) was designated with a letter A (7). Thus, all fractures A1.1 to A2.1 can be declared as stable fractures, while fractures from A2.2 to A3.3 are unstable. The available research still raises the question as to which is the optimal implant for fixing unstable intertrochanteric fractures. Dynamic hip screw (DHS), the most representative implant of extramedullary fixation, is considered the gold standard for the treatment of intertrochanteric fractures. There are two types of partial endoprosthesis, unipolar (Austin Moore's and Thompson's prosthesis) and bipolar or biarticular prosthesis. The head of the bipolar prosthesis is made of two parts. It consists of the outer head of the prosthesis with a polyethylene insert that articulates with a smaller inner head (8).

AIM

The aim of this study was to determine which operative method had a better functional outcome, by comparing two operative methods (internal osteosynthesis - DHS or installation of a two-component partial endoprosthesis) in unstable intertrochanteric hip fractures in the third age patients.

MATERIALS AND METHODS

The study assessed 96 patients of the third age with X-ray verified unstable intertrochanteric fractures of femur surgically treated at the Clinic of Orthopedics and Traumatology of the Clinical Center University of Sarajevo, in the period from January to September 2022. Patients were divided into two groups depending on the type of the internal osteosynthesis implanted during the surgery. For the assessment of the surgery results surgical incision length, Harris Hip Score, VAS pain score and Barthel Index were used. The study assessed patients through 4 regular check-ups: 1st postoperative day, 12th postoperative day and 1 and 3 months after the surgery. The Harris Hip Scale (HHS) was developed for the assessment of the results of hip surgery, and is intended to evaluate various hip disabilities and methods of treatment in an adult population. The HHS is divided into three sections. The first sections are questions about pain and its impact which are answered by the patient. The second and third sections require the clinician to assess the hip joint and function. VAS pain scale represents fast and widely used test for evaluation of the pain. It is used for measuring the subjective feeling of the pain from worst to best. Barthel Index represents a scale for measuring activities of daily life. It consists of a 10-item questionnaire that measures functional independence after discharge from the hospital and the degree of dependence on other persons. Statistical data processing was done through IBM SPSS Version 20.0 for Windows. Analysis of categorical variables was performed using Pearson's χ^2-test or Fisher's exact probability test. Spearman rank correlation coefficients were used to examine the linear correlation. Statistical significance was set at the conventional level ($\alpha = 0.05$). The results were shown in the graph and contingency tables (numbers with three decimal places). The level of significance was $p< 0.0$. The study inclusion criteria: patients older than 65 years of age, patients with X-ray verified unstable intertrochanteric fractures of the proximal femur. The study exclusion criteria were: patients younger

than 65 years of age, pathological fractures, patients with X-ray verified stable, subtrochanteric, pertrochanteric, subcapital fractures of the femoral neck.

RESULTS

The study included 60 female patients (62.5%) and 36 male patients (37.5%). The analysis of the length of the operative incision showed that the average length of the incision during the DHS operative procedure was 11.40±2.47 cm, with a minimum value of 5 and a maximum of 16 cm. The value of the length of the incision in patients who underwent the installation of a partial prosthesis was on average 12.42±2.06, with a minimum value of 9 and a maximum of 16. No significant difference was found in the values of the length of the operative incision in patients with internal osteosynthesis 1 and patients in which a partial prosthesis was installed (p=0.134).

Table 1 **Analysis of the Harris Hip score in relation to the investigated procedures through a period of 6 months.**

Day	Procedure	N	Mean	Std.dev	Std. Mistake	t	p
1. postoperative day	Internal osteosynth.	48	40.63	4.281	0.618	-26.782	<0.001
	Hemiarthroplasty	48	66.60	5.181	0.748		
12. postoperative day	Internal osteosynth.	48	66.31	5.589	0.807	-13.374	<0.001
	Hemiarthroplasty	48	79.35	3.795	0.548		
1 month postoperative	Internal osteosynth.	48	73.67	6.612	0.954	-11.083	<0.001
	Hemiarthroplasty	48	85.92	3.864	0.558		
3 month postoperative	Internal osteosynth.	48	82.77	5.216	0.753	-4.927	<0.001
	Hemiarthroplasty	48	87.31	3.685	0.532		
6 month postoperative	Internal osteosynth.	48	84.06	4.787	0.691	-5.736	<0.001
	Hemiarthroplasty	48	88.94	3.430	0.495		

On the first postoperative day, it was determined that the average value of the Harris Hip score was 40.63±4.28 in the patients who underwent the internal osteosynthesis procedure, while it was 66.60±5.18 in the patients who were implanted with a partial prosthesis. It was found that patients in whom a partial prosthesis was implanted had a significantly higher Harris Hip score on the first postoperative day (t=-26.782, p<0.001). On the twelfth postoperative day, it was determined that the average value of the Harris Hip score was 66.31±5.589 in patients who underwent the internal osteosynthesis procedure, while it was 79.35±3.795 in patients who had a partial prosthesis implanted. It was found that patients in whom a partial prosthesis was implanted had significantly higher Harris Hip score values (t=-13.374, p<0.001) on the 12th day. One month after the operation, it was determined that the average value of the Harris Hip score was 73.67±6.612 in the patients who underwent the internal osteosynthesis procedure, while it was 85.92±3.864 in the patients who were implanted with a partial prosthesis. It was found that patients in whom a partial prosthesis was implanted had significantly higher Harris Hip score values (t=-11.083, p<0.001) one month postoperatively. Three months after the procedure, it was determined that the average value of the Harris Hip score was 82.77±5.216 in patients who underwent the internal osteosynthesis procedure, while it was 87.31±3.685 in patients who had a partial prosthesis implanted. It was found that patients in whom a partial prosthesis was implanted had significantly higher Harris Hip score values (t=-4.927, p<0.001), three months after the operation. Six months after the operation, it was determined that in patients who underwent the internal osteosynthesis procedure, the average Harris Hip score was 84.06±4.787, while in patients who had a partial prosthesis implanted, it was 88.94±3.43. It was found that patients in whom a partial prosthesis was implanted had significantly higher Harris Hip score values (t=-5.736, p<0.001). On the first postoperative day, it was determined that the average value of the VAS score was 6.85±1.44 in patients who underwent the internal osteosynthesis procedure, while it was 7.42±1.25 in patients who had a partial prosthesis implanted. It was found that patients in whom a partial prosthesis was implanted already had a significantly higher VAS score on the first postoperative day (t=-2.039, p=0.044). On the twelfth postoperative day, it was determined that the average value of the VAS score was 5.90±1.12 in the patients who underwent the internal osteosynthesis procedure, while it was 5.73±1.07 in the patients who had a partial prosthesis implanted. There was no significant difference in VAS scores between patients depending on the type of method on the 12th postoperative day (p=0.456). One month after the operation, it was determined that the average value of VAS score was 3.90±0.78 in patients who underwent the internal osteosynthesis procedure, while it was 4.13±0.70 in patients who were implanted with a partial prosthesis. No significant difference was found in the VAS scores between patients depending on the type of method one month after the operation (p=0.134). Three months after the procedure, it was determined that the average value of the VAS score was 2.54±0.65 in the patients who underwent the internal osteosynthesis

procedure, while it was 2.90±0.59 in the patients in whom the partial prosthesis was implanted. A significant difference in VAS score values between patients was determined depending on the type of method three months after the operation (p=0.006). Six months after the operation, it was determined that the average value of the VAS score was 2.21±0.68 in patients who underwent the internal osteosynthesis procedure, while it was 2.10±0.66 in patients who had a partial prosthesis implanted. No significant difference was found in the VAS score values between patients depending on the type of method six months after the operation (p=0.449).

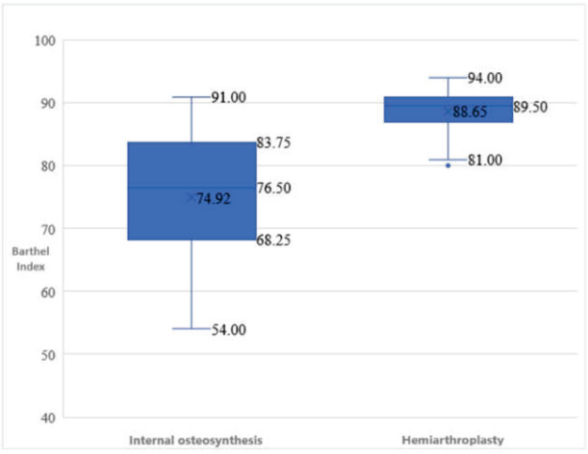

Figure 1 **Analysis of the value of the Barthel index after 6 months from the operation.**

Among the patients who underwent some method of internal ostesynthesis, the average value of the Barthel index was determined to be 74.92, with a median value of 76.5 and an interquartile range of 68.25 to 83.75. In patients who underwent the installation of a partial prosthesis, the average value of the Barthel index was 88.65, with a median value of 89.5 and an interquartile range of 87 to 91. A significant statistical difference was established (Mann Whitney U=187.0, Z =-7.088; p< 0.001), whereby patients with implanted partial dentures have significantly higher Barthel index values.

DISCUSSION

Internal osteosynthesis has its advantages, but in the long term, conducted studies have shown that internal osteosynthesis can cause greater intraoperative and late operative complications that often require revision surgery (9). Partial endoprosthesis can very quickly restore the function of the hip itself, it is mainly used for the treatment of femoral neck fractures in the elderly, including unstable intertrochanteric fractures and failed osteosynthesis of intertrochanteric fractures (10). It is recommended as the method of choice for fractures of weak stability, severe osteoporosis, poor prognosis after internal fixation and expected short life expectancy of the patient, but it is not recommended for pathological fractures or in oncology patients (11). In a meta-analysis conducted in 2019 by Ma H-H, et al., on the topic of the results of internal osteosynthesis or hemiarthroplasty in fractures of the upper edge of the femur, it was concluded that the installation of a partial endoprosthesis is associated with a lower percentage of the need for reoperation (12). A retrospective study conducted by Kregor PJ, et al., (2014), on the topic of operative results and the need for reoperation in unstable intertrochanteric fractures, showed that the installation of DHS results in a 56% need for reoperation compared to other osteosynthesis (13). In a retrospective study conducted in 2019 by Zhou S, et al., it was concluded that when installing a partial hip endoprosthesis, patient verticalization begins immediately on the first postoperative day with full support and is an average of 3.1 days, while when installing internal osteosynthesis, mobilization lasts an average of 28.2 days (14). Comparing the results obtained for HHS, the highest values were calculated in the partial endoprosthesis installation group, which corresponds to the fact that in the said operation, a complete replacement of the hip joint is performed, and as a result, patients have the greatest range of motion, and verticalization with full support begins immediately on the first postoperative day. By analyzing the VAS pain scale, no significant difference in VAS score values between patients was determined, depending on the type of method, after six months postoperatively. Analyzing the results of the Barthel Index in our research, we came to the conclusion that the value of the same among patients who were treated with internal ostesynthesis by DHS is 72 on average, with a median of 70 and an interquartile range of 65.5 to 79 In the group of patients who underwent surgery installation of a partial endoprosthesis, the average value was 88.65, the median value was 89.5 with an interquartile range of 87 to 91. A significant statistical difference was established, whereby patients with a partial prosthesis after 6 months from the operation had significantly higher index values.

CONCLUSION

Verticalization of the patient to full support on the operated leg is faster when installing a partial endoprosthesis compared to internal osteosynthesis and begins on the first postoperative day. No significant difference in VAS scores between patients depending on the type of method was found even six months after the operation. A partial endoprosthesis can very quickly restore the function of the hip itself, it is mainly used for the treatment of femoral neck fractures in the elderly, including unstable intertrochanteric fractures and failed osteosynthesis of intertrochanteric fractures. Implantation of a partial endoprosthesis is recommended as the method of choice for fractures of weak stability, severe osteoporosis, poor prognosis after internal fixation and expected short life expectancy of the patient. Comparing the results obtained for HHS, the highest values were calculated in the partial endoprosthesis installation group, which corresponds to the fact that in the said operation, a complete replacement of the hip joint is performed, and as a result, patients have the greatest range of motion, and verticalization with full support begins immediately on the first postoperative day. We expect that the operative treatment of unstable introchanteric fractures with a biarticular endoprosthesis will be the standard due to fewer complications, more successful functional status, and thus an improvement in the quality of life.

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Calcium, Phosphate and Parathyroid Hormone Levels in Postmenopausal Women with O steoporosis

Nivo kalcija, fosfata i paratireoidnog hormona kod postmenopauzalnih žena sa osteoporozom

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ABSTRACT

Introduction: osteoporosis is a progressive, systemic, metabolic disease of the skeletal system, which is characterized by increased bone fragility. This results in an increased tendency for fractures to occur. It is characterized by a decrease in bone mineral density (BMD) and strength, and damage to its microarchitecture. Aim: to examine whether the level of calcium, phosphate and parathyroid hormone in menopausal women is statistically significantly different in women with and without osteoporosis. Materials and methods: the study was designed as an observational, cross-sectional, controlled study involving 110 women sent by a family physician to do the screening for osteoporosis. Patients were divided into two groups: osteoporotic group (OG) and control group (KG). Results: a statistically significant difference between the duration of menopause in OG and KG was demonstrated. All anthropometric parameters differed statistically significantly between KG and OG, except for the waist/hip ratio. A statistically significant difference was found between the values of total calcium, magnesium and PTH between KG and OG. Conclusion: given that a statistically significant difference in the values of the parameters of bone formation in menopausal women with and without osteoporosis has been proven, it is necessary to conduct further prospective studies on a larger sample in order to clarify the established differences and possible connections and thereby facilitate the diagnosis and follow-up of menopausal patients with the osteoporosis.

Keywords: osteoporosis, postmenopause, bone mineral density-BMD

SAŽETAK

Uvod: osteoporoza je progresivna, sistemska, metabolička bolest skeletnog sistema, za koju je karakteristična povećana lomljivost kosti. Posljedica toga je povećana sklonost za nastanak prijeloma. Obilježena je smanjenjem mineralne gustoće kosti (BMD), te oštećenjima njene mikroarhitekture. Cilj: primarni cilj istraživanja je bio ispitati da li je nivo kalcija, fosfata i paratireoidnog hormona kod žena u menopauzi statistički značajno različit kod žena sa i bez osteoporoze. Materijali i metode: studija je dizajnirana kao observaciona, presječna, kontrolisana studija u koju je uključeno 110 žena upućenih od strane porodičnog ljekara radi skrininga na osteoporozu. Pacijentice su podijeljene u dvije grupe: osteoporoza grupa (OG) i kontrolna grupa (KG). Rezultati: dokazana je statistički značajna razlika između dužine trajanja menopauze kod OG i KG. Svi antropometrijski parametri su se statistički značajno razlikovali između KG i OG, izuzev odnosa struk/bokovi. Nađena je statistički značajna razlika između vrijednosti ukupnog kalcija, magnezijuma i PTH između KG i OG. Zaključak: s obzirom da je dokazana statistički značajna razlika u vrijednostima parametara koštane izgradnje kod žena u menopauzi sa i bez osteoporoze, potrebno je raditi dalja prospektivna istraživanja na većem uzorku kako bi se razjasnile utvrđene razlike i eventualne povezanosti i time olakšala dijagnostika i praćenje menopauzalnih pacijentica sa dijagnozom osteoporoze.

Ključne riječi: osteoporoza, postmenopauza, mineralna gustoća kosti

INTRODUCTION

Osteoporosis is a progressive, systemic, metabolic disease of the skeletal system, which is characterized by increased bone fragility, resulting in an increased tendency for fractures (1). Osteoporosis is characterized by a decrease in bone mineral density (BMD) and bone strength, as well as damage to the bone microarchitecture. Bone fractures (most often hip, spine and forearm) are the most dangerous consequence of osteoporosis, and one of the main causes of permanent disability and mortality in third age people. In general, osteoporosis occurs when the balance between bone formation and breakdown is disturbed, that is, when the amount of bone that is resorbed per unit of time is greater than the amount of newly formed bone (2).

According to epidemiological data, it is estimated that today approximately 25 million people in the world have osteoporosis, predominantly women. It is assumed that in the next 20 years this number could double (3).

Menopause is a physiological period in a woman's life that includes the complete cessation of menstrual bleeding for at least 12 months. Physiological menopause occurs in all women due to non-pathological estrogen deficiency (4). Menopause occurs on average at the age of 50 or 51. After the menopause, the postmenopause period begins, which lasts about 10 years. The main causes of cortical and trabecular bone loss in menopausal, osteoporotic women are the gradual development of secondary hyperparathyroidism and the effect of estrogen deficiency on systems other than bone: calcium absorption from the small intestine decreases, calcium excretion by the kidneys increases, and there is no suppressive effect of estrogen on PTH secretion. Due to the absence of these estrogenic effects in menopausal women with osteoporosis, the total amount of calcium in the body decreases, the secretion of PTH increases (negative feedback loop), and due to its effect, the total amount of phosphate in the body should decrease (5). Nevertheless, numerous studies have shown that in postmenopausal and senile osteoporosis (the most common forms), calcium and phosphorus in the serum and in the urine, as well as the total activity of alkaline phosphatase (ALP) are usually within normal limits, except immediately after a fracture when there is often a transient increase in ALP. An exception is hyperparathyroidism, where PTH, calcium and phosphorus in serum and urine are increased (5). Precisely because of these differences in the expectations and results of some studies, laboratory analyses, such as the level of calcium, phosphate, PTH, but also many other parameters, have not taken root as routine or auxiliary tests in the diagnosis, prognosis or monitoring of osteoporosis.

Although the role of all factors involved in bone remodeling is theoretically clear, in practice the quantitative relation between the main mineral substances of bone building (calcium, phosphate) and their regulation (PTH) remains unclear, as well as their relations with other parameters (especially BMD) in menopausal women with osteoporosis. The drugs that are mostly used today in the treatment of osteoporosis are mainly anti-catabolic agents based on reducing bone resorption. Newer drugs, which are still in the experimental phase, are anabolic agents that aim to create new bone tissue (6). Precisely for these reasons, it is necessary to do more research on parameters of bone remodeling, mineral substances of bone building, relations with regulatory factors and their variability when using various therapeutic agents. In this way, over time, the short-term relations between some parameters will turn into long-term and significant predictors of the diagnostic or therapeutic process of menopausal osteoporosis.

Considering the available literature data related to osteoporosis, and predictions about the increase in the number of patients, it is clear that additional research is necessary on the topic of examining the relations between serum values of bone formation parameters and BMD values, T and Z scores, in order to obtain knowledge that would in the future facilitate work in family medicine, clinics and make it easier to triage patients who need an additional procedure for osteoporosis diagnostics. Laboratory diagnostic tests are cheaper and more accessible than the DXA method, and proper triage would greatly reduce the costs of unnecessary and unjustified diagnostics, and increase the number of adequately diagnosed patients with early, timely detected osteoporosis.

With this paper, we are testing whether level of calcium, phosphate and parathyroid hormone in the serum during menopause is significantly different in women with osteoporosis compared to women with preserved bone mass.

MATERIALS AND METHODS

The research was designed as an observational, cross-sectional, controlled study conducted at the Clinic of Nuclear Medicine and Endocrinology and the Clinic of Radiology of the Clinical Center University of Sarajevo (CCUS).

The research was conducted in accordance with the basic principles of the Declaration of Helsinki (last revised in 2008) on the rights of patients involved in biomedical research. During the implementation of this study, the identity and all personal data of the patients were permanently protected in accordance with the regulations on the protection of identification data. For the purpose of protecting personal data, each patient was assigned an identification number that was used in statistical data processing.

The research included menopausal patients who were referred by family medicine doctors to the CCUS for osteoporosis screening, namely: directly to the Radiology Clinic of the CCUS, where BMD was measured using the DXA method, or to the Clinic of Nuclear Medicine and Endocrinology, where an ultrasound examination (screening) of the calcaneus was performed. Patients primarily referred to the Clinic of Nuclear Medicine and Endocrinology subsequently had their BMD measured using the DXA method at the CCUS Radiology Clinic.

Menopausal women whose T-score values (measured at the hip or lumbar spine using the DXA method) were in the range of osteopenic values (< -1.0 and > -2.5), were excluded from the study. Additional selection of test subjects in the study was done at the Clinic of Nuclear Medicine and Endocrinology, where patients with endocrinopathies, rheumatic diseases, gastrointestinal diseases, confirmed processes that have an effect on bone marrow activity (multiple myeloma, acute and chronic leukemia, lymphomas, metastatic cancers, systemic mastocytosis) and those who used drugs and/or supplements that affect bone mass (vitamin D, calcitonin, hormone replacement therapy, bisphosphonates, corticosteroids, anticonvulsants, heparin, methotrexate, lithium, cyclosporine A, GnRH agonists), as well as patients with long-term immobilization.

The final sample consisted of 110 menopausal women, average age 59.1 ± 8.2 years, who were divided into 2 groups based on BMD values:

1. Osteoporosis group (OG) which included 55 newly diagnosed menopausal women with osteoporosis whose T-score values were < -2.5 (measured at the lumbar spine and/or hip).
2. Control group (CG) which included 55 menopausal women with preserved bone mass whose T-score values were > -1 (measured at the lumbar spine and hip)

Additional data on the patients were taken from the registry of the CCUS Clinic of Nuclear Medicine and Endocrinology, and related to appropriate anamnestic data, data obtained on the basis of physical examination and results of laboratory tests.

Serum concentrations of total calcium, ionizable calcium, magnesium, and phosphate were determined at the Department of Clinical Biochemistry and Immunology, CCUS.

Bone mineral density was measured using Hologic QDR 4500 DXA equipment (Hologic Inc., Waltham, MD, USA) at the CCUS Radiology Clinic. BMD measurement was performed at the lumbar spine (L1-L4) and at all hip areas, including the entire hip, femoral neck, and intertrochanteric area.

The results were processed using standard statistical methods using the computer program Excel (Microsoft Office Excel 2003) and the SPSS computer program for statistical analyzes (SPSS-Statistical Package for Social Sciences) version 13.0 (Chicago, IL, USA). The results are expressed as the mean value ($\overline{X}$) and standard deviation (SD) for continuous independent variables that followed a normal distribution. The correlation coefficient was determined using the Pearson or Spearman method. Values of $p<0.05$ were considered statistically significant.

RESULTS

No statistically significant difference was found in age, age of first menstruation, age of menopause and length of reproductive period between subjects in OG and KG. The mean duration of menopause was statistically significantly higher ($p< 0.001$) in OG (15.0 ± 7.7 years) compared to KG (9.6 ± 7.8 years) of menopausal subjects (Table 1).

Table 1 **Demographic characteristics in the group of menopausal women with osteoporosis (OG) and the control group (CG).**

	Total (N=110)	OG (N=55)	CG (N=55)	p
Age (Years)	59.1 ± 8.2	60.5 ± 7.9	57.7 ± 8.3	0.073
Age of first menstruation (years)	13.0 (13.0-14.25)	13.0 (13.0-15.0)	13.0 (13.0-14.0)	0.658
Age of menopause starting (years)	46.1 ± 5.8	45.6 ± 6.7	46.6 ± 4.8	0.350
Reproductive period duration (years)	32.6 ± 6.04	32.0 ± 6.9	33.1 ± 5.0	0.362
Menopause duration	12.3 ± 8.2	15.0 ± 7.7	9.6 ± 7.8	**< 0.001**

Values are presented as mean ± standard deviation (± SD) and as median and interquartile range (25–75 percentiles); N - number of respondents; p – probability

The average value of BMI in the total sample and in OG subjects with menopause corresponded to excessive body mass, while the BMI of subjects in KG had a borderline value for obesity. The BMI and waist circumference values of the test subjects in the OG group were statistically significantly lower ($p <0.001$) compared to the values of the mentioned parameters of the test subjects in the KG group (Table 2).

Table 2 **Anthropometric parameters in the group of menopausal women with osteoporosis (OG) and the control group (CG).**

	Total (N=110)	OG (N=55)	CG (N=55)	p
Height (cm)	163.5 ± 6.2	162.3 ± 5.7	164.7 ± 6.4	0.055
Body mass (kg)	75.1 ± 12.5	68.6 ± 11.04	81.7 ± 10.3	**< 0.001**
BMI (kg/m^2)	28.2 ± 4.8	26.0 ± 4.0	30.3 ± 4.7	**< 0.001**
Waist circumference (cm)	93.2 ± 11.8	89.2 ± 11.2	97.3 ± 11.1	**< 0.001**
Waist/hip ratio	0.85 (0.80-0.89)	0.84 (0.81-0.89)	0.86 (0.80-0.89)	0.837

Values are presented as mean ± standard deviation (± SD) and as median and interquartile range (25–75 percentiles); N - number of respondents; p - probability; BMI - Body mass index

The serum concentration of total calcium was statistically significantly lower (p=0.007), while the concentration of magnesium and PTH in the serum was statistically significantly higher (p=0.04; p=0.024) in OG subjects with menopause compared to KG. No statistically significant differences were demonstrated between the serum concentrations of ionized calcium and phosphorus between OG and KG subjects in menopause (Table 3).

Table 3 **Systemic factors that contribute to bone mineralization in the group of menopausal women with osteoporosis (OG) and the control group (KG).**

	Total (N=110)	OG (N=55)	CG (N=55)	p
Total calcium (mmol/L)	2.42 ± 0.093	2.39 ± 0.07	2.44 ± 0.1	**0.007**
Ionizing calcium (mmol/L)	1.016 ± 0.042	1.01 ± 0.04	1.02 ± 0.04	0.526
Magnesium (mmol/L)	0.82 (0.74 - 0.88)	0.83 (0.73 - 0.87)	0.79 (0.72 - 0.87)	**0.04**
Phosphorus (mmol/L)	1.17 ± 0.16	1.17 ± 0.16	1.16 ± 0.15	0.962
PTH (pg/mL)	54.1 (43.3 - 68.2)	55.4 (47.9 - 74.2)	49.6 (39.2 - 61.8)	**0.024**

Values are presented as mean ± standard deviation (± SD) and as median and interquartile range (25–75 percentiles); N - number of respondents; p - probability; PTH - parathyroid hormone

DISCUSSION

With the development of technology and medicine, the standard of living in developed countries increases, life expectancy is significantly extended, and therefore the incidence of diseases characteristic for old age, among which is osteoporosis, also increases.

According to the results of our research, statistically significant differences were not proven in individual characteristics (age, age of first menstruation, age of entry into menopause, duration of the reproductive period) between subjects OG and CG.

The results of many researches proved that age, in addition to the duration of menopause, is a significant risk factor for the occurrence of osteoporosis. According to these studies, the risk of developing osteoporosis increases by 8% with every year of life of the test subjects (7). The results of our study follow the trend of the results of other studies, since in our study the age of subjects with osteoporosis was higher compared to subjects without proven osteoporosis. However, the established difference in age between the observed groups in our study was not statistically significant, which is probably a consequence of the relatively small sample on which our study was conducted.

Unlike our results, the age of entering menopause plays a very important role for a woman's overall health. Sullivan SD, et al. (8) proved that women whose menopause occurs earlier (before the age of 40) have a much higher risk of fractures than women whose menopause occurs between the ages of 40 and 49, i.e. after 50 years. The authors also state that calcium and vitamin D supplementation does not diminish the significance of a woman's age at menopause, which is considered an independent risk factor for bone fractures in the postmenopausal period. The difference in the results might be explained again with the relatively small sample on which our study was conducted

In our research, duration of menopause was proven to be statistically significantly higher in OG compared to CG.

Bearing in mind the changes in bone metabolism that occur in middle-aged women, it is expected that women with a longer duration of menopause have a greater chance of developing osteoporosis. The research conducted by Kim J, et al. (9) just confirmed the above. In the aforementioned study, which included 134 test subjects with osteoporosis and 137 test subjects without verified osteoporosis, aged 52 to 68 years, the duration of menopause in test subjects with osteoporosis was 15.9 ± 8.3 years, while in the control group of test subjects it was 13.6 ± 7.1 years.

Kapetanović A, et al. conducted their research on a sample of female subjects without a history of estrogen deficiency, and also concluded that the duration of menopause significantly affects bone loss and the onset of osteopenia/osteoporosis (10). The results of the mentioned research are in accordance with what has been scientifically confirmed today, namely that after the age of 30 there is a gradual loss of bone mass, which intensifies and continues during menopause. In the first year of menopause, the loss of bone mass is the greatest and amounts to an average of about 5%, while the recorded loss of bone mass in the later years of menopause is from 1% to 1.5%.

The results of the analysis of the anthropometric parameters of the subjects included in our research showed that, although the subjects with osteoporosis, based on the BMI values, belonged to the category of persons with excessive body mass, their body mass, BMI and waist circumference were statistically significantly lower compared to the values of these parameters in the group of subjects without osteoporosis. Also, the values of the waist/hip ratio were smaller in the group of subjects with osteoporosis compared to the subjects in the control group, although the determined difference was not statistically significant. The results of our research are largely in line with the results of other, thematically related studies. According to the results of the SAPOS study (11), women with a higher BMI and regular physical activity have a lower prevalence of reduced bone density. Matijević R, et al., (12) studied 1,372 women from Vojvodina and found a higher frequency of osteoporosis and osteopenia in subjects who had an increased BMI, more precisely 57.14% of women with a BMI<18 kg/m2 had a diagnosis of osteoporosis, while 21.4% had a reference T score value. According to Lee LH, et al., (13), the optimal BMI values that

are associated with a minimal risk of developing osteoporosis for postmenopausal women are between 23 kg/m2 and 25 kg/m2. These authors state that an additional increase in BMI reduces the risk of developing osteoporosis, but at the same time significantly increases the risk of developing other diseases such as diabetes mellitus type 2. In addition to the above, numerous other authors have established an inverse relationship between BMI and the risk of developing osteoporosis in women from different age groups and from different geographical climates (14-18).

Conflicting results emerged from a study conducted on a large sample of women in North India. According to these results, it was concluded that BMI, although an important determinant of bone mineral density, does not have a significant influence on the occurrence of osteopenia in postmenopausal women, and that moderate to pathological obesity is in no case a preventive factor in the occurrence of osteopenia (19).

The results of the analysis of systemic factors that contribute to bone mineralization in the subjects included in our research showed that the serum concentration of total calcium was statistically significantly lower, while the concentration of magnesium and PTH was statistically significantly higher in subjects in OG compared to CG. The level of total calcium was slightly below reference values in women from the OG group, while it was within reference values in women from CG.

Numerous studies have proven that calcium and magnesium, as well as vitamin D, are extremely important both in the process of formation and in the process of bone resorption. For this reason, adequate daily intake of calcium, magnesium and vitamin D in the body through food and/or dietary supplements is of great importance.

Tranquili AL, et al., (20) proved a reduced intake of calcium and magnesium in postmenopausal women. The intake of calcium and magnesium through food was not at the level of the recommended daily amounts, primarily in subjects with osteoporosis, but also in those who had not been diagnosed with osteoporosis. In the conclusion of the study, the authors state recommendations according to which the use of calcium and magnesium dietary supplements is necessary even before menopause, and that in the postmenopausal period it is necessary to pay attention to the creation of an adequate nutrition program that would ensure optimal daily intake of calcium and magnesium.

Cano A, et al., (21) found that the optimal daily intake of calcium is from 700 to 1200 mg, regardless of whether it is through supplements or food. The authors also state that a daily intake of calcium greater than 2000 mg/day is potentially harmful to health. The results of a double-blind, randomized study on a sample of 120 subjects over 45 years of age showed that in peri- and post-menopausal women, supplementation with calcium and vitamin D leads to the prevention of bone resorption. Subjects who did not use supplements during the research period of 30 months lost an average of 0.4% BMD per year.

CONCLUSION

In this study, we found that the duration of menopause was statistically significantly longer in subjects with osteoporosis. Test subjects with osteoporosis had significantly lower values of body mass, BMI, waist circumference and lower values of the waist/hip ratio. And finally, subjects with osteoporosis had significantly lower values of total calcium, and significantly higher values of magnesium and PTH in the serum. Given that a statistically significant difference in the values of the parameters of bone formation in menopausal women with and without osteoporosis has been proven, it is necessary to conduct further prospective studies on a larger sample in order to clarify the established differences and possible connections and thereby facilitate the diagnosis and follow-up of menopausal patients with the osteoporosis.

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Relationship Between Carotid Artery Stenosis and Degree of Age Related Macular Degeneration

Povezanost između stenoze karotidne arterije i stepena makularne degeneracije povezane sa godinama starosti

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ABSTRACT

Introduction: AMD (Age-related Macular Degeneration) is a term that refers to acquired degenerative changes in the retina through non-neovascular (retinal pigment epithelium and retinal pigment epithelium abnormalities) and neovascular (choroidal neovascular membrane) factors. Advanced disease may include focal areas of retinal pigment epithelium (RPE) loss, subretinal or sub-RPE hemorrhage or serous fluid, and subretinal fibrosis. Research has shown that a genetic background is associated with individuals of European descent, although environmental, nutritional, and developmental (i.e., aging) processes influence the degeneration observed in the macula. Newly discovered biochemical pathways combined with the lack of treatment options for most ARMDs (i.e., dry ARMD) have created fertile ground for new therapeutics. AMD is divided into: early, intermediate, and advanced forms of the disease, where the advanced form of the disease is divided into geographic atrophy and choroidal neovascular membrane. A combination of risk factors affects changes in the complex that includes Bruch's membrane/choroid, retinal pigment epithelium, and photoreceptor cells. The initiating events affect one, both, or all of the tissue components. It is believed that changes in one of these tissue components affect the others in such a way that a 'mechanism of intermediate disease' is established. The degenerated retina undergoes the final endpoint of geographic atrophy, choroidal neovascularization, and pigment epithelial detachment. Risk factors for this disease include: age, cigarette smoking, genetic predisposition, hypertension, cardiovascular disease, female sex, positive family history, hypercholesterolemia, poorly pigmented iris, white race, hyperopia. AMD is a growing disease with a prevalence of approximately 12.6% in people over 40 years of age according to data from the US (CDC). This prevalence increases dramatically with increasing age of patients. AMD is the leading cause of low vision in the elderly population (besides cataracts). (1) Aim: to evaluate relationship between carotid artery stenosis and degree of age related macular degeneration. Material and methods: this study was conducted as an observational descriptive cross-sectional study on 50 subjects (aged 60-85 years), who met the set criteria, and whose data were derived from the KCUS Eye Diseases Clinic database, in the period from July 1, 2022 to July 31, 2024. Null and alternative hypotheses were set. The Chi Square method was used for statistical correlation analysis. Results: the value of α=0.05 was taken for the significance level. The p value based on the obtained values is 0.29, which implies that the obtained values are not statistically significant. Conclusion: given that we now have the values x^2 (obtained) = 4.96 and x^2 (tabulated) = 9.49, and given that the obtained value is less than the tabulated value, the null hypothesis is accepted, which reads H0: There is no statistically significant relationship between a higher degree of carotid artery stenosis and a higher degree of AMD.

Keywords: age related macular degeneration (AMD), drusen, stenosis of the carotid artery, Color Doppler of the carotid artery, atherosclerosis of the carotid artery

SAŽETAK

Uvod: AMD (makularna degeneracija povezana sa godinama starosti) je termin koji se odnosi na stečene degenerativne promjene na mrežnici kroz ne-neovaskularne (anomalije pigmentnog epitela retine i pigmentnog epitela retine) i neovaskularne (horoidna neovaskularna membrana) faktore. Uznapredovala bolest može uključivati žarišne oblasti gubitka pigmentnog epitela retine (RPE), subretinalno ili sub-RPE krvarenje ili seroznu tekućinu i subretinalnu fibrozu. Istraživanja su pokazala da je genetska pozadina povezana s pojedincima evropskog porijekla, iako okolišni, nutritivni i razvojni (tj. starenje) procesi utiču na degeneraciju opaženu u makuli. Novootkriveni biohemijski putevi u kombinaciji s nedostatkom mogućnosti liječenja za većinu AMD (tj. suhi AMD) stvorili su plodno tlo za nove terapeutike. AMD se dijeli na: rani, srednji i uznapredovali oblik bolesti, gdje se uznapredovali oblik bolesti dijeli na geografsku atrofiju i horoidalnu neovaskularnu membranu. Kombinacija faktora rizika utiče na promjene u kompleksu koji uključuje Bruchovu membranu/koroideu, pigmentni epitel retine i fotoreceptorske ćelije. Početni događaji utiču na jednu, obe ili sve komponente tkiva. Vjeruje se da promjene u jednoj od ovih komponenti tkiva utiču na ostale na način da se uspostavlja 'mehanizam intermedijarne bolesti'. Degenerirana mrežnica prolazi kroz krajnju tačku geografske atrofije, horoidalne neovaskularizacije i odvajanja pigmentnog epitela. Faktori rizika za ovu bolest su: godine, pušenje cigareta, genetska predispozicija, hipertenzija, kardiovaskularne bolesti, ženski spol, pozitivna porodična anamneza, hiperholesterolemija, slabo pigmentirana šarenica, bijela rasa, hipermetropija... AMD je bolest

koja raste sa prevalencijom od približno 12,6% kod osoba starijih od 40 godina prema podacima iz SAD (CDC). Ova prevalencija dramatično raste sa povećanjem starosti pacijenata. AMD je vodeći uzrok slabog vida kod starije populacije (pored katarakte). (1) Cilj: procijeniti vezu između stenoze karotidne arterije i stepena starosne makularne degeneracije. Materijal i metode: Ova studija je sprovedena kao opservaciona deskriptivna studija preseka na 50 ispitanika (starosti 60-85 godina), koji su ispunjavali postavljene kriterijume, a čiji su podaci izvedeni iz baze podataka Klinike za očne bolesti KCUS-a, u periodu od god. Od 1. jula 2022. do 31. jula 2024. Postavljene su nulte i alternativne hipoteze. Za statističku analizu korelacije korištena je metoda Chi Square. Rezultati: za nivo značajnosti uzeta je vrijednost α=0,05. Vrijednost p na osnovu dobijenih vrijednosti je 0,29, što implicira da dobijene vrijednosti nisu statistički značajne. Zaključak: s obzirom da sada imamo vrijednost i x^2 (dobijeno) = 4,96 i x^2 (tabelarno) = 9,49, a s obzirom da je dobijena vrijednost manja od tabelarne vrijednosti, prihvata se nulta hipoteza koja glasi H0: Nema statistički značajna veza između višeg stepena stenoze karotidne arterije i višeg stepena AMD.

Ključne riječi: makularna degeneracija povezana sa godinamastarosti (AMD), druze, stenoza karotidne arterije, color doppler karotidnih arterija, arteroskleroza karotidnih arterija

INTRODUCTION

AMD (Age-related Macular Degeneration) is a term that refers to acquired degenerative changes in the retina through non-neovascular (retinal pigment epithelium and retinal pigment epithelium abnormalities) and neovascular (choroidal neovascular membrane) factors. Advanced disease may include focal areas of retinal pigment epithelium (RPE) loss, subretinal or sub-RPE hemorrhage or serous fluid, and subretinal fibrosis. Research has shown that a genetic background is associated with individuals of European descent, although environmental, nutritional, and developmental (i.e., aging) processes influence the degeneration observed in the macula. Newly discovered biochemical pathways combined with the lack of treatment options for most ARMDs (i.e., dry ARMD) have created fertile ground for new therapeutics. AMD is divided into: early, intermediate, and advanced forms o f the disease, where the advanced form of the disease is divided into geographic atrophy and choroidal neovascular membrane. A combination of risk factors affects changes in the complex that includes Bruch's membrane/choroid, retinal pigment epithelium, and photoreceptor cells. The initiating events affect one, both, or all of the tissue components. It is believed that changes in one of these tissue components affect the others in such a way that a 'mechanism of intermediate disease' is established. The degenerated retina undergoes the final endpoint of geographic atrophy, choroidal neovascularization, and pigment epithelial detachment. Risk factors for this disease include: age, cigarette smoking, genetic predisposition, hypertension, cardiovascular disease, female sex, positive family history, hypercholesterolemia, poorly pigmented iris, white race, hyperopia. AMD is a growing disease with a prevalence of approximately 12.6% in people over 40 years of age according to data from the US (CDC). This prevalence increases dramatically with increasing age of patients. AMD is the leading cause of low vision in the elderly population (besides cataracts) (1).

Carotid artery stenosis: The carotid arteries are the main blood vessels that carry blood and oxygen to the brain. When these arteries become narrowed, the condition is called carotid artery stenosis. The narrowing is usually caused by atherosclerosis. This is the buildup of fatty substances, calcium, and other waste products within the intima of the artery. Carotid artery stenosis reduces the flow of oxygen to the brain. The brain needs a constant supply of oxygen to function. Even a short interruption in blood supply can cause problems. Brain cells begin to die after just a few minutes without blood or oxygen. If the narrowing of the carotid arteries becomes severe enough to block blood flow, it can cause a stroke.

If a piece of plaque breaks off, it can also block blood flow to the brain. This can also cause a stroke. Also, because the ophthalmic artery, which gives rise to the ciliary and central retinal arteries, is a branch of the internal carotid artery, the occlusion itself also causes disruptions in their supply areas (2).

Carotid artery occlusion is classified as mild (up to 50% of the lumen), moderate (50–69%), and severe (70-99%).

Risk factors for carotid artery stenosis include: age, male gender, smoking, physical inactivity, obesity, diabetes, and genetic predisposition.

Since carotid artery stenosis is one of the most important indicators of the degree of atherosclerosis in the entire vascular system of the human body, and since atherosclerosis can affect the metabolism and processes in the vascular supply region of the branches of the internal carotid artery (central retinal and ophthalmic arteries), it is necessary to examine the correlation between the degree of carotid artery atherosclerosis and the degree of AMD in these patients (3).

Color Doppler is a highly accurate and reliable noninvasive ultrasound method for assessing the diameter of the carotid arteries, as well as their flow (4). This method uses ultrasound waves, which use a computer to change the sound waves into different colors that show the speed and direction of blood flow in real time. Doppler ultrasound is a risk-free and painless procedure that requires little preparation and provides important information about blood flow (5).

AIM

The aim of the study was to evaluate relationship between carotid artery stenosis and degree of age related macular degeneration.

HYPOTHESIS

H0: There is no statistically significant relationship between higher degree of carotid artery stenosis and higher degree of AMD.

H1: (alternative hypothesis): There is a statistically significant relationship between higher degree of carotid artery stenosis and higher degree of AMD.

MATERIALS AND METHODS

This study was conducted as an observational descriptive cross-sectional study on 50 subjects (aged 60-85 years), who met the set criteria, and whose data were derived from the CCUS Eye Diseases Clinic database, in the period from 1 July 2022 to 31 July 2024. Null and alternative hypotheses were set. The Chi Square method was used for statistical correlation analysis of the relationship between the degree of AMD and the degree of carotid artery stenosis.

Inclusion criteria:

1. Age 60+
2. Color Doppler of carotid arteries
3. Confirmed diagnosis of AMD by fundoscopic examination and/or OCT fundus findings

Exclusion criteria:

1. Diabetic retinopathy (DR)
2. Other retinal diseases
3. Significant eye trauma

Data

1. Presence and degree of carotid artery stenosis: Color Doppler ultrasound was used to assess the presence and degree of carotid artery stenosis (mild <50%, moderate 50-69% and severe >70%)
2. AMD assessment: where this disease is classified as early, intermediate and advanced (which manifests itself in two forms: geographic atrophy and choroidal neovascularization)

Statistical analysis:

1. Statistical analysis was used to summarize demographic data and the degree of disease prevalence
2. Chi-Square test was used to assess the association between the degree of carotid stenosis and the degree of AMD

RESULTS

Demographic data: out of 50 patients included in this study, n=29 were female (58%) and n=21 (42%) were male.

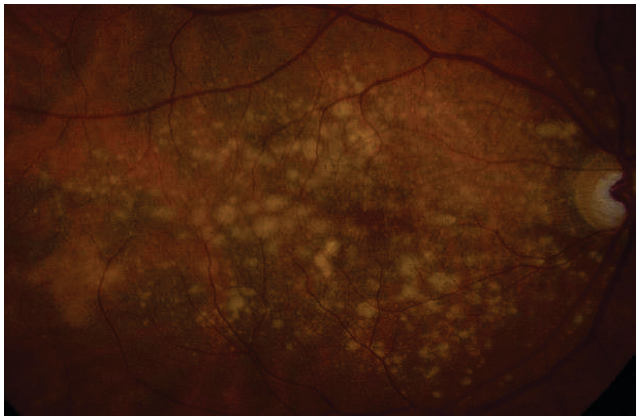

Figure 1 **Intermediate AMD.**

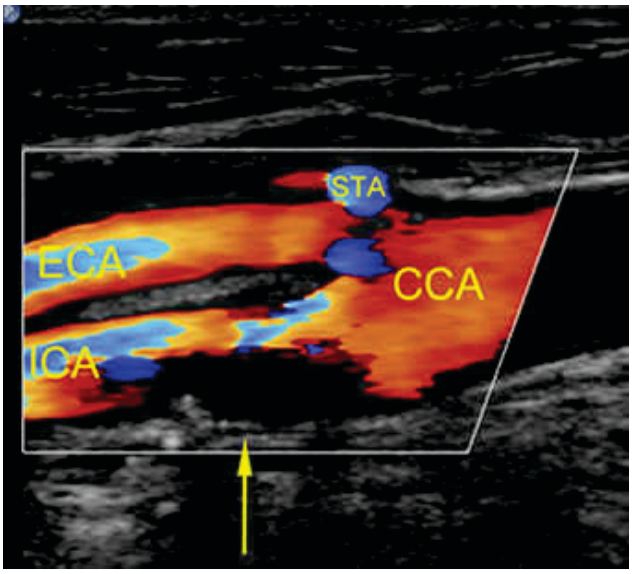

Figure 2 **Stenosis of the internal carotid artery.**

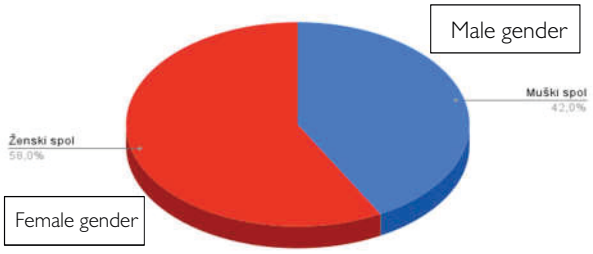

Figure 3 **Gender structure of the patients included in this study.**

The average age was 71.9 years.
The standard deviation for the age category was: 5.14.

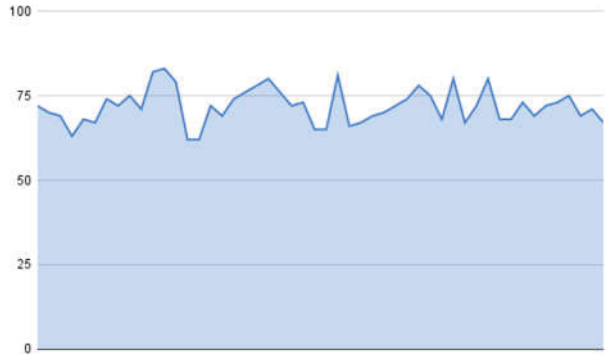

Figure 4 **Average age of the patients included in this study.**

On average, male patients in the study were 2.2 years older than female patients. The mean age of male patients was 73.1 years and that of female patients was 70.9 years.

AMD: n=12 patients (24%) had early AMD (single drusen or pigment disintegration), n=23 (46%) had intermediate AMD (more pronounced atrophy and confluent drusen), and n=15 (30%) had late AMD (geographic atrophy or choroidal neovascularization).

Carotid artery stenosis: the number of patients with mild carotid artery stenosis was n=39 (78%), with moderate stenosis n=7 (14%), and with high stenosis n=4 (8%).

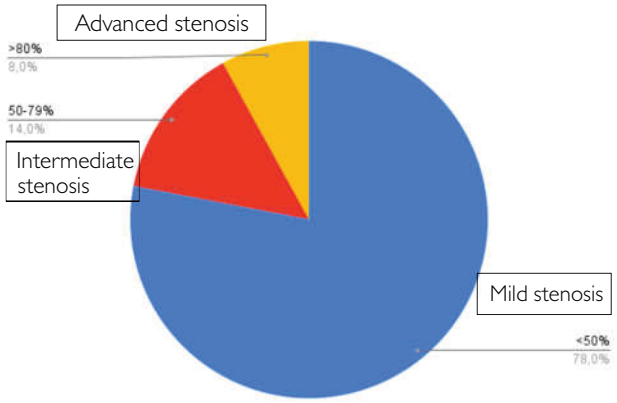

Figure 5 **Structure of degree of carotid artery stenosis (mild, intermediate and advanced).**

The total number of patients who had clinically significant carotid artery stenosis (>50% lumen stenosis) was n=11 (22%), of which n=7 were female (14%) and n=4 were male (8%).

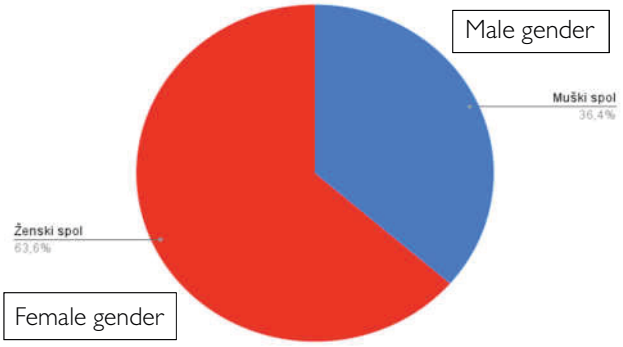

Figure 6 **Gender structure of the patients with significant carotid artery stenosis.**

DISCUSSION

Contrary to some earlier research and the general opinion that systemic vascular diseases can affect the development of AMD, in addition to its biggest risk factor - age (7,8).

Statistical analysis showed that there is no statistically significant difference between the 2 variables, and accordingly the null hypothesis was accepted, and the alternative was rejected.

This study is limited by a relatively small number of subjects, which may affect the generalization of the results, and due to the possible bias of the results caused by the smaller group of subjects involved.

The strength of this research is primarily reflected in the clearly defined inclusion and exclusion criteria, which, considering the small number of respondents, were very necessary. Also, the accuracy of this study was contributed by the high-precision diagnostic method (carotid CD), as well as the well-defined stages of stenosis and stages of AMD disease.

Also, this study could provide an opportunity for future research and prospective studies, with a larger number of subjects, as well as the possible existence of a control group, in order to examine the relationship between these two variables in more depth.

Especially if the study design and available data were chosen to include some other risk factors such as hypertension and hyperlipidemia, as some previous cohort studies and confirmed a positive association between the above and AMD (9).

There have been many studies that have considered cardiovascular disease and macular degeneration as two entities (10,11,12,13), between which they have tried to find a link, and although Although certain risk factors were common and increased the risk of developing AMD, a clearly defined and significant cause-and-effect line has not yet been found.

CONCLUSION

The presence and degree of carotid artery stenosis and the degree of AMD are independently associated. This study showed that the degree of AMD is independent of the degree of stenosis of the carotid arteries, which has been confirmed by others similar to this one.

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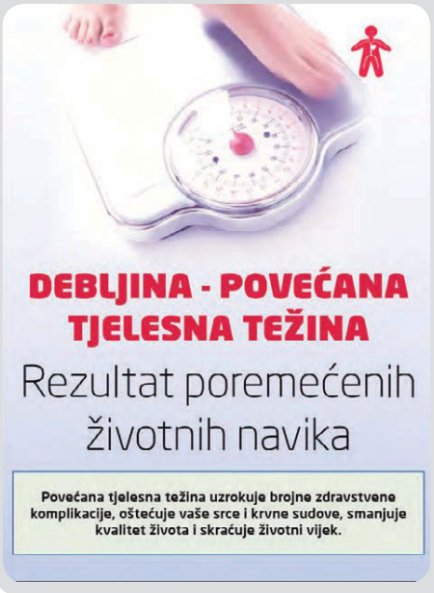

Assessment of the Relationship between Gender and Pulmonary Embolism

Procjena odnosa spola i plućne embolije

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ABSTRACT

Introduction: Pulmonary Embolism (PE) is frequent medical emergency; in fact, it is the third most common cause of cardiovascular death worldwide. While gender differences are well studied in coronary artery disease, less is known about how gender factors impact on PE. Only few studies regarding gender differences in PE were conducted. Aim: to determine whether there is a gender difference in subjects with confirmed and excluded PE. Materials and methods: the study included 100 patients with suspected PE, which was confirmed or excluded by using MSCT and/or V/P SPECT and for all patients data regarding gender were recorded. Results: out of 100 subjects, PE was not diagnosed in 37 subjects, while 63 subjects were diagnosed with PE. All subjects were divided into 2 groups: a group of subjects with confirmed PE and a group of subjects with excluded PE. The number of female and male patents was calculated for both groups. Statistical analysis showed that there was no significant gender difference in the group of patients without PE, while there was a significant gender difference in the group of patients with diagnosed PE. Conclusion: the results of our study indicate that the gender does not influence the incidence of PE.

Keywords: pulmonary embolism, gender, MSCT, V/P SPECT

SAŽETAK

Uvod: plućna embolija (PE) je često hitno medicinsko stanje tj. radi se o trećem najčešćem kardiovaskularnom uzroku smrti u svijetu. Dok je utjecaj spola dobro proučen u razvoju koronarne arterijske bolesti, malo se zna o utjecaju spola na PE. Proveden je mali broj studija koje su proučavale utjecaj razlika u spolu na PE. Cilj: utvrditi da li postoji razlika u spolu kod ispitanika sa potvrđenom i isključenom PE. Materijali i metode: u studiju je uključeno 100 pacijenata kod kojih je postojala sumnja na PE, koja je potvrđena ili isključena korištenjem MSCT i/ili V/P SPECT-a i za sve ispitanike je registriran podatak o spolu. Rezultati: od ukupnog broja ispitanika kod njih 37 nije dijagnosticirana PE, dok je kod 63 ispitanika dijagnosticirana PE. Svi pacijenti su podijeljeni u 2 skupine: skupina pacijenata kod kojih je potvrđena PE i skupina pacijenata kod kojih je isključena PE. Za svaku od navedenih skupina je izračunat broj ženskih i muških ispitanika. Statistička analiza je pokazala da ne postoji značajna razlika po pitanju spola u skupini pacijenata kod kojih nije dokazana PE, dok je u skupni pacijenata sa dijagnosticiranom PE postojala signifikantna razlika po pitanju spola. Zaključak: rezultati naše studije ukazuju na činjenicu da spol ne utječe na incidenciju PE.

Ključne riječi: plućna embolija, spol, CT, V/P SPECT

INTRODUCTION

Pulmonary embolism (PE) is a life-threatening medical emergency where the main pulmonary arteries and/or their branches are obstructed by thrombotic masses, which leads to compromised blood flow (1,2). PE is the third most common cardiovascular disease with an incidence of about 0.5 to 1.0 per 1000 inhabitants (3).

While gender differences in the incidence of other cardiovascular diseases are well studied, relatively few studies have examined gender differences in the incidence of PE.

Risk factors for developing PE are numerous and can be stratified into weak, intermediate, and strong. Weak risk factors are advanced age, obesity, bed immobilization for more than three days, recent laparoscopic surgery, and pregnancy. Intermediate risk factors include the presence of an active neoplasm, the use of chemotherapy, heart failure, thrombophilia, the use of estrogen-progestogens, and the puerperium. Strong risk factors are major general surgery (DVT, orthopedic, oncological, neurosurgical, and major trauma) and atrial fibrillation (4). Some of these risk factors are more common in women (the use of oral contraceptives, the need for hormone therapy and therapy with the selective estrogen receptor modulator, pregnancy, and the postpartum period), while

others are more common in men (cigarette smoking, increased BMI, abdominal obesity with consequent development of metabolic syndrome, higher incidence of deep venous thrombosis) (5,6,7).

There is no clear position in the literature on whether gender influences the incidence rate of PE, as some authors state that PE is more common in women, while others believe that male gender is a risk factor for the development of PE (8).

AIM

The aim of this study was to determine whether there was a gender related difference in the incidence of PE.

MATERIALS AND METHODS

The prospective study conducted at the Clinical Center University of Sarajevo included 100 consecutive adult subjects with preserved renal function in whom the competent clinician suspected the presence of PE and who underwent to MSCT and/or V/P SPECT examination.

The study did not include minors, pregnant women and subjects with impaired renal function (creatinine clearance <60 ml/min).

The subjects with clinically suspected PE were referred for MSCT and/or V/P SPECT examination of the thoracic organs.

All MSCT examinations were performed on a machine with 64 or more rows of detectors. After obtaining the topogram and determining the scanning field that covers the area of the thoracic organs from the tops to the bases of the lungs, a contrast series of scans commenced. Iodine-based contrast agent was applied with an automatic syringe in the amount of 80 to 100 ml, depending on the subject's body weight, at a rate of 4 mL/S. The following parameters were used for scanning: SMART PREP technique, breath-hold scanning in layers of 0.5 mm (120 kV, 250 mA, gantry rotation time 0.75 s). If, during the analysis of the scans, the existence of a partial or complete defect in the contrast filling in the pulmonary arteries and their branches was determined, the examination was classified as positive for PE (6).

V/P SPECT examinations were performed according to a one-day standardized protocol recommended by the European Association of Nuclear Medicine (5). As the first part of the examination, ventilation tomography was performed with previous inhalation of Technegas. Immediately after the completed ventilation tomography, perfusion tomography was performed, after the application of Tc-99m-MAA. Acquisition - Ventilation: 30-50 MBq of Technegas; Acquisition - Perfusion: 100-120MBq 99mTc MAA. A wide-field gamma camera with a low-energy, high-resolution collimator with the following parameters was used for acquisition: matrix size 64 x 64, 128 projections/360°; duration: 10 sec/frame-V; 5sec/frame P. The analysis of V/P SPECT findings was performed according to the interpretation criteria of the European Association of Nuclear Medicine (2). The examination was classified as positive for PE if at least one segmental perfusion defect or two subsegmental perfusion defects were observed, while at the same time ventilation was preserved in the same region/regions - "mismatch".

Subjects with PE confirmed by at least one of the imaging methods (MSCT and V/P SPECT) were classified as positive for the presence of PE.

Data regarding gender were registered for all subjects.

For statistical analysis of the results the Microsoft Excel 365 (Microsoft Corporation, Redmond, Washington, USA) and IBM SPSS ver. 26.0 (IBM, Armonk, New York, USA) software was used. The significance level $\alpha = 0.05$ was chosen, and p values lower than this were considered statistically significant.

Independent-Samples Mann-Whitney U Test was used to analyze the distribution of body mass index in both groups of patients.

The distribution of body mass index in not normal (Kolmogorov-Smirnov Test, $p = 0.013$) - because of this we used median and interquartile range (IQR) as measures of central tendency and dispersion, respectively.

RESULTS

A total of 100 clinically suspected PE subjects who undergone to MSCT and V/P SPECT imaging studies were included in the study. Out of the total number of subjects, 45 were male and 55 were female. The median age of the subjects was 60 years ($\Delta Q = 26$).

Out of the total number of subjects included in the study (n = 100), 37 of them were not diagnosed with PE, while 63 subjects were diagnosed with PE and underwent anticoagulant treatment (Figure 1).

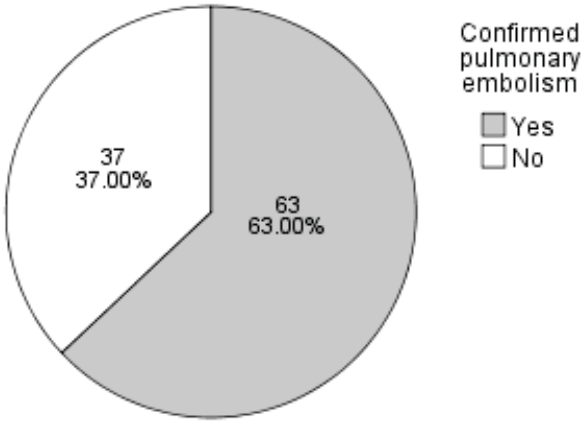

Figure 1 **The percentage of subjects with excluded and confirmed pulmonary embolism.**

All subjects were divided into 2 groups: a group of subjects with confirmed PE and a group of subjects with excluded PE, based on the finding of imaging methods.

The number of female and male patients was calculated for both groups.

Table 1 **The number of female and male patients with excluded and confirmed pulmonary embolism.**

	Confirmed pulmonary embolism					
	Yes		No		Total	
	N	%	N	%	N	%
Male	26	41,3%	19	51,4%	45	45,0%
Female	37	58,7%	18	48,6%	55	55,0%
Total	63	100,0%	37	100,0%	100	100,0%

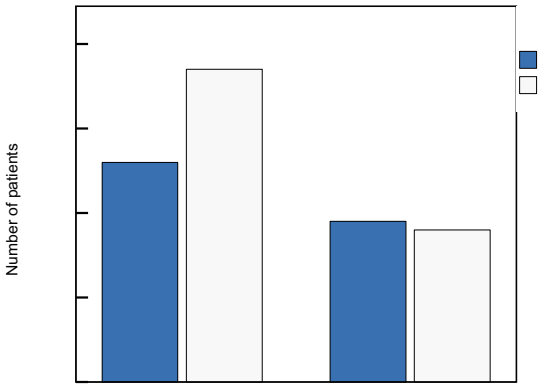

Figure 2 **The distribution of gender of subjects with excluded and confirmed pulmonary embolism.**

We didn't find significant differences in frequencies of pulmonary embolism for male and female patients included in the study (Fisher's exact test, $p = 0.406$).

DISCUSSION

As it can be seen from the results, in our study we did not prove a significant difference in the frequency of PE embolism depending on gender, i.e. PE was similarly frequent in both men and women.

The above results do not deviate from the literature. In the literature there is no unanimous opinion on whether gender has an impact on the incidence of PE.

In fact, some of the conducted studies determined an increased frequency of PE in women, which was tried to be explained by a greater influence of risk factors during the fertile age (oral contraceptives, pregnancy and puerperium) (9,10), but these authors also state that the effect of risk factors associated with hormonal status ceases in menopause. Considering that the average age of our subjects was 60 years, which according to the World Health Organization (WHO) is classified as an older age, the risk factors for PE that are related to the hormonal status of women had less influence on the female subjects.

On the other hand, part of the studies indicate that the male gender is a risk factor for the occurrence of PE, which is explained by the greater representation of risk factors for the occurrence of cardiovascular diseases in the male sex, as well as a greater tendency for the occurrence of DVT, which is often associated with PE. In recent studies, body height and its combination with other anthropometric factors, inflammation and metabolic dysregulation are mentioned as factors that contribute to a higher frequency of PE in men (11,12,13).

Currently in everyday clinical practice is given limited importance to the influence of gender on frequency of PE and consequently more extensive studies should be conducted in order to assess more precisely the influence of this factor in our population.

CONCLUSION

The results of our study did not confirm the existence of an association between gender and PE. Considering the relatively small number of subjects included in the study, it would be desirable to conduct a more extensive study in order to assess in more detail the association between gender and PE.

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Evaluation of HbA1c Values in Different Therapeutic Regimes of Type 2 Diabetes Mellitus and Type 1 Diabetes Mellitus in the Adult Population

Evaluacija vrijednosti HbA1c kod različitih terapijskih režima tipa 2 diabetes mellitusa i tipa 1 diabetes mellitus-a kod odrasle populacije

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ABSTRACT

Introduction: the most commonly used parameter for controlling diabetes mellitus is HbA1c, which shows how much glucose is bound from the blood to the hemoglobin of erythrocytes over 3 months. Good regulation of diabetes mellitus reduces the risk of cardiovascular incidents. The target value of HbA1c is individualized for individual groups of patients. There is a wide range of therapeutic possibilities for treating type 2 diabetes. Aim: to show the diabetes regulation of our patients in the Endocrinological Consultancy, according to the HbA1c value, to check whether there are significant differences depending on the therapeutic regimen they use. Materials and methods: retrospectively, the endocrinological findings of patients from the Sarajevo Canton with type 1 and 2 diabetes mellitus, prediabetes, and gestational diabetes, who reported to the Endocrinological Consultation Center within one month, were selected from the BIS. The values of their HbA1c, gender, age, and duration of diabetes, as well as the therapeutic regimen used in the treatment of diabetes, were recorded. Statistical analysis was performed in IBM SPSS Statistics v. 26. Results: out of 300 patients with DMt1, there were 45 patients (15%), with DMt2 there were 232 patients (77.33%), with prediabetes 19 patients (6.33%) and 4 patients (1.33%) with gestational diabetes. The average HbA1c in patients with DMt1 was 7.6 ± 1.66, in DMt2 7.75 ± 1.97, in prediabetes 5.7 ± 0.29, in gestational diabetes 5.6 ± 0.15. Patients were classified according to therapeutic regimens into subgroups: 1. with one oral antidiabetic (PAD)-33 patients, 2. with two PAD-31, 3. with three PAD-23, 4. with some insulin + PAD -61, 5 . only on insulin therapy without PAD -14, 6. with GLP 1 RA + PAD or GLP-1RA + insulin + PAD-66 and 7. with GLP-1RA (GLP-1 receptor agonists) + insulin - 4 patients. Mean values of HbA1c were according to these groups 6.5 ± 0.95; 7.5 ± 1.92; 7.6 ± 1.84; 8.5 ± 2.01; 11.3 ± 0.1; 8 ± 2.04; 7.7 ± 0.69. Conclusion: only patients with gestational diabetes and patients with DMt2 who were on therapy with one PAD had the target mean value of HbA1c (<7%), and the highest mean value of HbA1c in patients with DMt2 was in patients who were only on insulin therapy.

Keywords: HbA1c, diabetes mellitus, therapeutic regimen

SAŽETAK

Uvod: najčešće korišten parametar za kontrolu diabetes mellitus-a je HbA1c, koji pokazuje koliko se prosječno glukoze veže u krvi za hemoglobin eritrocita u toku 3 mjeseca. Dobra regulacija diabetes mellitusa smanjuje rizik od kardiovaskularnih incidenata. Ciljna vrijednost HbA1c je individualizirana za pojedine skupine pacijenata. Široka je terapijska mogućnost za liječenje diabetesa tipa 2. Cilj: pokazati kakva je regulacija diabetesa naših pacijenata u Endokrinološkom savjetovalištu, prema vrijednosti HbA1c, provjeriti da li postoje signifikantne razlike ovisno o terapijskom režimu koji koriste. Materijali i metode: retrospektivno su izdvojeni iz BIS-a endokrinološki nalazi pacijenata iz sarajevskog kantona sa diabetes mellitus-om tip 1 i 2, predijabetesom i gestacijskim dijabetesom, koji su se javili u Endokrinološko savjetovalište u toku jednog mjeseca. Zabilježene su vrijednosti njihovog HbA1c, spol, životna dob i trajanje diabetesa, kao i terapijski režim koji koriste u tretmanu diabetesa. Statistička analiza provedena je u IBM SPSS Statistics v. 26. Rezultati: od 300 pacijenta, sa DMt1 je bilo 45 pacijenata (15%), sa DMt2 je bilo 232 pacijenta (77.33 %), sa predijabetesom je bilo 19 pacijenata (6.33 %) i 4 pacijenta (1.33%) sa gestacijskim dijabetesom. Prosječni HbA1c kod pacijenata sa DMt1 je bio 7,6 ± 1,66, kod DMt2 7,75 ± 1,97, kod predijabetesa 5.7 ± 0.29, kod gestacijskog dijabetesa 5.6 ± 0.15. Pacijenti sa DMt2 su svrstani prema terapijskim režimima na podgrupe: 1. sa jednim peroralnim antidijabetikom (PAD)-33 pacijenta, 2. sa dva PAD-31, 3. sa tri PAD-23, 4. sa nekim od inzulina + PAD -61, 5. samo na inzulinskoj terapiji bez PAD -14, 6. sa GLP- 1RA +PAD ili

GLP-1RA + inzulin + PAD-66 i 7. sa GLP-1RA (GLP-1 receptor agonisti) + inzulin- 4 pacijenta. Srednje vrijednosti HbA1c su bile u tim podgrupama: 6,5 ± 0,95; 7,5 ± 1,92; 7,6 ± 1,84; 8,5 ± 2,01; 11,3 ± 0,1; 8 ± 2,04; 7,7 ± 0,69. Zaključak: ciljnu terapijsku srednju vrijednost HbA1c imale su pacijentice sa gestacijskim dijabetesom, dok pacijenti sa DMt1, DMt2 i predijabetesom nisu. Srednje vrijednosti HbA1c su bile značajno različite kod različitih terapijskih režima za DMt2, najniže su bile kod terapijskog režima sa jednim PAD, potom sa dva PAD, sa tri PAD, sa GLP -1RA+inzulin, pa GLP-1RA +inzulin+PAD, inzulin +PAD, i sa samo inzulinom u terapiji. Uspjeh terapije diabetes mellitusa sa optimalnim nivoom HbA1c zavisi od adekvatnog izbora terapijskog režima, koji je individualiziran za svakog pacijenta i zavisi od životne dobi pacijenta, očekivanog životnog vijeka, trajanja diabetesa, komorbiditeta, rizika od hipoglikemija, socioekonomskog statusa, motivacije pacijenta i pridržavanja terapije.

Ključne riječi: HbA1c, diabetes mellitus, terapijski režim

INTRODUCTION

The value of HbA1c is the most commonly used parameter for assessing the control of diabetes mellitus, in addition to the value of blood glucose (BG) fasting and 2 hours postprandial (1).

HbA1c is a parameter that shows the average glucose in plasma during the previous three months (the lifetime of erythrocytes is 3 months). HbA1c is used to monitor glycemic control in patients with diabetes, it is well correlated with the risk of diabetes complications (2). Good regulation of diabetes mellitus reduces the risk of cardiovascular incidents (3).

The target therapeutic value of HbA1c for most patients without comorbidities is less than 7%, for the elderly population (over 70 years) less than 8%, and for gestational diabetes less than 6% (4). It is possible to use different therapeutic regimens in the treatment of diabetes. type 2 diabetes (DMt2), which is individualized, depending on the patient's age, liver and kidney function, lifestyle (eating habits and physical activity), and body mass index (BMI).

AIM

The aim of this study was to show the diabetes regulation of our patients who come to the Endocrinological Consultation Center, according to the HbA1c value, to check if there are significant differences depending on the therapeutic regimen they use.

MATERIALS AND METHODS

The study was retrospective and it included patients of both sexes, of all age groups, with DM type 1 and 2, prediabetes, and gestational diabetes, who visited the Diabetes Advisory Center of the Clinic for Endocrinology of the Clinical Center University of Sarajevo (CCUS) in the March 2024. All patients were registered on the computer in the Hospital Information System (BIS). We took all monitored parameters for the study from BIS and followed the endocrinological findings of patients from Sarajevo Canton. Their HbA1c values, gender, age, duration of diabetes as well as the therapeutic regimen used in the treatment of diabetes were monitored. The included patients of both sexes were between the ages of 18 and 69. Patients without diabetes mellitus, gestational diabetes or prediabetes were excluded from the study. We divided all patients into 4 groups: G-I, DMt1; G-II, DMt2; G- III, gestational diabetes and G-IV, prediabetes. Patients with DMt2 were classified according to therapeutic regimens (TR) into subgroups: I. with one oral antidiabetic drug (PAD), II. with two PAD, III. with three PAD, IV. with some insulin + PAD, V. only on insulin th (TR) without PAD, VI. with GLP 1 RA with or without insulin+PAD -66 and VII. with GLP 1 RA + insulin. A total of 897 endocrinological patients were registered, of which 300 were included in the study. Statistical analysis was performed in IBM SPSS Statistics v. 26. Data on patients with diabetes are presented as mean values with standard deviation and percentages. The difference in mean parameter values was tested by a one-way ANOVA test followed by Tukey's post-hoc analysis. Differences in the mean values of HbA1c in men and women were examined by Student's t-test. Differences in the mean values of HbA1c in patients with diabetes on different therapies were examined by Student's t-test and One-Way ANOVA. Statistical significance was set at $p < 0.05$.

RESULTS

In the course of one month, a total of 897 endocrinological patients from Sarajevo Canton came to the Endocrinological Counseling Center for examination, of which 300 patients have diabetes alone or combined with another endocrinological disease, the rest are patients with diseases of the thyroid gland, adrenal glands, pituitary gland, and osteoporosis. There were 41 patients with DMt1, 236 with DMt2, 19 with prediabetes, and 4 with gestational diabetes.

Out of 300 patients with diabetes, 41 patients (15%) had DMt1, there were 236 patients (77.33%) with type 2, 19 patients (6.33%) with prediabetes and 4 patients (1.33%) with gestational diabetes. The average HbA1c in patients with DMt1 was 7.6 ± 1.66, in DMt2 7.75 ± 1.97, in prediabetes 5.7 ± 0.29, in gestational diabetes 5.6 ± 0.15. Patients were classified according to therapeutic regimens into subgroups: 1 1. with one oral antidiabetic (PAD)-33, 2. with two-31, 3. with three PAD-23, 4. with some insulin + oral antidiabetic-61, 5 . only on in. th without oral antidiabetic drugs-14, 6. with GLP 1 RA +PAD or GLP-1RA + insulin+PAD-66 and 7. with GLP 1 RA + insulin- 4 patients. Mean values of HbA1c were according to these subgroups: I- 6.5 ± 0.95; II-7.5 ± 1.92; III-7.6 ± 1.84; IV-8.5 ± 2.01; V- 11.3 ± 0.1; VI-8 ± 2.04; VII- 7.7 ± 0.69.

Table 1 **The mean values of the investigated parameters in patients by group with diabetes mellitus.**

	I DMt1 (N = 45)	II DMt2 (N = 232)	III GD (N = 4)	IV Prediab (N = 19)	F	p
Age	27 ± 13.13	64 ± 11.32	31.5 ± 2.87	49 ± 15.25	88.146	**<0.000**
Sex Females Males	 48.89 % 51.11 %	 53.02 % 46.98 %	 100 % /	 94,74 % 5.26 %	6.276	0.098
Duration (years)	10 ± 12.45	4 ± 5.94	0.2 ± 0.1	1 ± 1.01	23.694	**<0.001**
HbA1c	7.6 ± 1.66	7,75 ± 1,97	5.6 ± 0.15	5.7 ± 0.29	12.591	**<0.001**

Legend: DMt1 – diabetes mellitus type 1; DMt2- diabetes mellitus type 2; GD – gestational diabetes; Prediab- prediabetes, F- Fisher's value, p-value of significance, N – number of patients; HbA1c – hemoglobin A1c.

Table 2 **The mean values of HbA1c according to gender in patients with DMt1.**

HbA1c(M)	HbA1c (F)	p value
7.89 ± 1.97	7.25 ± 1.24	**<0.001**

Legend: HbA1c (M) - mean value of HbA1c in male patients with DMT1, HbA1c (F) - mean value of HbA1c in female patients with DMT1.

Table 3 **The mean values of HbA1c according to gender in patients with DMt2.**

HbA1c (M)	HbA1c (F)	p value
8.2 ± 2.17	8.06 ± 1.78	**<0.001**

Legend: HbA1c-hemoglobin A1c, (M)- male gender (F)- female gender.

Table 4 **The mean values of HbA1c in subgroups I-VII, depending on the therapeutic regimen in patients with DMt2.**

TR1	TR2	TR3	TR4	TR5	TR6	TR7	p-value
6.5 ± 0.95	7.5 ± 1.92	7.6 ± 1.84	8.5 ± 2.01	11.3 ± 0.1	8 ± 2.04	7.7 ± 0.69	**<0.000**

Legend: TR- therapeutic regimen

Table 5 **The mean HbA1c values in patients on Metformin therapy and patients who were on a diet for gestational diabetes.**

Metformin	Diet	p-value
5.65 ± 0.07	5.8 ± 0.14	0.997

Legend: Metformin - mean value of HbA1c in the group with gestational diabetes on metformin therapy, Diet - mean value of HbA1c in the group with gestational diabetes on diet therapy

Table 6 **The mean HbA1c values in patients with prediabetes on Metformin therapy and diet.**

Metformin	Diet	p-value
5.66 ± 0.3	5.7 ± 0.14	**0,005**

Legend: Metformin - mean value of HbA1c in the group with prediabetes on metformin therapy, Diet - mean value of HbA1c in the group with prediabetes on diet therapy

DISCUSSION

The oldest patients (Table 1) are with type 2 diabetes (DMt2), followed by prediabetes, about the mean age of pregnant women and patients with type 1 diabetes (DMT1). The youngest patient was 18 years old, and the oldest was 69 years old. The highest representation of women is in patients with prediabetes - 94.74%, followed by DMT2 - 53.02%, while there is a higher representation of men in DMT1 - 51.11%. A study in Sweden from 1983 to 2002 found a higher annual incidence rate for DMT1 in men - 16.4/100,000 for men and 8.9/100,000 for women (5). In our study, the duration of diabetes is the longest in patients with DMT1, followed by DMT2 and prediabetes. There were 25 patients with newly diagnosed diabetes mellitus (17 with DMT2, 6 with prediabetes, and 2 patients with gestational diabetes), the shortest duration of diabetes was 0.83 years, and the longest duration was 50 years. The highest mean value of HbA1c is in patients with DMT2, then in DMT1, then with prediabetes, and the lowest is in

patients with gestational diabetes. For the lower mean value of HbA1c in patients with type 1 compared to the group with type 2 diabetes in our study, the explanation could be that most patients with type 1 diabetes use continuous glucose monitoring (CGM) for self-control of glycemia. The level of HbA1c in type 1 is affected by several factors: age when the disease was diagnosed, availability of modern technology, optimal glycemic control, and level of education. (6) The mean value of HbA1c in patients with DMT1 (Table 2) is significantly higher in men than in women, as is the case in patients with DMT2 (Table 3). There are different therapeutic regimens in DMt2 (Table 4). The mean value of HbA1c is the lowest when using one oral antidiabetic (PAD), followed by treatments with two PADs, three PADs, then with insulin + GLP-1R A, then with the GLP-1RA + regimen PAD with or without insulin and the highest mean value. HbA1c had a therapeutic regimen with only insulin therapy. Patients with gestational diabetes (Table 5) had a lower mean value of HbA1c with metformin therapy than those on diabetic diet alone. The same relationship between mean HbA1c values during metformin therapy and diabetic diet was also observed in patients with prediabetes (Table 6). Groups of patients with diabetes who received GLP-1-R A therapy had a lower mean value of HbA1c than patients who used only insulin therapy. The expected reduction of HbA1c (%) with monotherapy is the highest with insulin therapy 1.5-3.5%, then with GLP-1+GIP RA 2-2.5%, then GLP-1RA up to 2%, as well as with diet, metformin, and sulfonylurea up to 2%, for DPP -4 inhibitors up to 0.8%, and SGLT2 inhibitors up to 0.7%. Body weight reduction as an advantage of GLP-1 RA therapy, along with a fairly favorable expected potential reduction in HbA1c value, could explain the better HbA1c value in groups of patients with DMT2 who used this antidiabetic drug in therapy (7). A significant risk factor for the development of DMT2 is overweight and obesity (8). Obese patients with DMT2 may benefit from weight loss, with improved abnormal blood glucose and lipid metabolism, reduced insulin resistance, and increased insulin sensitivity (9).

Given that diabetes mellitus is a frequent disease of modern man, this and similar research are always current and should be continued and developed.

CONCLUSION

HbA1c is not a sufficient parameter for evaluating diabetes control, because it can be influenced by other factors, such as frequent hypoglycemia, frequent changes in hypoglycemia and hyperglycemia, and various comorbidities: anemia, liver and kidney diseases. Daily regular control of SUK with adequate corrected therapy with insulin and PAD with a hygienic diet and physical activity can keep HbA1c values within normal limits.

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Evaluation of the Protective Effect of Fentanyl on Testicular Ischemia -Reperfusion Injury in an Experimental Model: Histopathological Changes

Evaluacija protektivnog dejstva Fentanila na ishemijsko reperfuzionu leziju testisa na eksperimentalnom modelu: histopatološke promjene

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ABSTRACT

Introduction: testicular torsion (TT) is one of the most serious urological emergencies that occur in newborns, children, and adolescents. The main pathophysiological event resulting from TT is testicular ischemia-reperfusion injury (IRI), which can result in male infertility. Research in animal models has shown that various substances can help lessen testicular reperfusion injury. However, the results are controversial and unclear enough to apply to humans. Aim: to determine a possible long-term protective effect of fentanyl on rat spermatogenesis through the reduction of IRI in both the ipsilateral affected testis based on the assessment of spermatogenesis according to Johnsen's testicular Biopsy Score (JS) and determination of mean seminiferous tubular diameter (MSTD) in a 4-week follow-up period corresponding to a 3-year follow-up after testicular detorsion in humans. Materials and methods: a prospective experimental study on an animal model of TT was conducted. Experimental subjects (twenty-four adult, male, albino laboratory rats, Wistar soybeans) were divided into three groups: control (sham) group (n=8), torsional/detorsion group (T/D) group (n=8), and T/D fentanyl group (n=8). Assessment of preserved spermatogenesis after testicular detorsion was done based of Johnsen's Testicular Biopsy Score (JS) and determination of mean seminiferous tubular diameter (MSTD). Results: the JS of the testes of the T/D fentanyl group was statistically significantly higher compared to the JS of the testes of the T/D group ($p<0.001$). The MSTD of the testes of the T/D fentanyl group was higher compared to the MSTD of the T/D group but was not statistically significantly different ($p=0.064$). Conclusion: our the study proved that the JS of the torsed testes in the T/D fentanyl group was statistically significantly higher compared to the JS of the testes in the T/D group, suggesting that fentanyl at a dose of 300 μg/kg administered intraperitoneally during TT leads to improved spermatogenesis 4 weeks after surgery.

Keywords: testicular torsion, experimental model, ischemia-reperfusion injury, fentanyl, histopathology

SAŽETAK

Uvod: torzija testisa (TT) je jedno od najozbiljnijih uroloških hitnih stanja koje se javlja kod novorođenčadi, djece i adolescenata. Glavni patofiziološki događaj koji je rezultat TT je ishemijsko-reperfuzijska ozljeda testisa (IRI), koja može rezultirati muškom neplodnošću. Istraživanja na životinjskim modelima pokazala su da različite supstance mogu pomoći u smanjenju reperfuzijske ozljede testisa. Međutim, rezultati su kontroverzni i nedovoljno jasni da bi se mogli primjeniti na ljude. Cilj: odrediti mogući dugoročni zaštitni efekat fentanila na spermatogenezu štakora kroz smanjenje IRI u torkviranom testisu na osnovu procjene spermatogeneze prema Johnsenovom testis biopsijskom skoru (JS) i određivanja srednjeg dijametra spermatičnih tubula (MSTD) tokom praćenja od 4 sedmice poslije detorzije što odgovara periodu praćenja od 3 godine kod ljudi. Metode: provedena je prospektivna eksperimentalna studija na životinjskom modelu TT. Eksperimentalni subjekti (dvadeset četiri odrasla, muška, albino laboratorijska štakora, Wistar soja) podijeljeni su u tri grupe: kontrolnu (sham) grupu (n=8), (T/D) grupu (n=8) i T/D fentanil grupu (n=8). Procjena očuvanosti spermatogeneze nakon detorzije testisa urađena je na osnovu Johnsenovog testis biopsijskog skora

(JS) i određivanja srednjeg dijametra seminifernih tubulara (MSTD). Rezultati: JS testisa T/D fentanil grupe bio je statistički značajno veći u odnosu na JS testisa T/D grupe (p<0,001). MSTD testisa T/D fentanil grupe bio je veći u odnosu na MSTD T/D grupe, ali nije pokazao statistički značajnu razliku (p=0,064). Zaključak: naša studija je dokazala da je JS torkviranih testisa u T/D fentanil grupi statistički značajno veći u odnosu na JS testisa u T/D grupi, što sugerira da fentanil u dozi od 300 μg/kg primijenjen intraperitonealno tokom TT dovodi do poboljšanja spermatogeneze 4 sedmice nakon operacije.

Ključne riječi: torzija testisa, eksperimentalni model, ishemijsko-reperfuzijska povreda, fentanil, histopatologija

INTRODUCTION

Testicular torsion (TT) is one of the most serious urological emergencies that occurs in newborns, children, and adolescents (1). It is defined as the rotation of the spermatic cord (SC) and testicular structures around its longitudinal axis by 360 degrees or more, resulting in biochemical and histological changes that ultimately lead to testicular dysfunction if detorsion is not performed promptly (2). The incidence of TT is 1:4,000 men younger than 25 years (4). The prevalence of TT among all conditions of acute scrotum is 25-50% (2). TT is characterized by a bimodal occurrence distribution with peaks in the neonatal and pubertal periods (4). The main pathophysiological event resulting from TT is testicular ischemia-reperfusion injury (IRI), which can result in male infertility (3). IRI is defined as a paradoxical exacerbation of cellular dysfunction and death following restoration of blood flow to previously ischemic tissues. Reperfusion injury is a multifactorial process that results in extensive tissue destruction. IRI activates a complex cascade of cellular and molecular responses that are not yet fully understood. Restoration of blood supply to ischemic testes is believed to be associated with excessive production of reactive oxygen species (ROS) and the generation of testicular oxidative stress that activates mitogen-activated protein kinases (5,6).

Research in animal models has shown that various substances can help lessen testicular reperfusion injury, including agonists of erythropoietin receptors, anesthetics, antioxidants, calcium channel blockers, interaction with neutrophils, interaction with renin-angiotensin system, modulators of inflammation, physical therapies, phytotherapeutics, platelet inhibitors, sex steroid precursors, vasodilator agents and others (6). However, the results are controversial and unclear enough to apply to humans.

In this experimental study, we aimed to determine a possible long-term protective effect of fentanyl on rat spermatogenesis through the reduction of IRI in both the ipsilateral affected testis based on the assessment of spermatogenesis according to Johnsen's testicular Biopsy Score (JS) and determination of mean seminiferous tubular diameter (MSTD) in a 4-week follow-up period corresponding to a 3-year follow-up after testicular detorsion in humans.

MATERIALS AND METHODS

This prospective experimental study on an animal model of testicular torsion in rats was conducted at the Faculty of Medicine and the Faculty of Veterinary Medicine, University of Sarajevo in the period from 6 January to 3 February 2024.

For the purpose of the study, 24 adult, male, healthy albino laboratory rats, Wistar soybeans, bodyweight 250-280 g, were provided. The rats were from the Faculty of Veterinary Medicine, University of Sarajevo's own breeding. Access to water and food was ad libitum with the appropriate nutritional composition of the food under the species, strain, and age of the animal. The vivarium in which the animals were housed met standard conditions under laboratory principles: temperature 23°C±2°C; humidity 55% +/- 10% with a good ventilation system; light/dark cycle--12/12 hours and noise whose level did not exceed 55-60 dB.

Experimental research on testicular torsion in an animal model involved 3 phases:

Phase 1. Animal adaptation period - preoperative period - (1 week)

Phase 2. Operative procedure - surgical torsion/detorsion procedure

Phase 3. Postoperative observation of animals and sampling for biochemical and histological analyses.

In the experimental part of the study, animals were randomly divided into 3 groups as follows:

1. Control (sham) group (n=8)
2. Torsional/detorsion group (T/D) group (n=8) - a group of animals that underwent torsion and detorsion;
3. T/D fentanyl group (n=8) - a group of animals that underwent torsion and detorsion and received intraperitoneal (i.p.) fentanyl.

Surgical procedure

The testis was accessed by a trans-scrotal longitudinal incision through the raphe scrotum. Torsion was performed in all rats from the T/D group and the T/D fentanyl group by rotating the left testis 720° clockwise, viewed cranially, on the day of the experiment. The torqued testis was fixed to the inner side of the scrotal wall for 90 minutes. Previous scientific studies have shown that testicular torsion by 720° for less than 60 minutes does not lead to histological changes (7). The surgical procedure was performed under ketamine-xylazine anesthesia (100 mg/kg ketamine and 10 mg/kg xylazine). The rats were under constant supervision, and in case of signs of awakening, a lower dose of anesthetic was administered to ensure optimal conditions for the termination of the experiment.

In the first, control "sham" group, a longitudinal incision was made along the raphe scroti, exteriorization of the left testicle that was not torqued, the testicle remained intact, and then it was immediately returned to the scrotum in a physiological position and the scrotum was sutured.

In the second, T/D group, the left testis was torqued 720°, returned to the scrotum, fixed to the inner wall of the scrotum with a 6-0 multifilament synthetic suture, and the scrotum was sutured. After 90 minutes, the sutures were removed, and the testicle was retorqued and returned to the scrotum, which was then sutured again.

The left testis of the third, T/D fentanyl group, was torqued 720°, returned to the scrotum, fixed to the inner wall of the scrotum with a 6-0 multifilament synthetic suture, and then the scrotum was sutured. 60 minutes after torsion (30 minutes before detorsion), 300 μg/kg fentanyl (FENTANYL PANPHARMA GmbH) was administered intraperitoneally. After 90 minutes of torsion and subsequent ischemia, the left testicle was detorsed and returned to a state corresponding to physiological conditions, and the scrotum was sutured (Figure 1A-C).

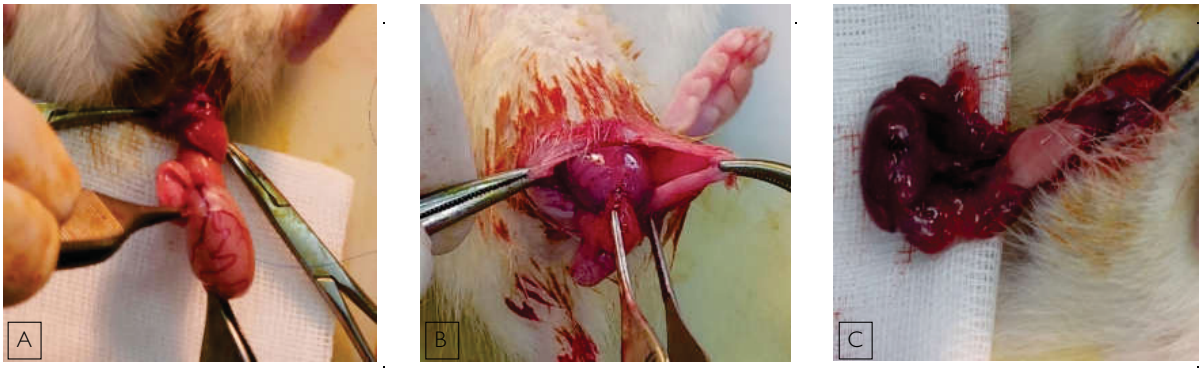

Figure 1A-C. A: Testis twisted for 720°; B: After induced torsion, the testis is returned to the scrotum and fixed to the scrotal wall; C: State after testicular detorsion.

Procedure for taking biological material.

The remaining 8 rats from each group (total 24) were followed postoperatively for 28 days. Observation of rats for 28 days corresponds to a period of 3 years in humans. After orchidectomy, the tunica albuginea of the testicles was incised to allow the fixative (4% formaldehyde) to penetrate the parenchyma. All interventions were performed under general anesthesia, the animals did not suffer pain. After completing all phases of the experimental study, the rats were euthanized by applying the preparation T-61 (1ml/kg) i.v.

Assessment of preserved spermatogenesis according to Johnsen (Johnsen's Testicular Biopsy Score (JS))

Johnson's tubular biopsy (Johnes score) is a quantitative method developed to assess spermatogenesis after testicular injury histologically. In each group, 10 randomly selected tubules from each individual were subjected, using an Olympus BX53 light microscope, at x400 magnification, to histological analysis of the degree of spermatogenesis damage according to JS (Figure 3A-C). In this way, spermatogenesis was quantified numerically from 1 to 10.

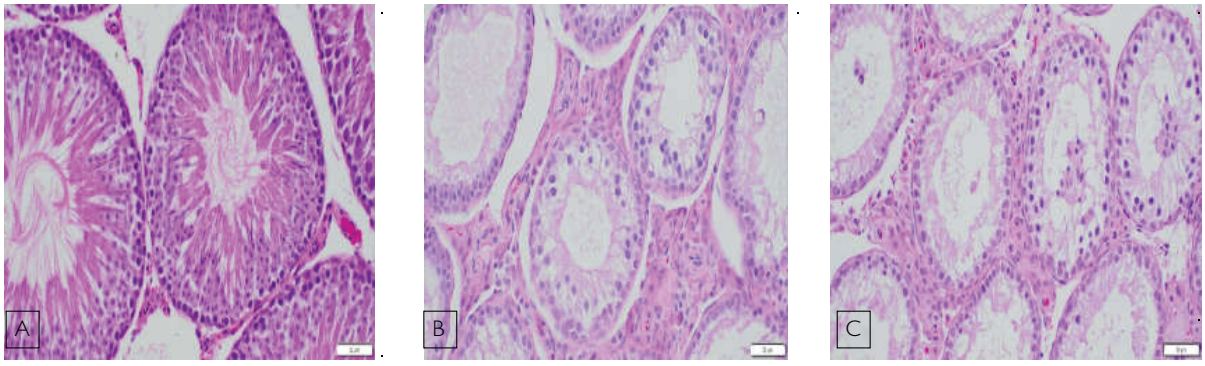

Figure 3A-C - Randomly selected testicular spermatic tubules of all three groups where the Johnsen score (JS) was measured (H.E. x400).

Determination of mean seminiferous tubular diameter (MSTD)

Using an Olympus BX53 light microscope, at x200 magnification, with the help of the cellSens Dimension® software, the diameter of the spermatic tubules was measured in two axes to obtain the average diameter - MSTD. The diameters of the spermatic tubules were measured on the longer (a) and shorter (b) axes on 10 randomly separated tubules from each individual from all three groups, looking as close as possible to a circle. The mean value (a+b)/2 was calculated for each separated tubule, and then the average value of the diameter of the spermatic tubules for each individual.

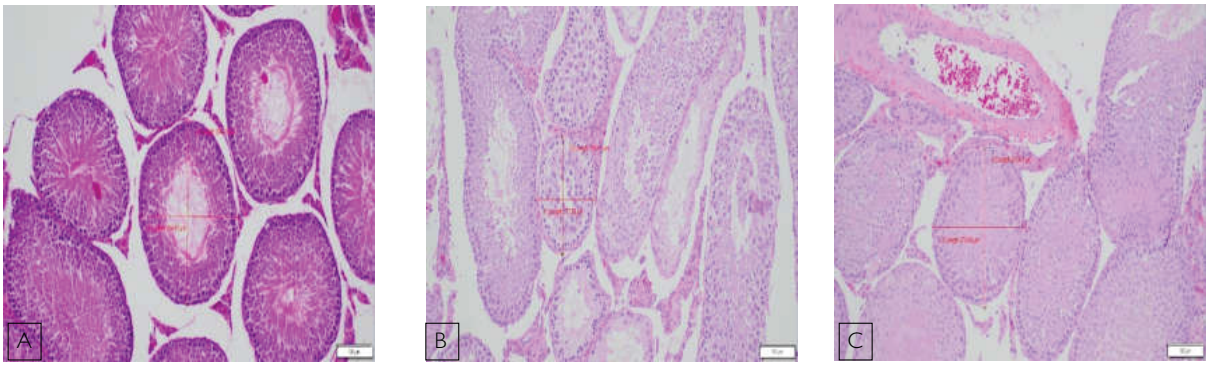

Figure 2A-C. Randomly selected spermatic tubules of the testes of all three groups, with the longer (a) and shorter (b) axes marked, based on which the average diameter of the spermatic tubules (a+b)/2 was calculated as one of the analyzed parameters of the degree of spermatogenesis damage (H.E. x200).

The study was approved by the Ethics Committee of the Faculty of Veterinary Medicine, University of Sarajevo (Number: 07-03-593 - 5/23) dated 27.09.2023 and the Ethics Committee of the Faculty of Medicine, University of Sarajevo (Number: 02-3-4-AK-658023) dated 28.09.2023.

Statistical analysis

Statistical analysis of data was performed using the SPSS (Statistical Package for Social Sciences) computer program, version 18.0. The Shapiro-Wilk test was used to determine the normal distribution of continuous variables. The results were presented as the mean (X) and standard deviation (SD) for variables that followed a normal distribution, or as the median and interquartile interval for variables that did not follow a normal distribution, and as absolute and relative numbers. Comparison of mean values, for variables with a normal distribution, was performed using the Student t-test for independent samples for 2 groups, or one-way analysis of variance (ANOVA) for three or more study groups, after which Bonferroni's test for multiple comparisons was applied. The significance of the difference for quantitative variables that did not follow a normal distribution was tested using the Mann-Whitney test when there were two study groups or the Kruskal-Wallis test for three or more study groups. A statistically significant difference is considered if $p<0.05$.

RESULTS

The JS of the analyzed testes of the control group was 9.25±0.33 and was statistically significantly higher compared to the JS of the torqued testes of the T/D group, where it was 4.21±0.61 ($p<0.001$), as well as compared to the JS of the torqued testes of the T/D fentanyl group, which was 5.72±0.90 ($p<0.001$). The JS of the testes of the T/D fentanyl group was statistically significantly higher compared to the JS of the testes of the T/D group ($p<0.001$). Details related to the JS of the experimental subjects are shown in Table 1. and Figure 3.

Table 1 Average Johnsen score values of randomly selected spermatic tubules of individuals from the control, torsion-detorsion, and torsion-detorsion fentanyl groups.

	Control group (n=10)	Torsion-detorsion group (n=10)	Torsion-detorsion fentanyl group (n=10)
1.	* 9.6	4.2	6.4
2.	8.8	5.2	6.6
3.	9.0	3.6	5.2
4.	9.4	3.8	5.8
5.	9.6	3.8	6.2
6.	9.4	3.6	4.2
7.	9.4	4.8	4.8
8.	8.8	4.7	6.2
Average values	** 9.2	4.2	5.7

n - number of randomly selected testicular spermatic tubules for each individual in the control, torsion/detorsion and torsion/detorsion fentanyl groups
*- average JS of spermatic tubules for each individual in the control, torsion/detorsion and torsion/detorsion fentanyl groups
**- average JS of spermatic tubules for the control, torsion/detorsion and torsion/detorsion fentanyl groups

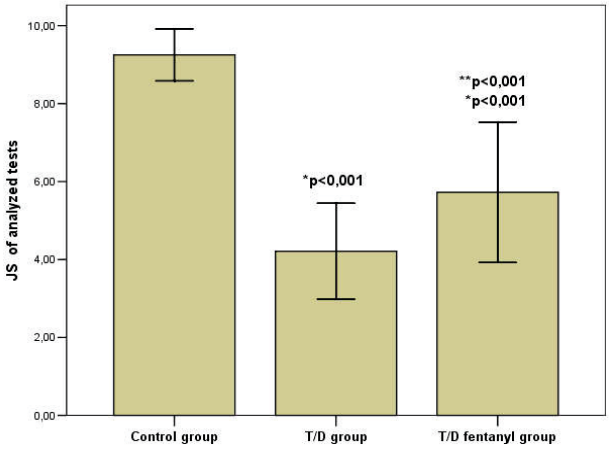

Figure 3 **Johnsen testicular score in the group of experimental subjects who underwent torsion/detorsion with and without the use of fentanyl, as well as in the control group.**

Results are presented as mean ± standard deviation (x± SD); * T/D fentanyl versus control group; ** T/D fentanyl versus T/D group.

The mean seminiferous tubular diameter (MSTD) of the analyzed testes of the control group was 282.20±5.81 and was statistically significantly higher compared to the MSTD of the testes of the T/D group 187.24±13.66 (p<0.001), as well as testes of the T/D fentanyl group 202.14±14.50 (p<0.001). The MSTD of the testes of the T/D fentanyl group was higher compared to the MSTD of the T/D group but was not statistically significantly different (p=0.064). Detailed data are presented in Table 2 and Figure 2.

Table 2 **The average diameter of the spermatic tubules of the control, torsion/detorsion and torsion/detorsion fentanyl groups.**

	Control group n=10 (a+b)/2 μm	Torsion-detorsion group n=10 (a+b)/2 μm	Torsion-detorsion fentanyl group n=10 (a+b)/2 μm
1.	289.63	208.62	225.24
2.	282.95	201.81	215.76
3.	282.27	189.65	190.67
4.	280.98	171.18	190.34
5.	289.39	191.15	189.61
6.	282.87	186.04	208.99
7.	277.74	177.82	187.12
8.	271.82	170.81	209.41
Average values	282.20	187.25	202.14

*μm – micrometer; Diameter (μm) of 10 randomly selected testicular spermatic tubules for each individual, on the long (a) and short (b) axes. The mean diameter values (a+b)/2 for each individual in the control, torsion/detorsion and torsion/detorsion fentanyl groups are shown, as well as the total mean diameter value of spermatic tubules for each group.

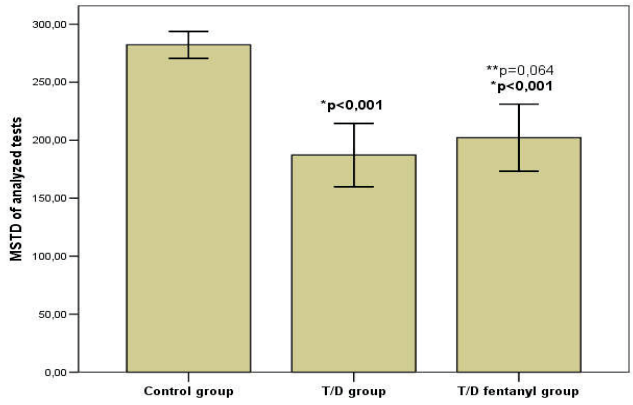

Figure 2 **Mean testicular spermatic tubule diameter (MSTD) in the experimental group of subjects who underwent torsion/detorsion with and without fentanyl administration, as well as in the control group.**

Results are presented as mean ± standard deviation (x± SD); *T/D fentanyl versus control group; ** T/D fentanyl versus T/D group.

DISCUSSION

The primary finding of our experimental study is that fentanyl has a protective effect on testicular IRI by reducing germ cell damage, which we proved by histological analysis by evaluating the preservation of spermatogenesis by JS and measuring the average MSTD. Although no significant difference in JS and MSTD values was found between the T/D and T/D fentanyl groups compared to the control group of subjects in our study, the observed statistically significant difference in the analyzed JS between the T/D group and the T/D fentanyl group indicates the potency of fentanyl in preserving spermatogenesis after TT. These findings are in agreement with the results of the only study in the literature that applied fentanyl after TT induction in experimental rats (11). In their study, Moderniz et al applied 3 μM fentanyl intraperitoneally 30 minutes before detorsion of the yastrogenic TT and 24 hours after the detorsion and subsequent reperfusion of the affected testis and found that JS was statistically significantly higher in the group of experimental subjects who received fentanyl compared to the control group that did not receive fentanyl (11). Our study differed from the aforementioned study in terms of the dose of fentanyl and the duration of reperfusion of the affected testis, while obtaining similar results. In our study, intraperitoneal administration of fentanyl at a single dose of 300 μg/kg leads to incomplete recovery of spermatogenesis in the torqued testis, which suggests that, possibly, increasing the dose and changing the fentanyl administration regimen could restore spermatogenesis function to a greater extent.

Previous studies have shown that opioid analgesics, including fentanyl, stimulate μ, δ, and κ opioid receptors present in various tissues in the body (12). These studies have shown that opioids exert their protective effects on IRI through δ opioid receptors in peripheral tissues (12). These receptors are also present in testicular tissue. Based on the above, fentanyl may directly reduce germ cell damage by binding to δ receptors and indirectly by preventing the activation and migration of PMNL, the main source of ROS, by preventing the conversion of superoxide radicals into more toxic ROS (13). Germ cells are among the most sensitive

cells to hypoxia. Germ cell injury is caused by increased ROS production during reperfusion (7). Polymorphous neutrophil leukocytes (PMNL) release ROS by adhering to the endothelium of blood vessels and then migrating into ischemic tissue, which activates the xanthine oxidase system in germ cells (8). Scientific studies investigating the effect of opioids on IRI have shown that opioids reduce endothelial and PMNL activities by reducing adhesion molecules responsible for PMNL migration, which is an anti-inflammatory effect of opioids. Based on the results of these studies, fentanyl administered before testicular detorsion can suppress the negative effects of ROS, the source of which is PMNL and the xanthine oxidase system, resulting in the prevention of germ cell damage (7,10).

Various other anesthetics with analgesic or sedative effects have been used in experimental models to reduce IRI in torsed testes. Taskara E, et al. examined the long-term effects of propofol on testicular IRI in experimental rats and in the part of the study related to histological changes determined that there was no expected effect of propofol on IRI (14). Namely, JSs in the T/D group were lower than the values recorded in the control and sham-operated experimental groups; however, no positive effect was determined with the use of propofol in the T/D groups (14). A similar histopathological finding related to JS was also obtained by Tuglu D, et al. and Xiao J, et al. after receiving dexmedetomidine (15,16).

In a study conducted by Salmasi AH, et al., morphine administration showed an increase in ipsilateral intratesticular antioxidant markers during the reperfusion phase after unilateral TT (17). However, histopathological changes assessed by JS did not show any difference between the groups of experimental subjects who received or did not receive morphine (17) Similar to the results of our study that showed no significant effect of fentanyl administration on MSTD, Salmasi AH, et al., also did not observe such an effect after morphine administration (17). Further prospective experimental studies that would include a larger number of subjects and provide a longer period of long-term follow-up after surgical testicular detorsion are necessary to better understand the protective role of fentanyl in preserving spermatogenesis after TT.

CONCLUSION

Our study found that the JS of the torsed testes in the T/D fentanyl group was statistically significantly higher compared to the JS of the testes in the T/D group, suggesting that fentanyl at a dose of 300 μg/kg, administered intraperitoneally during TT, leads to improved spermatogenesis 4 weeks after surgery. Furthermore, our study found that the average diameter of the spermatic tubules of the torsed testes in the T/D and T/D fentanyl groups was significantly lower than MSTD in the control group, indicating that fentanyl does not lead to complete recovery of spermatogenesis. However, although not statistically significant, MSTD of the torsed testes of the T/D fentanyl group was higher compared to MSTD of the torsed testes of the T/D group.

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Differentiating Hypertensive Urgencies from Emergencies in Prehospital Settings Staffed with Emergency Physicians

Razlikovanje hipertenzivnih urgencija i emergencija u prehospitalnim uslovima od strane ljekara urgentne medicine

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ABSTRACT

Introduction: a hypertensive emergency is a life-threatening form of hypertensive crisis characterized by the presence of acute damage to vital organs and requires hospital treatment. A hypertensive urgency is a milder, non-life-threatening form of hypertensive crisis that is treated on an outpatient basis. Triage and recognition of these types occur in prehospital settings by emergency medicine physicians, where all the necessary diagnostic tools to confirm organ damage are not available. Triage is based on clinical presentation and limited diagnostic resources, which can pose a significant challenge, especially since there are no adequate official guidelines to assist in decision-making. Aim: to explore the demographic and clinical characteristics of patients with hypertensive emergency (HE) vs. hypertensive urgency (HU) which could be useful in the recognition of each type of hypertensive crisis for the emergency physician in prehospital settings. Materials and methods: this study retrospectively observed 160 consecutive patients over a 3 months period with hypertensive crisis that reported to the emergency department of a tertiary care hospital Clinic of Emergency Medicine of the Clinical Center University of Sarajevo previously referred from a primary care facility Institute for Emergency Medical Assistance of Canton Sarajevo. Results: the mean age was 63.18 (+/- 12.49), with 56.25% female and 43.75% male patients. Newly discovered cases took up 21.25% of all hypertensive cases, whilst 66.88% patients had chronic hypertension with prescribed treatment and 11.88% without treatment. HE vs. HU made up 25.00% vs.75.00% of cases with no statistically significant difference in age, sex or chronic and de novo cases ($p>0.05$). HE patients were symptomatic in all patients observed, while HU patients were asymptomatic in 7.50% cases. 31.67% of HU patients had specific symptoms, while 20.50% patients with HE had unspecific symptoms. The mean values of blood pressure of HE and HU were 201.75 (+/-21.87) / 114.5 (+/-11.17) and 194.75 (+/-16.98) / 108.67 (+/-13.70) respectively ($p<0.05$). Conclusion: the parameters of differentiating between hypertensive emergencies and urgencies in out of hospital settings in the absence of hospital diagnostic possibilities are unspecific. Further research is needed in order to establish the parameters available to this level of healthcare and to provide the emergency physicians with adequate guidelines.

Keywords: hypertensive emergency; hypertensive urgency; recognition; prehospital settings

SAŽETAK

Uvod: hipertenzivna emergencija je po život opasan oblik hipertenzivne krize koji je karakteriziran prisustvom akutnog oštećenjem vitalnih organa i zahtijeva hospitalni tretman. Hipertenzivna urgencija je blaži bezopasan oblik hipertenzivne krize koji se tretira ambulantno. Trijaža i prepoznavanje ovih tipova se odvija u prehospitalnim uslovima od strane ljekara urgentne medicine, gdje nisu dostupna sva potrebna dijagnostička sredstva za utvrđivanje prisustva oštećenja organa. Trijaža se radi na osnovu kliničke prezentacije i oskudnih dijagnostičkih sredstava što može predstavljati veliki problem i postoji opasnost od pogreške tim više što ne postoje adekvatne zvanične smjernice koje bi pomogle u donošenju odluke. Cilj: ispitati demografske i kliničke karakteristike pacijenata sa hipertenzivnim emergencijama (EH) i hipertenzivnim urgencijama (HU) koje bi mogle biti od pomoći ljekaru urgentne medicine u prepoznavanju svakog od ovih tipova hipertenzivnih kriza na prehospitalnom nivou. Materijal i metode: retrospektivna studija je obuhvatila 160 konsekutivnih pacijenata koji su se u tromjesečnom intervalu javili na Kliniku urgentne medicine Kliničkog centra Univerziteta u Sarajevu kao ustanovu tercijarnog nivoa gdje su proslijeđeni iz Zavoda za hitnu medicinsku pomoć Kantona Sarajevo kao ustanove primarnog nivoa. Rezultati: srednja vrijednost starosti je bila 63,18 (+/- 12,49) godina, sa 56.25% žena i 43.75% muškaraca. Novotkrivenih slučajeva je bilo 21.25% od svih hipertenzivnih kriza, dok je 66.88% pacijenata imalo prethodnu hroničnu hipertenziju i bili su pod terapijom, a 11.88% je bilo bez terapije. HU i HE slučajevi su bili zastupljeni sa 25.00% i 75.00% respektivno bez statistički značajne razlike prema dobi, spolu i udjelima de novo slučajeva i onih sa hroničnom hipertenzijom

(p>0.05). Svi HE pacijenti su imali simptome, dok je 7.50% HU pacijenata bilo asimptomatskih. Specifične simptome je imalo 31.67% HU pacijenata, dok je 20.50% HE pacijenata imalo nespecifične simptome. Srednje vrijednosti krvnog pritiska HE i HU pacijenata su bile 201,75 (+/-21,87) / 114,5 (+/-11,17) i 194,75 (+/-16,98) / 108,67 (+/-13,70) respektivno (p<0,05). Zaključak: parametri razlikovanja hipertenzivnih emergencija i urgencija u prehospitalnim uslovima gdje su nedostupna potrebna dijagnostička sredstva su nespecifični, Potrebna su dalja istraživanja kako bi se ustanovili parametri dostupni na ovom nivou i kreirale adekvatne smjernice za ljekare urgentne medicine.

Ključne riječi: hipertenzivna emergencija, hipertenzivna urgencija, prepoznavanje, prehospitalni uslovi

INTRODUCTION

A hypertensive crisis is the state of acutely elevated blood pressure with values above 180/110mmHg (1). There are two different forms of hypertensive crisis described as hypertensive emergency and hypertensive urgency. These two forms require different initial treatment, which is particularly important for the management of these conditions by emergency physicians.

Hypertensive emergencies are life threatening conditions associated with acute hypertension-mediated organ damage (HMOD) and present with different types of severe symptoms depending on the affected organ. Hypertensive urgencies are conditions with elevated blood pressure but without clinical evidence of HMOD (2,3).

The most common organ damage connected with hypertensive emergencies are dissecting aortic aneurysm, acute pulmonary oedema, acute myocardial infarction, unstable angina pectoris, acute renal failure, acute intracranial haemorrhage, acute ischemic stroke, hypertensive encephalopathy, eclampsia, or pre-eclampsia. Initial treatment in the emergency department demands intravenous treatment and immediate hospital admission (4).

The treatment of hypertensive urgencies usually refers to the gradual lowering of arterial blood pressure with the recommended oral therapy at the emergency department and does not require hospital admission (5).

Regardless of the above mentioned, the recommendations addressing hypertensive emergencies and urgencies are not yet evidence based (6) and differ between different medical scientific societies (7). This presents a great everyday challenge for the emergency physician when it comes to the triage and treatment of these patients.

The triage of patients with hypertensive crises and the recognition of HMOD is made harder by the lack of diagnostic means necessary at the prehospital level of healthcare. This is the reason that a great number of patients with urgency hypertension are referred to the hospital, causing an overload of patients at this level. In Canton Sarajevo, emergency healthcare is divided into the prehospital (primary) level, secondary hospital level and tertiary hospital level. The prehospital level is comprised of field services and stationary services, the first obviously not having the necessary laboratory and diagnostic means in the field to determine whether HMOD has occurred. Stationary services of prehospital level emergency medicine are also only equipped with basic laboratory tests and x-ray, which are not enough to distinguish urgency from emergency hypertension in terms of HMOD. The hospital levels of the emergency healthcare system, secondary and tertiary levels, have all the necessary diagnostic means to determine whether HMOD is present, which leads to a very large number of patients with hypertensive urgencies referred to the hospital even though these patients do not require hospital treatment according to protocol (5).

Currently, there is insufficient epidemiological data on the prevalence and clinical presentations of hypertensive urgencies and emergencies that would facilitate physicians practicing at a prehospital level in distinguishing urgency from emergency hypertension. Furthermore, the predictive value of blood pressure values, risk factors and compliance to therapy in the role of HMOD occurrence is unknown.

AIM

The aim of this research was to investigate the demographic and clinical characteristics of patients with hypertensive crisis reporting to the emergency department. Additional aim was to explore the different characteristics of patients with emergency vs. urgency hypertension which could be useful in the recognition of each type of hypertensive crisis to the emergency physician practicing in prehospital settings. This would facilitate triage and decision making in the treatment process and ensure a greater quality service provided to patients with hypertensive crisis. Also, it would reduce overcrowding at hospital level emergency departments, enabling them to focus on patients truly in need of critical care.

MATERIAL AND METHODS

Patients and study design

This study included 160 consecutive patients with hypertensive crisis who reported to the Emergency Medicine Clinic of the Clinical Centre University of Sarajevo, as a tertiary care level facility. They were referred from the Institute for Emergency Medical Assistance of Canton Sarajevo, a primary emergency medicine healthcare facility staffed with physician led teams.

The inclusion criteria were: systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg measured with a manual sphygmomanometer, and age ≥18 years.

The exclusion criteria were: incomplete medical documentation, death before the completion of diagnostic procedures, and age ≤18 years.

Data about patients was gathered retrospectively from the hospital electronic patient records over a three month period (1 March 2024 to 1 June 2024). The collected data included: demographic information on gender and age, information on the prior presence or absence of chronic hypertension and the use of antihypertensive therapy, as well as data on diastolic and systolic blood pressure levels. Data on the symptoms these patients experienced during their visit due to a hypertensive crisis were also collected from medical records. The symptoms reported by the patients were categorized as nonspecific (headache, dizziness,

nausea, and nosebleeds) and specific (chest pain, syncope, one-sided weakness, and shortness of breath).

The acquired data was analyzed in order to gain insight in to the demographic and clinical characteristics of the patients included in the study.

Patients were treated according to the Clinic's protocols, and available diagnostic methods were used, including a clinical examination with blood pressure measurement, laboratory tests, ECG, X-ray diagnostics, and CT diagnostics. Patients were divided into two groups based on definitive diagnoses following a complete diagnostic workup:

1. Hypertensive emergencies – confirmed presence of target organ damage (HMOD).
2. Hypertensive urgencies – absence of confirmed target organ damage (HMOD).

For the purposes of the study, a comparison of patients in these two groups was conducted based on the previously mentioned demographic and clinical parameters.

Statistical methods

The data was processed and statistical analysis was conducted in the programs Windows Excel and IBM SPSS. Chi-Square and Fisher's Exact test were used to compare discrete variables and t-tests were used for continuously distributed variables. A p value of <0.05 was regarded statistically significant. All results are displayed in tables and graphs.

RESULTS

The demographic data of all 160 observed patients was analyzed. The mean age of patients with hypertensive crisis included in the study was 63.18 (+/- 12.49), of which females 56.25% and males 43.75% (Table 1).

Table 1 **Demographic characteristics of the patients**.

Sex				
Characteristics	Number	Percentage		
Male	70	43.75		
Female	90	56.25		
Total	160	100.00		
Age				
Mean	SD	Minimum	Maximum	Median
63.18	12.49	24	92	65

Out of the total number of patients, 78.75% had previously verified chronic hypertension. 66.88% of all patients included in the study had chronic hypertension and were regularly taking the medication that was prescribed. 11.88% of patients had verified chronic hypertension but were not taking any medication. 21.25% of all patients did not have previously verified hypertension (Table 2).

Table 2 **Patient presentation according to whether or not they had previously verified chronic hypertension**.

Chronic hypertension		New cases
78.75%		21.25%
Adherence to medication	Non-adherence to medication	
66.88%	11.88%	

Along with these results regarding the total number of observed patients, an analysis was made after the patients were divided into either of the groups: emergency and urgency hypertension. Data within both groups was analyzed and compared.

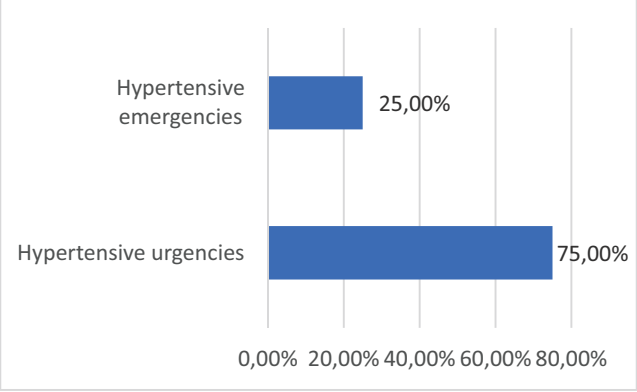

Figure 1 **The share of patients with emergency and urgency hypertension.**

Out of the total number of observed patients, 40 (25.00%) had emergency and 120 (75.00%) had urgency hypertension (Figure 1).

The demographic data of the patients shows that the mean age of the patients with emergency hypertension was 62.10 (+/- 11.08), and those with urgency hypertension 63.87 (+/-12.90), showing no statistically significant difference between the two groups p>0.05. Also, there was no statistically significant difference between each of the groups and the mean age of the total number of patients. (p>0.05) (Table3).

Table 3 **Demographic data of the observed groups of emergency and urgency hypertension.**

Age		
Variable	Hypertensive urgencies	Hypertensive emergencies
Mean	63.87	62.10
SD	12.90	11.08
Minimum	24	44
Maximum	92	82
Median	65.5	61.50
Sex		
Female N(%)	72 (60.00%)	18 (45.00%)
Male N (%)	48 (40.00%)	22 (55.00%)

In the group of patients with emergency hypertension there were 45.00% of females and 55.00%, and in the urgency hypertension group 60.00% of females and 40.00% of males which shows no statistically significant difference p>0.05 (Table 3).

Patients with emergency hypertension had verified hypertension beforehand in 77.50% of the cases, whilst 22.50% of the patients were newly discovered cases of hypertension. In the urgency hypertension group, there were chronic cases of hypertension in 80.00% of the patients and 20,00% were not diagnosed before, which doesn't show a statistically significant difference between the two groups (p>0,05). These results are shown in Figure 2.

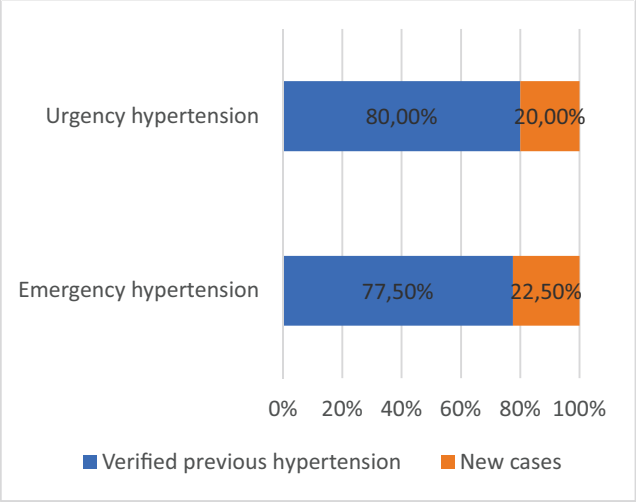

Figure 2 **Patients of both the emergency and urgency hypertension group in regards to previously verified hypertension.**

In the group of urgency hypertension patients referred to the hospital 7.50% were asymptomatic. The clinical presentation of the symptomatic patients differed and was unspecific in 60.83% of cases: headache, dizziness, nausea and nose bleeds. More specific symptoms occurred in the remaining one third (31.67%) of patients in the hypertensive urgency group: chest pain, syncope, one sided weakness and shortness of breath. On the other hand, in the emergency hypertension group of patients, there were no asymptomatic patients. Specific symptoms occurred in 77.50% of patients in this group, while the rest of the patients (20.50%) had unspecific symptoms. These results are shown in Figure 3.

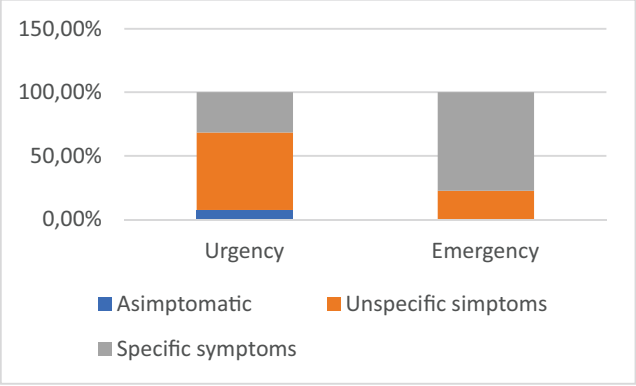

Figure 3 **Patient presentation in both groups according to symptoms.**

The mean values of blood pressure in the patients of the emergency hypertension and urgency hypertension were 201.75 (+/-21.87) / 114.5 (+/-11.17) and 194.75 (+/-16.98) / 108.67 (+/-13.70) respectively, the difference between the two groups was statistically significant when it comes to the systolic as well as the diastolic blood pressure p<0.05. These results are shown in Table 4.

Table 4 **Blood pressure values of the emergency and urgency hypertension groups of patients.**

Characteristics	Emergency hypertension		Urgency hypertension	
	Mean	SD	Mean	SD
Systolic blood pressure	201.75	21.87	194.75	16,98
Diastolic blood pressure	114.5	11.17	108.67	13.70
p-value	0.019602		0.008314	

DISCUSSION

This study included 160 patients, with hypertensive crisis. The mean age of the included patients was 63.18 years, with female patients being the majority of patients included (56.25%) and male patients 43.75%. This was expected, given that above the age of 60, most women are in the second stage of hypertension, whereas above the age of 65 hypertension has prevalence in males (8).

A hypertensive crisis can occur as a new manifestation of hypertension or as a complication of already verified chronic hypertension (9). In our study, only 21.25% of the observed patients were newly discovered cases of hypertension. The rest (78.75%) were patients who previously suffered from chronic hypertension which is confirmed by the findings of other studies found in literature which state that these kinds of patients made up for 70% of all hypertensive crises reporting to emergency departments (10). Hypertensive crises usually occur due to inadequate medication, hypertension management or an inadequate response to therapy (11). Therefore, it is not surprising that 66.88% of patients regularly used the medication prescribed to them, and 11.8% didn't use it at all.

Patients with hypertensive crisis are frequently seen in emergency departments, which is clear given that 160 were referred to the emergency department of a tertiary healthcare level in a very short period of two months. Taking into account the previously stated data, insight into the inadequate management of patients with chronic hypertension in the area covered by this emergency department is gained, as well as into the insufficient awareness and patient consciousness of the importance of adherence to medication. This significantly attributes to the frequency of hypertension related complications such as hypertensive crisis which in turn leads to the overcrowding of emergency departments. Non-adherence to antihypertensive medications is deemed to be the largest risk factor for the origin of hypertensive crisis (12). Better management of hypertensive patients, regular checkups and therapy modification with the goal of improving patients' response can significantly lessen the number of complications and emergency department visits (13).

Following physical examination and diagnostic evaluation, it is determined that ¾ of the total number of patients observed fell in to the category of hypertensive urgency (75.00%), while just ¼ were classified as hypertensive emergencies (25.00%). This vast majority of patients with urgent hypertension seem surprising given that the facility they are referred to from the prehospital level is a tertiary care facility. According to current guidelines, patients with hypertensive urgencies require orally administered medication to lower blood pressure (2,3,5) and these issues can therefore be addressed by physicians practicing in prehospital settings. However, the results of studies carried out in other emergency departments at a hospital level also show a similar or even less portion of emergency hypertensive patients. Balahura AM, et al., demonstrated a significantly lower share (12.2%) of emergency hypertensive crises at a tertiary level institution (14), Pierin AMG, et al., 19.1 % at a secondary level hospital, and (15) Salveti et al., 20.1 % (16).

There is a question as to whether it is necessary for patients experiencing an urgency hypertension crisis to be referred to a tertiary level hospital emergency department. Many authors have already pointed this problem out, stating that an overflow of these patients unnecessarily burdens emergency departments of hospitals alleging the inadequate involvement of the prehospital ambulatory system (17). The malfunction of the prehospital level in terms of triage and the treatment of patients is thought as the cause of unnecessary additional examinations and diagnostics, especially to ionizing radiation generating further damage and along with it great expenses for the healthcare system (18). However, even these authors admit that there are not enough objective and clearly defined criteria to adequately base the triage of patients with hypertensive crisis at the primary level of healthcare on (17).

There is no routine evaluation for hypertensive urgencies. The goal is to rule out target organ damage (19). Given that the classification of hypertensive crises as emergency or urgency is based on the presence or absence of HMOD, determining a definitive diagnosis, along with acquiring anamnestic information and a physical examination including an ECG, also requires laboratory and imaging diagnostics (20,21). In those cases metabolic panels, urinalysis, chest X-ray, and computed tomography may be useful (22). Very commonly, prehospital stationary institutions or mobile units do not have the necessary diagnostic means. Triage is carried out based on patient history, blood pressure values, symptoms and assessment for cardiovascular risk, which is not enough to adequately anticipate HMOD (23).

In this study we did an analysis and comparison of the main characteristics of patients with urgency and emergency hypertension in an attempt to determine possible demographic, anamnestic and clinical factors which could be of help in the examination and triage of hypertensive patients at the prehospital level. The mean age of patients with emergency and urgency hypertension was 62.10 and 63.87, respectively, which does not present a significant difference. Also, there was no statistically significant difference in the gender structure of these two groups of patients, even though male patients prevailed in the group of emergency hypertension patients, and women in the urgency hypertension group. This points out that demographic data are of no use in making a distinction between urgency and emergency hypertension patients.

The groups of observed patients did not significantly differ when it comes to de novo established hypertension in comparison to previously verified chronic hypertension, so in accordance with this, patient history of previous illnesses cannot be a helpful tool in differentiating urgency from emergency hypertension.

All patients with emergency hypertension crisis had symptoms, however a great majority of patients with urgency hypertension also experienced symptoms, with only 7.50% of them being asymptomatic. According to available data, a greater portion of patients with urgency hypertension have unspecific symptoms, in comparison to patients with emergency hypertension. This isn't a reliable guideline for practicing physicians as both types of hypertensive crises can manifest with both mild and severe clinical presentations (21).

The results of our research confirmed this given that one third of patients with urgency hypertension had specific symptoms. Also, 22.50% patients in the emergency hypertension group had unspecific symptoms what was similar to result from a review study of 24.0% (23). These results emphasize the hard task of adequate recognition of these two types of crises based solely on symptoms.

Blood pressure values were also an investigated parameter in this research. Even though results showed statistically significant greater values of systolic and diastolic blood pressure in patients with emergency compared to patients with urgency hypertension (201.75/114.5 and 194.75/108.67 respectively), similar to the findings of other authors (16), blood pressure values cannot be a reliable criteria for distinguishing these two categories of patients from one another as there is no cut off value. The reason for this is obvious, as both groups of patients, by definition have blood pressure values above 180/110 (1).

Judging by the results of this research, but also other available data, determining urgency from emergency hypertensive crises from each other at a prehospital level is very challenging due to the lack of complete diagnostic evaluation most facilities or emergency services are faced with. Triage is based solely on the assumption and suspicion of present organ damage based on sparingly available parameters acquired during patient history taking, physical examination, electrocardiography and blood pressure measurements, which is not enough for an appropriate confirmation. To achieve this, an extensive physical examination (20) including resources only available at a hospital level are required.

CONCLUSION

Patients with hypertensive crisis are very common in emergency departments and prehospital emergency medical services. Most of these cases are complications arising from inadequate medication, or incompliance to prescribed medication. By improving the management of this illness by the practicing physician as well as patient adherence to medication, the overcrowding of emergency departments can be avoided and patient health benefit elevated. The parameters by which emergency can be distinguished from urgency hypertension are unspecific. Further research is needed in order to determine parameters which would help the emergency physician make this decision and improve the outcome for these patients.

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The Use of Transcranial Magnetic Stimulation (TMS) in the Treatment of Schizophrenia

Primjena transkranijalne magnetne stimulacije (TMS) u tretmanu shizofrenije

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ABSTRACT

Transcranial magnetic stimulation (TMS) is a non-invasive brain modulation procedure. Magnetic field pulses created in the electromagnetic coil produce electrical activity in the brain. TMS represents an important milestone in the treatment of psychological disorders, especially in the treatment of schizophrenia. Although schizophrenia is the most common and well-known psychotic disorder, it is not synonymous with psychosis but is just one of its many causes. Treatment of pharmacotherapy-resistant schizophrenia has become one of the most important problems in psychiatry which indicate the need for alternative treatments. There are several treatment options as electroconvulsive therapyelectrostimulation therapy (ECT) and transcranial magnetic stimulation (TMS). Among these methods, the most preferred today is TMS because it is a non-invasive method with the least side effects

Keywords: non-invasive method, treatment, schizophrenia

SAŽETAK

Transkranijalna magnetna stimulacija (TMS) je neinvazivna procedura modulacije mozga. Impulsi magnetskog polja stvoreni u elektromagnetnoj zavojnici proizvode električnu aktivnost u mozgu. TMS predstavlja važnu prekretnicu u liječenju psihičkih poremećaja, posebno u tretmanu shizofrenije koja je najčešći i dobro poznati psihotični poremećaj, nije samo sinonim za psihozu, već je samo jedan od mnogih njenih uzroka. Liječenje farmako rezistentne shizofrenije postalo je jedan od najvažnijih problema u psihijatriji koji ukazuje na potrebu za alternativnim tretmanima. Postoji nekoliko opcija liječenja kao što su elektrokonvulzivna terapija (EKT) i transkranijalna magnetna stimulacija (TMS) pri čemu je najpoželjnija metoda TMS jer je neinvazivna metoda sa najmanje nuspojava

Ključne riječi: neinvanzivna metoda, terapija, shizofrenija

INTRODUCTION

Schizophrenia is arguably the most debilitating of psychiatric illnesses, psychologically, socially, and financially. Starting in late adolescence to early adulthood and with a lifelong course that typically is characterized by relapses, the impact of schizophrenia on the individual who suffers from it is both pervasive and prolonged. People with schizophrenia may seem like they have lost touch with reality, which can be distressing for them and for their family and friends. Schizophrenia symptoms can differ from person to person, but they generally fall into three main categories: positive, negative, and cognitive. Positive symptoms include hallucinations, delusions, disorganized speech, and grossly disorganized or catatonic behavior, while the negative symptoms include affective flattening, alogia, anhedonia, and avolition. Cognitive symptoms include problems in attention, concentration, and memory. These symptoms can make it hard to follow a conversation, learn new things, or remember appointments. A person's level of cognitive functioning is one of the best predictors of their day-to-day functioning. Current treatments for schizophrenia focus on helping people manage their symptoms, improve day-to-day functioning, and achieve personal life goals, such as completing education, pursuing a career, and having fulfilling relationships. Pharmacotherapy with antipsychotic medication remains the mainstay in the acute and maintenance treatment of this disorder.

Antipsychotic agents (first, second, and third generations) have been shown to be most effective in reducing the positive symptoms, but unsatisfactory in reducing negative symptoms and the propensity to relapse. Furthermore, almost one-third of patients with positive psychotic schizophrenia do not respond to antipsychotic medication. Medication nonadherence is also a significant issue in the treatment of schizophrenia, with nonadherence rates of over 70 percent during the course of one year. There is also a significant side effect burden with antipsychotic medications, including extrapyramidal symptoms, weight gain, and metabolic abnormalities, which may make antipsychotic medications less acceptable to patients and their families (1, 2).

Neuromodulation is a new frontier in the investigation of effective treatment options for schizophrenia in particular transcranial magnetic stimulation (TMS). It can be combined with electromyography (TMS-EMG) and electroencephalography (TMS-EEG) to evaluate the excitatory and inhibitory functions of the cerebral cortex in a standardized manner. It has been postulated that schizophrenia is a disorder of functional neural connectivity underpinned by a relative imbalance of excitation and inhibition (3).

AIM

The aim of the paper was to present new knowledge about the role of transcranial magnetic stimulation in the treatment of schizophrenia.

What is transcranial magnetic stimulation (TMS)?

Transcranial magnetic stimulation (TMS) is a procedure that uses magnetic fields to stimulate nerve cells in the brain. TMS applies a high intensity oscillating magnetic field. In this way, the neural elements in the cerebral cortex are stimulated by a series of pulses. A TMS device has one or two copper coils. It can be placed against the head over different parts of the brain to deliver brief magnetic pulses to the scalp. The strong magnetic pulses form a mild electric current in the outer surface of the brain. It shouldn't hurt. That current affects activity in the brain cells or neurons. Through repeated therapeutic procedures, the method also modulates brain neuroplasticity, inducing changes in synapses and neuronal network connectivity (4).

TMS shows promise in targeting certain symptoms of schizophrenia; however, its effectiveness can depend on the type of symptoms and individual patient characteristics. Research suggests that TMS may help reduce positive symptoms and could also alleviate some negative symptoms, though results are mixed (5,6,7).

TMS and Positive Symptoms

Positive symptoms of schizophrenia are those that add abnormal experiences, such as hallucinations, delusions, disorganized speech, and unusual behaviors. TMS, when applied to the left temporoparietal cortex, has shown potential in reducing the intensity of these symptoms. For instance:

- Studies have found significant reductions in auditory hallucinations, with up to 75% of participants showing improvement after low-frequency TMS.
- Some patients experienced relief that lasted up to 15 weeks following treatment.
- In other studies, higher doses and specific protocols have reported better outcomes.

However, the effectiveness of TMS for positive symptoms is not consistent across all studies. Some trials involving patients with severe or treatment-resistant forms of schizophrenia did not find significant differences between TMS and sham treatments. Factors like small study sizes, varying TMS protocols, and medication use may contribute to these mixed results.

TMS and Negative Symptoms

Negative symptoms refer to the absence or reduction of normal functions like emotional expressions, motivation, and social engagement. High-frequency TMS targeting the left dorsolateral prefrontal cortex has shown some promise alleviate these symptoms:

- Improvements in social withdrawal and motivation were observed in five out of ten controlled studies.
- Some participants experienced a significant reduction in negative symptoms after two weeks of daily TMS.
- Other trials saw additional benefits for depressive symptoms alongside negative symptoms.

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive and relatively painless neuromodulation technique that was approved by the U.S. Food and Drug Administration for clinical use in 2008 and is widely used in fields such as depression, anxiety disorders, obsessive-compulsive disorder, and schizophrenia (8). rTMS locates specific markers close to the surface of the scalp. Electromagnetic induction is used to generate strong and brief magnetic pulses that enter the cerebral cortex and its network of neurons through the skull. The treatment principle involves the use of magnetic fields of different intensities, durations, and frequencies that can have different effects on the nervous system (9).

Currently, rTMS has been explored as a potential treatment for ameliorating negative symptoms and cognitive dysfunction in schizophrenic patients. There are a certain number of meta-analyses exploring the efficacy of rTMS in treating negative symptoms and cognitive dysfunction in schizophrenia, but the outcome is still uncertain. There is controversy over the treatment methods and efficacy. Therefore, this study combined data from a systematic review and meta-analysis to further analyze the feasibility of rTMS for ameliorating negative symptoms and cognitive dysfunction in patients with schizophrenia to seek additional evidence. By applying repeated magnetic pulses (several days or weeks in a row), a long-term change in the function of certain brain regions is achieved. The treatment involves the delivery of repetitive magnetic pulses, so it is also called repetitive transcranial magnetic stimulation (rTMS). rTMS represents a unique method of applying pulsed magnetic fields for therapeutic purposes, with an intensity similar to those used in magnetic resonance imaging (MRI), but at the same time it is fundamentally different from the popular use of various "magnets" (in belts, shoes, etc.), which generate static magnetic fields of low intensity. Such products deliver very weak and non-directional static fields that are unable to activate brain cells. The electromagnetic device is placed above a certain point on the head from where it stimulates the nerves in the cerebral cortex with a series of short magnetic pulses (10, 11).

Deep transcranial magnetic stimulation (dTMS) is a new technology that enables non-invasive stimulation of relatively deep areas of the brain. dTMS therapy is delivered using an H-coil device designed to stimulate areas of the deep prefrontal cortex that include neural pathways associated with the brain's reward system. A promising new development is deep transcranial magnetic stimulation (dTMS), which addresses the limitations of traditional TMS. Traditional TMS is limited in its ability to accurately stimulate localized targets, as in 27% to 32% of patients the intended stimulation site is not reached.

For example, Yu Mo, et al. found that low-frequency dTMS did not have a statistically significant effect on auditory hallucinations or other psychopathology in schizophrenia. A systematic review examined the efficacy and safety of dTMS in schizophrenia based on one RCT and a single-arm perspective study, with obvious heterogeneity in methodology between studies; furthermore, this systematic review did not incorporate a recent double-blind RCT on the efficacy and safety of dTMS in schizophrenia. To understand the current literature on the role of dTMS in schizophrenia and provide a more comprehensive and robust basis for clinical application, the present systematic review included three RCTs that evaluated the therapeutic efficacy and safety of dTMS in schizophrenia (14).

Duration of the TMS procedure

During the treatment, the person is awake and aware, because TMS does not require any sedation or general anesthesia. TMS therapy consists of a series of treatments. The duration of one cycle is ten to twenty applications. Applications can be carried out daily for 20-30 minutes; the therapy is applied 5 days during the week with a break over the weekend. This average may vary depending on individual response to treatment. During the treatment, 3000 pulses are released at a specific location of the frontal lobe of the left hemisphere. The exact number of treatments cannot be predicted in advance. The number of applications depends on the patient's mental state, response to treatment and professional assessment of the psychiatrist.

DISCUSSION

Auditory hallucination is a common characteristic of several psychiatric disorders, including schizophrenia, in which patients experience a false perception of sound. Among the studies that we reviewed, several focused on the effect of TMS administration on auditory hallucination reported that auditory hallucination in medication-refractory schizophrenia patients with higher superior temporal gyrus perfusion is reduced by 50% or more following 10 days of rTMS therapy (15). Similarly, Lee J, et al., reported that 10 days of daily rTMS at 1 Hz benefits treatment-resistant patients with schizophrenia in reduction of auditory hallucinations (16). In contrast, however, Kindler et al. reported that exposure of patients with schizophrenia or schizoaffective disorder to either cTBS or 1 Hz TMS similarly improves auditory verbal hallucinations (17). Deep TMS is a variation wherein an H-coil is utilized to create a synergistic magnetic field that reaches deeper structures in the brain and requires a shorter length of treatment. Lonergan M, et al. delineated a lower efficacy and higher rate of side effects for deep TMS compared with surface TMS machines (18). Fitzgerald P, et al., studied potential abnormal responses to rTMS in patients with schizophrenia and its relation to cortical inhibition deficits. Low-frequency (1 Hz) rTMS was induced. Although participants showed similar motor cortical excitability at baseline, rTMS did not reduce cortical excitability or increase the cortical silent period in the patient population, regardless of whether they were medicated or not, while it did decrease in healthy controls. Others utilized low-frequency (1 Hz) rTMS to explore its effect on auditory hallucination in schizophrenia patients (19). Homan et al. concluded that only patients with higher superior temporal gyrus perfusion benefited from rTMS as an additional therapy to their ongoing treatment (15). In a double-blind randomized controlled study, Lee et al. reported that a 10-day daily low-frequency (1 Hz) rTMS over the left or right temporoparietal cortex will significantly reduce auditory hallucination in schizophrenia patients.

In contrast, in a large randomized controlled trial (16). Slotema CW, et al., reported no significant changes in the severity of general psychotic symptoms (eg, auditory hallucination) between the 3 groups of functional magnetic resonance image–guided (to the site of maximum hallucinatory activation) low-frequency rTMS, left temporoparietal rTMS, and sham rTMS (20).

CONCLUSION

It appears that use of TMS for physiologic assessment or treatment of schizophrenia is beneficial. To establish a robust conclusion and resolve controversies however, further studies are needed. In summary, from the clinical perspective, it is generally believed that deep TMS stimulates a deeper and larger area and therefore takes less time to achieve the same results compared with rTMS. In regard to treatment of schizophrenia symptoms, although many controversies exist in use and benefits of rTMS and deep TMS, it appears that use of low-frequency rTMS (1 Hz) and deep TMS benefits patients with schizophrenia by reducing auditory hallucination. Deep TMS (20 Hz) appears to improve both negative symptoms and cognitive deficits of schizophrenia when added as an additional treatment to antipsychotic medication. Based on this review, there is insufficient evidence to support or refute the use of TMS to treat symptoms of schizophrenia. Although some evidence suggests that TMS, and in particular temporoparietal TMS, may improve certain symptoms (such as auditory hallucinations and positive symptoms of schizophrenia) compared to sham TMS, the results were not robust enough to be unequivocal across the assessment measures used. There was insufficient evidence to suggest any added benefit with TMS used as an adjunctive therapy to antipsychotic medication.

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The Importance of Emotional and Cognitive States in Predicting Stigma among Patients with Epilepsy

Značaj emocionalnog i kognitivnog stanja u predikciji stigme kod pacijenata sa epilepsijom

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ABSTRACT

Introduction: epilepsy disrupts all aspects of life and often imposes a physical, psychological, and social burden on patients and their families. In addition to its direct impact on health, such as frequent seizures and the risk of injuries, epilepsy can lead to stigmatization and social isolation, further complicating daily functioning. Aim: to examine the predictive significance of happiness, depressive symptoms, and cognitive state assessment on the presence of stigma. Materials and methods: the study sample included 100 randomly selected patients of both sexes treated at the Epilepsy Outpatient Clinic of the Neurology Department, Clinical Center University of Sarajevo. All participants completed the Mini-Mental State Examination, the Beck Depression Inventory, and the Revised Epilepsy Stigma Scale. Additionally, a linear self-assessment of happiness was utilized. Results: the study included more women (55%) who were younger than the male participants (34.69%). Depression was negatively correlated with happiness (rho= -0.619, p = 0.0001) and cognitive state (rho = -0.361, p = 0.0001). The happiness of epilepsy patients, measured on a scale of 0–100, was positively correlated with cognitive status assessed using the Mini-Mental State Examination (rho = 0.552, p = 0.0001). This correlation was moderate in strength and positive. Conclusion: depressive symptomatology was present in 39% of the participants. Patients with preserved cognitive status exhibited lower levels of depression, underscoring the importance of mental health. The participants' happiness showed a positive correlation with cognitive functions. The findings of this study can inform the development of effective interventions aimed at reducing stigmatization and improving the emotional health of individuals with epilepsy, with a particular emphasis on social aspects and the need for adequate support.

Keywords: epilepsy, emotional health, cognitive abilities, stigma

SAŽETAK

Uvod: epilepsija remeti sve aspekte života, i često predstavlja fizičko, psihičko i socijalno breme kako oboljelim, tako i njihovim porodicama. Pored direktnog uticaja na zdravlje, kao što su učestali napadaji i rizik od povreda, ova bolest može dovesti do stigmatizacije i izolacije, što dodatno otežava svakodnevno funkcionisanje. Cilj: ispitati prediktivni značaj osjećaja sreće, prisutne depresivnosti i procijene kognitivnog stanja na prisutnost stigme. Materijali i metode: uzorak ispitivanja obuhvata 100 ispitanika, oba spola, liječenih u Dispanzeru za epilepsije Klinike za neurologiju Kliničkog Centra Univerziteta u Sarajevu koji su uključeni metodom slučajnog odabira. Svi ispitanici su ispunili Mini Mental Status Test i test na depresiju koristeći Bekovu skalu depresivnosti i revidiranu Epilepsija Stigma Skalu. Također, korištena je linearna samoprocijena za osjećaj sreće. Rezultati: istraživanje je obuhvatilo više žena (55%) koje su bile mlađe od muške populacije (34,69%). Depresivnost je imala negativnu korelaciju sa srećom (rho=-0,619, p=0,0001) i kognitivnim stanjem (rho=-0,361, p=0,0001). Sreća ispitanika sa epilepsijom mjerena skalom sreće (0-100) je u korelaciji sa kognitivnim stanjem mjerenim uz pomoć Mini Mental Skale, rho=0,552, p=0,0001. Korelacija je srednje jaka i pozitivna. Zaključak: sa depresivnom simptomatologijom bilo je 39% ispitanika. Ispitanici sa očuvanim kognitivnim statusom su imali niži nivo depresije, što ukazuje na važnost mentalnog zdravlja. Osjećaj sreće ispitanika pokazuje pozitivnu korelaciju s kognitivnim funkcijama. Rezultati ove studije mogu poslužiti za razvoj učinkovitih intervencija usmjerenih na smanjenje stigmatizacije i poboljšanje emocionalnog zdravlja osoba s epilepsijom, s posebnim naglaskom na socijalne aspekte i potrebnu podršku.

Ključne riječi: epilepsija, emocionalno zdravlje, kognitivne sposobnosti, stigma

INTRODUCTION

Epilepsy can be defined as a paroxysmal disorder of central nervous system function that is recurrent, stereotypical, and associated with synchronized neuronal discharges, termed epileptic seizures (1). The median prevalence of epilepsy in developed countries is 5.8/1,000, while in developing countries it reaches up to 15.4/1,000 (2,3). The incidence is higher among young children and the elderly. The greater prevalence in developing countries is attributed to inadequate patient care due to healthcare limitations

and the higher frequency of infections (4). Epilepsy is a significant public health issue, accounting for 0.5% of the global health burden, positioning it as a prevalent and impactful neurological disorder that substantially affects global population health (5).

What makes epilepsy particularly challenging to manage is the coexistence of physical and cognitive impairments with psychiatric disorders, which impose a significant burden on patients, their families, and society (6). Depression and anxiety are the most common psychiatric disorders among epilepsy patients. Historically, psychiatric disorders were thought to result from difficulties adapting to this chronic and highly stigmatized disease. However, it is now recognized that there is a bidirectional relationship between epilepsy and psychiatric disorders, particularly depression (7).

The development of depression in individuals with epilepsy is influenced by psychosocial factors, including:

a) Lack of acceptance and poor adaptation to epilepsy;
b) Stigma associated with the diagnosis of epilepsy;
c) Sudden and recurrent loss of control over one's life due to unexpected seizures;
d) Lack of social support and the necessity for significant lifestyle adjustments, such as relinquishing driving or changing jobs (8).

Due to insufficient awareness about epilepsy, patients may not recognize their condition, and many refrain from seeking medical assistance out of fear of negative repercussions for their employment or career advancement. Studies on various forms of stigma among epilepsy patients have identified multiple factors associated with stigma (9,10).

The unique challenge of epilepsy lies not only in the severity and frequency of seizures but also in numerous psychosocial issues, restrictions, and limitations that, at certain stages of the disease, may disrupt the quality of life more than the disease itself, adding a significant psychosocial dimension to epilepsy (11).

AIM

The aim of this study was to examine the predictive significance of happiness, depressive symptoms, and cognitive state assessment on the presence of stigma. Investigating these relationships not only contributes to academic understanding of stigma but also has practical implications for the development of support programs and strategies to mitigate this social phenomenon.

MATERIALS AND METHODS

The study was conducted as a prospective, descriptive-analytical investigation, with elements of epidemiological research but primarily of clinical application, under the approval of the Ethics Committee of the Clinical Center of the University of Sarajevo. The sample included 100 randomly selected participants of both sexes, treated at the Epilepsy Outpatient Clinic of the Neurology Department, Clinical Center University of Sarajevo (CCUS). All participants completed the Mini-Mental State Examination and those scoring 27 or higher proceeded to the assessment of depression using the Beck Depression Inventory (BDI) and the Revised Epilepsy Stigma Scale (rESS). Happiness was also measured using a linear self-assessment scale, where participants rated their happiness on a scale of 0 to 100.

The inclusion criteria encompassed epilepsy patients of both sexes, aged 18 to 65 years, who provided informed consent. Exclusion criteria included individuals unable to independently provide information, those with prior depressive episodes or other psychiatric disorders, and those without adequate cognitive status to comprehend and complete self-assessment scales.

Statistical Analysis

Data were analyzed using SPSS and Microsoft Excel. Nominal and ordinal variables were evaluated using the χ^2 test, while continuous variables were assessed using the Kolmogorov-Smirnov test. Depending on the data distribution, various tests were employed, including the Mann-Whitney U test, Kruskal-Wallis test, and independent t-test. The reliability of the rESS was determined using the Cronbach's α coefficient, and correlations between variables were analyzed using Spearman's correlation coefficient. Statistical significance was defined as $\alpha = 0.05$. Results are presented through tables and charts.

RESULTS

Case one

The study included 100 participants diagnosed with epilepsy, of which 45% were male and 55% female. Although females were more represented, the difference was not statistically significant ($\chi^2 = 1.0$, $p = 0.317$).

Table 1 **Age Structure of the participants·**

	N	Mean	S.D	Min.	Maks.	Percentiles		
						25th	50th (Median)	75th
Age/years	100	37.46	11.89	18.00	65.00	29.00	36.50	46.00

The average age of participants (n=100) was 37.46 ± 11.9 years, with an age range of 29-46 years. The youngest participant was 18 years old, while the oldest was 65 years old (Table 1). Men were, on average, older (40.84 ± 11.9 years) than women (34.69 ± 11.2 years) in the study sample, and the observed difference was statistically significant (p = 0.009) (Figure 1).

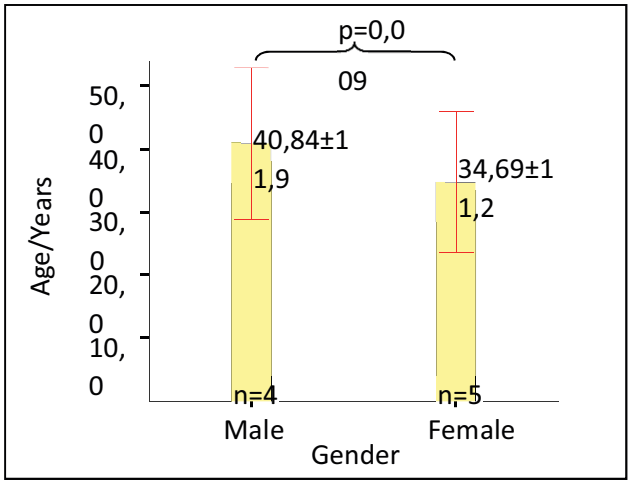


Figure 1 **Age distribution by gender of participants.**

Table 2 **Beck Depression Inventory (BDI).**

		N	Percent
BDI	No Depression 0-9	69	69,0%
	Mild Depressive State 10-15	5	5,0%
	Mild to Moderate Depressive State 16-19	10	10,0%
	Moderate to Severe Depressive State 20-29	9	9,0%
	Severe Depression 30-63	9	9,0%
	No Depression 0-9	7	7,0%
	Total	100	100,0%

According to the BDI scale, participants were categorized based on the degree of depression. The majority (69%) of participants showed no depression, while other categories were represented by 10% or less (Table 2).

The happiness of participants with epilepsy, measured using a happiness scale (0–100), was correlated with cognitive status assessed using the Mini-Mental State Examination (rho = 0.552, p = 0.0001). The correlation was moderate and positive (Figure 2).

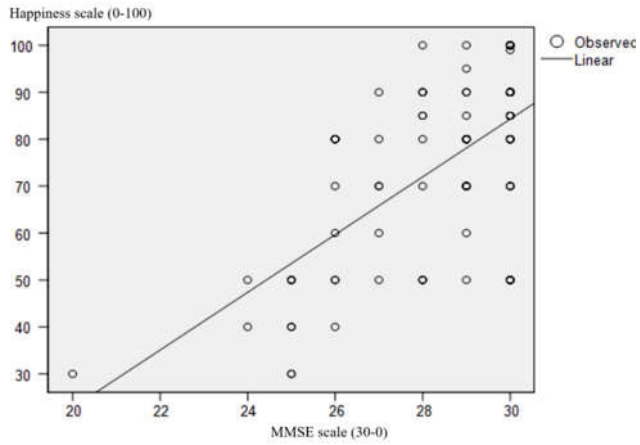


Figure 2 **Relationship between happiness and cognitive status in participants with epilepsy.**

Table 3 **Correlation between ress and depression (BDI), happiness, and cognitive status (MMSE)**

	Correlation Coefficient Spearman's rho	Beck Depression Inventory	Happiness Scale	MMSE
Revised Epilepsy Stigma Scale (rESS)	Spearman's rho	.136	-0,357	-0,526
	p	.177	.001	.0001
	N	100	100	100

The level of stigma among participants, measured using the rESS scale, showed a negative correlation with participants' happiness, measured using the happiness scale, with rho = -0.357 and p = 0.001. This correlation is moderate in strength (Table 3).

The level of stigma measured by the rESS scale was also correlated with cognitive status, assessed using the MMSE scale, with rho = -0.526 and p = 0.0001. This correlation is moderate and negative (Figure 3).

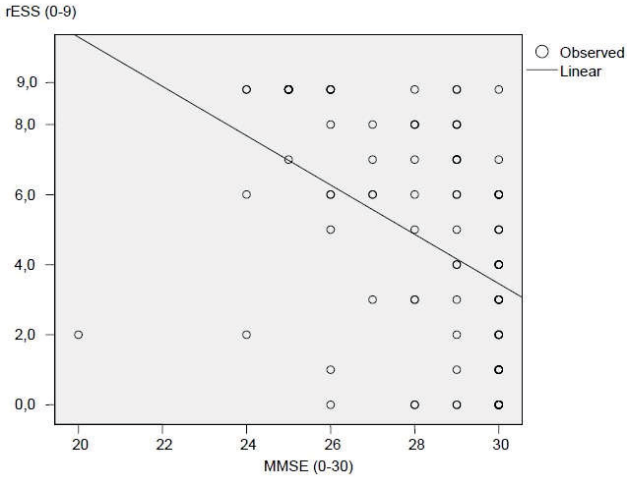


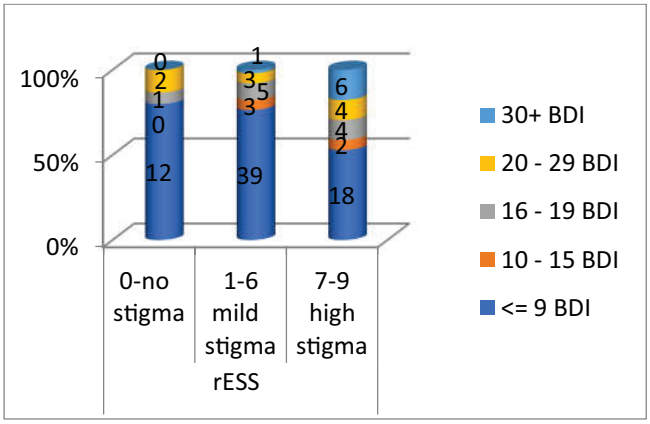
Figure 3 **Relationship between stigma and cognitive ability in participants with epilepsy.**

Within the Beck Depression Inventory (BDI) scores, 15 participants experienced no stigma. Of these, 12 (80.0%) had a score of ≤9, and none had a score in the range of 10 to 15. One participant (6.7%) had a score between 16 and 19, while 2 participants (13.3%) had a score between 20 and 29. Additionally, no participants had a score of ≥30.

Among 51 participants who experienced mild stigma, 39 (76.5%) had a score of ≤9, 3 (5.9%) had a score between 10 and 15, 5 (9.8%) had a score between 16 and 19, and 3 (5.9%) had a score between 20 and 29. One participant (2.0%) had a score of ≥30.

Out of 34 participants who experienced high stigma, 18 (52.9%) had a score of ≤9, 2 (5.9%) had a score between 10 and 15, 4 (11.8%) had a score between 16 and 19, and 4 (11.8%) had a score between 20 and 29. Additionally, 6 participants (17.6%) had a score of ≥30.

It was determined that the degree of depression and the level of stigma are significantly correlated, p=0.011 (Figure 4).



In the multivariate regression analysis using the Backward Wald method, it was determined that only the MMSE factor had a statistically significant impact among the examined factors. The results show a p-value of 0.0001, indicating very high significance, with a Beta coefficient of 5.114 (Table 4).

Table 4 **Multivariate predictive significance of happiness, depression, and cognitive abilities on stigma.**

		Unstandardized Coefficient		Standardized Coefficient			95% Confidence Interval for B	
		B	SDa	Beta	t	p	Lower Bound	Upper Bound
1	(Constant)	22.439	5.724		3.920	.0001	11.075	33.803
	Happiness scale	-.018	.025	-.114	-.738	.463	-.068	.031
	Beck Depression Inventory	-.017	.041	-.058	-.411	.682	-.098	.064
	MMSE	-.598	.194	-.390	-3.077	.003	-,984	-.212
	Age	.017	.027	.063	.627	.532	-.037	.071
2	(Constant)	21.425	5.143		4.166	.000	11.216	31.634
	Happiness scale	-.012	.019	-.074	-.619	.538	-.050	.026
	MMSE	-.586	.191	-.382	-3.064	.003	-.965	-.206
	Age	.018	.027	.068	.681	.497	-.035	.072
3	(Constant)	22.519	4.814		4.678	.0001	12.965	32.074
	MMSE	-.657	.152	-.428	-4.318	.0001	-.959	-.355
	Age	.020	.027	.073	.733	.466	-.033	.072
4	(Constant)	24.578	3.899		6.303	.0001	16.840	32.316
	MMSE	-.704	.138	-.459	-5.114	.0001	-.977	-.431

DISCUSSION

In a total sample of 100 participants, 45% were male, and 55% were female. Although females were more represented, the difference was not statistically significant ($\chi^2 = 1$). A similar gender distribution was observed in other international studies investigating stigma among people with epilepsy (12).

The average age of participants in this study was 37.46 ± 11.9 years, with an age range of 29-46 years. When comparing age and gender, a statistically significant difference was found (p = 0.009), favoring older age among males. These results are consistent with other studies examining the general population. The average happiness scale score (0-100) for this study's sample was 80 (range 50-90) (13).

When analyzing the relationship between happiness and the presence of depression, a moderately strong negative correlation was established, indicating that happier participants tended to have lower levels of depression and vice versa. This finding is also supported by previous studies. (14) The study analyzed the participants' current sense of happiness while completing the questionnaire but did not assess specific factors that might support that feeling.

In contrast to this study, Aguirre C, et al. identified factors influencing whether patients feel satisfied and happy in a U.S.

general population study. More adults with epilepsy in their study reported being satisfied with life. This study also used a scale from 1 to 10, compared to the scale from 1 to 100 used in this research. However, in their study, adults with epilepsy reported significant frustration in areas of professional advancement (e.g., dissatisfaction with education and life goals) and social interaction (e.g., dissatisfaction with familial and social life) (15).

Sokrab M, et al., also explored the general perception of quality of life in their sample using a different method. They applied a happy/sad visual analog scale. Despite the physical and socio-economic challenges associated with epilepsy, the overall perception of quality of life ranged from very happy to neutral for the entire group. They attributed this to the empathetic environment provided by large family networks typical of communities in Qatar, which mitigated negative societal influences. A similar observation could be made in this study, where the average happiness scale score was 80 on a 1-100 scale. It can be concluded that interpersonal relationships within the family are crucial for the subjective sense of happiness in individuals with epilepsy (16).

Cognitive function is defined as a higher brain function, encompassing the ability to program adaptive behavior, solve problems, retain information, and direct attention. Anxiety disorders and neuropsychological deficits in depression are associated with episodic memory dysfunction, psychomotor speed, processing speed, and executive function. Anxiety and depression can worsen cognitive functions impaired by epilepsy itself (17).

This study confirmed a significant negative correlation between depression and cognitive status, suggesting that participants with better cognitive function have lower levels of depression ($p = 0.0001$). These findings align with Qin SK, et al., who noted that depressive symptoms contribute to cognitive decline. (18) Similarly, the results comparing happiness and cognitive status also show a significant positive correlation ($p = 0.0001$). Happier participants tend to perform better on cognitive tests, supporting the findings of Tan JH, et al., (19). This study highlights that positive emotional states, such as happiness, can enhance cognitive functions.

According to the Beck Depression Inventory, this study categorized participants based on depression levels. The majority (69%) were without depression, while other categories ranged from 10% to less than 10%, from mild depressive states to severe depression. The results indicate that depression levels are not high but remain noteworthy. As depressive states deepen, additional psychiatric problems arise, leading to further exclusion of these patients from normal community functioning, creating a "vicious cycle" of stigma, depression, and poor psychosocial functioning. (20)

CONCLUSION

The results of the study showed a negative correlation between depression and cognitive status. Participants with normal cognitive status had lower levels of depression. The sense of happiness among participants showed a positive correlation with cognitive status. The findings of this study can serve as a foundation for developing interventions aimed at reducing stigmatization, improving emotional health, and generally enhancing the quality of life for individuals with epilepsy. Implementing support focused on emotional and social aspects can significantly contribute to reducing stigma and improving social inclusion for those affected.

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Comparison of Laparoscopic and Open Techniques in the Surgical Treatment of Complicated Appendicitis

Komparacija laparoskopskih i otvorenih tehnika u hirurškom tretmanu komplikovane upale slijepog crijeva

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ABSTRACT

Introduction: acute appendicitis (AA) is the most common cause of acute abdomen and appendectomy is the most common surgical procedure performed in emergency surgery. Open appendectomy has been a standard procedure for acute appendicitis for more than 100 years. Because of lack of consensus about the most appropriate technique, appendectomy is still being performed by both open and laparoscopic methods. However, in the last 20 years, after many studies, laparoscopic appendectomy has become a first line treatment for complicated appendicitis in many centers. Aim: to evaluate and compare the clinical outcome of laparoscopic(LA) versus open appendectomy (OA) in patients with complicated appendicitis regarding the postoperative morbidity, such as surgical site infection, intraabdominal infection, postoperative ileus, also to compare the length of hospital stay, operative time, time for flatus passage and readmission/reoperation rate. Materials and methods: this prospective randomized clinical study was conducted at the Clinic of General and Abdominal Surgery of the Clinical Center University of Sarajevo in the period from April 2021 to April 2024. The study included 60 patients with the diagnosis of perforated appendictis, who met the predefined inclusion and exclusion criteria and were randomly allocated into two equal groups: 30 patients operated by laparoscopic appendectomy and 30 patients operated on by open appendectomy. Results: a total of 60 patients were included in the study. Groups were demographically similar and there was no statistically significant difference between the age structure and gender distribution. Average time of operation was the same in both groups ($p = 0.751$). Hospital stay was shorter in patients who underwent laparoscopic appendectomy ($p<0.05$). Statistically significant difference was found in case of hospital stay in days ($p<0.05$) in favor of shorter hospital stay of patients who underwent laparoscopic appendectomy. The comparison of postoperative complications indicate that there are statistically significant differences in occurrence of intra-abdominal infection and surgical/port site infections in term of lower frequency among patients underwent laparoscopic appendectomy ($p<0.05$). Although, there is lower number of postoperative ileus cases in LA group than OA group, there is no statistically significant difference. Conclusion: the treatment of complicated appendicitis by laparoscopic appendectomy in comparison to open approach surgery provides a better result in terms of length of hospital stay, recovering time, and postoperative morbidity. In the treatment of complicated appendicitis, laparoscopic appendectomy can be applied as the first-line treatment.

Keywords: acute appendicitis, laparoscopic appendectomy, open appendectomy

SAŽETAK

Uvod: akutni appendicitis je najčešći uzrok akutnog abdomena i apendektomija je najčešća urgentna hirurška procedura. Klasična apendektomija je standardni operativni tretman za akutni appendicitis već više od 100 godina. Zbog nedostatka konsenzusa o univezalnoj hirurškoj metodi, apendektomija se i dalje izvodi i klasičnom i laparaskopskim pristupom. Međutim, u posljednjih 20 godina nakon mnogih studija laparaskopska apendektomija postala je prvi izbor u liječenju kompliciranog appendicitisa u mnogim centrima. Cilj: uporediti ishode operativnog liječenja laparaskopske i klasične apendektomije kod slučajeva perforisanog apendicitisa u smislu postoperativog morbiditeta, kao što su infekcija operativne rane, formiranje intraabdominalnih apscesa, postoperativni ileus, također da se uporede dužina hospitalizacije, vrijeme trajanja operacije, vrijeme uspostavljanja pasaže crijeva i stopa ponovnog prijema/reoperacija. Materijali i metode: ova prospektivno randomizirana studija je provedena na Klinici za opštu i abdominalnu hirurgiju Kliničkog centra Univerziteta u Sarajevu u periodu od aprila 2021 do aprila 2024 godine. Studija je uključivala 60 pacijenata sa dijagnozom perforisanog apendicitisa, koji su zadovoljili prethodno definisane kriterije za uključivanje u studiju. Metodom randominizacije, pacijenti su podijeljeni u dvije skupine: jedna operisana laparaskopskom apendektomijom, a druga otvorenom apendektomijom. Rezultati: ukupno 60 pacijenata je bilo uključeno u studiju. Grupe su bile demografski slične i nije bilo statistički signifikantne razlike u dobnoj i starosnoj strukturi. Prosječno vrijeme operacije je bilo u obje grupe isto ($p=0,751$). Dužina hospitalizacije je bila signifikantno kraća kod

pacijenata koji su operisani laparaskopskom metodom (p<0,05). Upoređivanje postoperativnih komplikacija ukazuje da postoji statistički signifikantna razlika u pojavi intraabdominalnih infekcija I infekcija operativne rane u korist laparaskopske apendektomije (p<0,05). Iako je broj postoperativnih ileusa bio veći u grupi operisanih laparoskopskom tehnikom, ta razlika nije bila statistički signifikantna. Zaključak: tretman kompliciranih apendicitisa laparaskopskom apendektomijom u poređenju sa klasičnom tehnikom daje bolje rezultate u smislu dužine hospitalizacije, vremena oporavka i posoperativnog morbiditeta. U tretmanu kompliciranih apendicitisa laparaskopska apendektomija se može smatrati terapijom izbora.

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Ključne riječi: akutni appendicitis, laparaskopska apendektomija, klasična apendektomija

INTRODUCTION

Appendicitis, which was first described by Dr. Fitz in 1886, is a global disease (1). The average annual incidence of appendicitis in the past 15 years is reported to be ≤81–≥150 per 100,000 which varies by country. The incidence is 100/100,000 in North America (1).

Acute appendicitis is the most common abdominal emergency worldwide, and it is the most common cause of abdominal surgeries in all the age groups (2).

Approximately 7-10% of the general population develops acute appendicitis with the maximal incidence in the second and third decades of life (3).

Appendicitis has an overall lifetime risk of 8.6% in men and 6.7% in women (4,5).

A definitive preoperative diagnosis of acute appendicitis is still a challenge and a possibility of appendicitis must be considered in any patient presenting with an acute abdomen (6,7).

Complicated appendicitis includes acute appendicitis accompanied by perforation, peri-appendicular abscess or appendicular mass.

Since its first description by McBurney in 1894, open appendectomy has become the procedure of choice for acute appendicitis (8).

For more than a century, open appendectomy has been the gold standard for treating patients with acute appendicitis, but the efficiency and superiority of laparoscopic approach compared to the open technique is the subject of many studies nowadays (9,10).

With the introduction of minimally invasive endoscopic surgery, laparoscopic appendectomy, which was first introduced by Kurt Semm, a German gynaecologist in 1981 (11), has become increasingly popular and is claimed to be more safe and superior to open appendectomy in terms of hospital stay, postoperative pain, wound complications, diagnostic abdominal exploration, return to normal activities and cosmetic result (12,13).

AIM

The aim of our study was to compare outcomes of open versus laparoscopic appendectomies. We focused on postoperative morbidity, including surgical site infections (SSI), intraabdominal infections, postoperative ileus, length of hospital stay, mean operative time, time to first flatus passage and readmission/ reoperation rate.

MATERIALS AND METHODS

Patients and study design

We conducted a prospective-retrospective study involving 60 patients who underwent either open or laparoscopic surgery for complicated appendicitis at the Clinic of General or Abdominal surgery, Clinical Center University of Sarajevo. Data and clinical outcomes were retrospectively collected from hospital archives for patients treated between April 2021 and April 2024. Informed consent was obtained after providing detailed information on the potential risks, benefits and complications of both surgical approaches. Patients aged 18 to 76 years, of both gender were randomly assigned to one of the two surgical techniques through a sealed envelope method. Demographic data were systematically recorded throughout the study. Ethical approval was obtained from the Local Ethical Committee and the study adhered to the principles outlined in the Declaration of Helsinki. The primary objective was to compare postoperative outcomes and morbidity between open and laparoscopic appendectomies for complicated appendicitis.

Diagnosis was primarily based on clinical examination, supported by laboratory test, ultrasound (US), and computed tomography (CT) scans. Common symptoms included periumbilical pain migrating to the right iliac fossa, nausea, anorexia and fever. Key clinical signs included pyrexia, localized tenderness in the right iliac fossa, muscle guarding and rebound tenderness. Additional diagnostic signs such as Poiting sign, McBurney's sign, Rovsing's sign, rebound tenderness (Release sign), Psoas sign and Obturator sign were also assessed to aid in the clinical diagnosis.

Laboratory investigations included a complete blood count (showing neutrophilic leukocytosis), routine urine analysis and microscopic examination to rule out urinary tract infections (UTIs). In females of reproductive age, a pregnancy test and β-HCG levels were measured. Ultrasound of the abdomen was routinely preformed and a CT scan of the abdomen and pelvis was conducted in selected cases. Once the diagnosis was confirmed, patients were prepared for surgery under general anesthesia. Preoperative management included the administration of antibiotics and resuscitation. Surgery was carried out as soon as an operating room became available. Both laparoscopic and open appendectomy procedures were performed under general anesthesia with the patient in the supine position. For the open appendectomy a McBurney incision was utilized in nearly all cases, involving a muscle-splitting approach in the right lower quadrant. Irrigation was performed for both laparoscopic and open appendectomies to minimize infection risk.

In both groups, closed aspiration drainage was used. The drain was typically removed one day after surgery if the drainage bag was empty. The nasogastric tube and urinary catheter were removed on the first postoperative day.

Analgesics were administered regularly throughout the hospital stay and a clear liquid diet was introduced once peristalsis resumed, with gradual advancement of the diet following the passage of flatus and based of the patient's tolerance. Intravenous antibiotics were continued for several days postoperatively and patients were discharged with a prescription for oral antibiotics to complete a 7- day course. In most patients the antibiotic regimen included a second-generation cephalosporin and metronidazole for 7 days, while a few patients received a 10 day course. Perioperative complications were defined as bleeding, iatrogenic injury, and enteric leakage. Postoperative complications included postoperative ileus, port/surgical

site infections (SSI) and intraabdominal infections. Additional outcomes evaluated included the operative time (measured in minutes), time to passage of flatus (measured in hours), and length of hospital stay (measured in days). The operative time was defined as the interval from the initial skin incision to the final skin closure, excluding the time for anesthesia and preparation.

Postoperatively regular abdominal auscultation for bowel sounds was performed to assess bowel sounds. A clear liquid diet was initiated once bowel sounds were audible. The diet was advanced to regular food once the patient tolerated the liquid diet and passage of flatus was confirmed. Wound infections were characterized by the presence of purulent drainage from the surgical site, accompanied by erythema and warmth at the wound margins. Paralytic ileus was defined as the failure of bowel sounds to return within 12 after surgery, while prolonged postoperative ileus was defined as the absence of bowel peristalsis within 72 hours postoperatively. Patients were discharged once they tolerated a regular diet, remained afebrile for 24 hours and met other clinical discharge criteria. Patients were discharged between the 2nd and 7th postoperative day. All surgeries were performed by the same surgical team. Upon discharge, patients were scheduled for weekly follow-up consultations. Stitches were removed at the first follow-up appointment. Long-term outcomes were monitored through a 3- month postoperative follow-up, during which the presence or absence of wound-related complications, postoperative issues (such as intraabdominal fluid collection) and the need for readmission were documented.

RESULTS

Statistical analysis

Results are presented in form of charts/graphs by number of cases and percentage, mean, standard deviation and range depending of data type.

Continuous variables do not meet the criteria of normal distribution according to the Shapiro-Wilk test and the nonparametric test, Fisher exact test and Mann-Whiney test, were used.

The results of the tests were considered statistically significant at the 95% confidence level, or with the p values below 0.05.

The analysis was performed using the statistical software for biomedical studies, MedCalc v13.0 (Antwerp, Belgium).

Table 1 **Sociodemographic data.**

			Type of surgery		Total
			Laparoscopic appendectomy (n=30)	Open appendectomy (n=30)	
Gender	Male	N	13	17	30
		%	43.3	56.7	50.0
	Female	N	17	13	30
		%	56.7	43.3	50.0
$\chi 2$=1,067; p=0,219					
Age	Mean±SD		34.73±13.00	38.80±18.11	36.77±15.76
	Range		21-76	18-84	18-84
Z=-0.607; p=0.544					

There was more female patients who underwent laparoscopic appendectomy and more male patients who underwent open appendectomy (17 : 13).

Mean age of the patients in total sample was 36,77±15,76 years, with slightly older patients who underwent open appendectomy - 38,80±18,11 years, than patient who underwent laparoscopic appendectomy.

Comparison of sociodemographic data, gender and age indicate that there is no statistically significant difference (p>0.05).

Table 2 **Comparison of intraoperative factors.**

			Type of surgery		Total
			Laparoscopic appendectomy (n=30)	Open appendectomy (n=30)	
Severely inflamed appendix with early mass formation	-	N	21	18	39
		%	70.0	60.0	65.0
	+	N	9	12	21
		%	30.0	40.0	35.0
$\chi 2$=0.659; p=0.417					
Gangrenous or perforated appendix with localized peritonitis	-	N	18	20	38
		%	60.0	66.7	63.3
	+	N	12	10	22
		%	40.0	33.3	36.7
$\chi 2$=0.287; p=0.395					
Generalized peritonitis	-	N	21	22	43
		%	70.0	73.3	71.7
	+	N	9	8	17
		%	30.0	26.7	28.3
$\chi 2$=0.082; p=0.500					

Comparison of intraoperative factors indicate that there is no statistically significant difference between open and laparoscopic appendectomy ($p>0.05$).

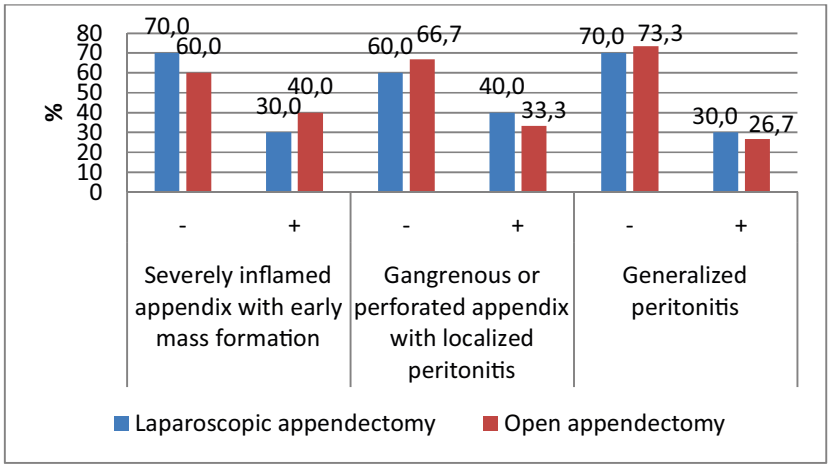


Table 3 **Comparison of operative time, time for flatus passage, and hospital stay.**

		Type of surgery		Total
		Laparoscopic appendectomy (n=30)	Open appendectomy (n=30)	
Operative time	Mean±SD	47.77±12.66	52.27±13.01	50.02±12.93
	Range	31.0-78.0	32.0-84.0	31.0-84.0
Z=-2.605; p=0.048				
Time for flatus passage in hours	Mean±SD	28.00±7.26	28.00±7.26	28.00±7.20
	Range	12.0-44.0	12.0-44.0	12.0-44.0
Z=0.000; p=1.000				
Hospital stay in days	Mean±SD	3.37±1.03	4.73±1.20	4.05±1.31
	Range	2.0-5.0	3.0-7.0	2.0-7.0
Z=-4.034; p=0.0001				
Total	N	30	30	60
	%	50.0	50.0	100.0

Although, there is a shorter mean operative time in LA group than in OA group there is no statistically significant difference. Time for flatus passage was the same.

Statistically significant difference was found in case of hospital stay in days ($p<0.05$) in favor of shorter hospital stay of patients who underwent laparoscopic appendectomy.

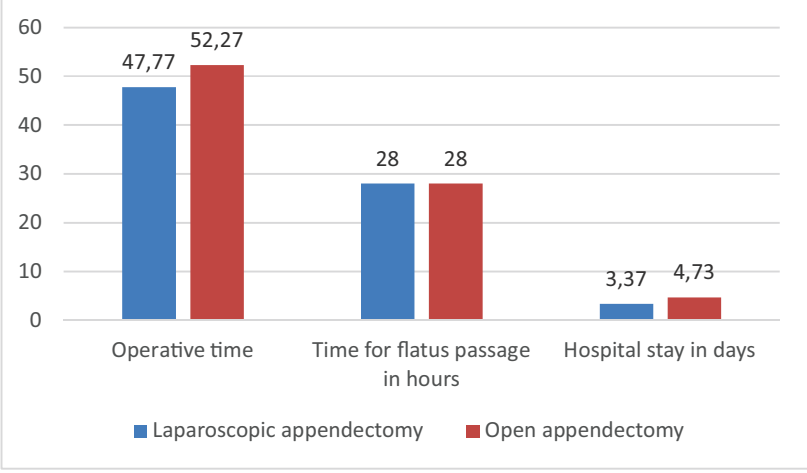
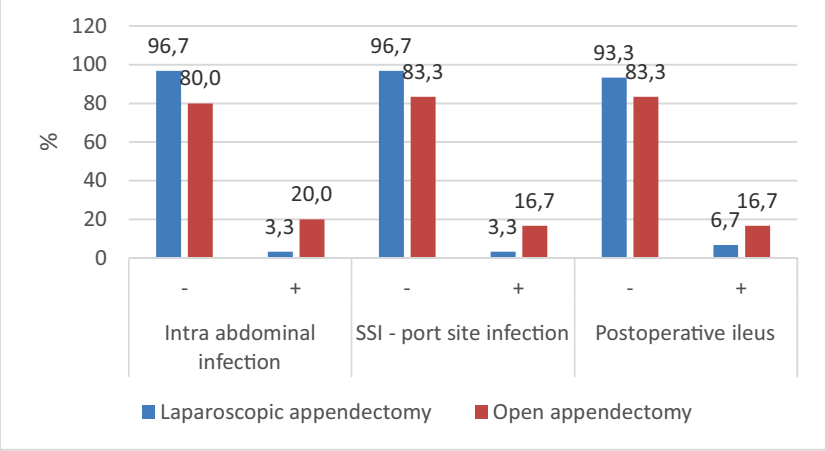


Table 4 **Postoperative complications**.

			Type of surgery		Total
			Laparoscopic appendectomy	Open appendectomy	
Intra abdominal infection	-	N	29	24	53
		%	96.7	80.0	88.3
	+	N	1	6	7
		%	3.3	20.0	11.7
$\chi 2$=5,043; p=0,041					
SSI - port site infection	-	N	29	25	54
		%	96.7	83.3	90.0
	+	N	1	5	6
		%	3.3	16.7	10.0
$\chi 2$=4,963; p=0,047					
Postoperative ileus	-	N	28	25	53
		%	93.3	83.3	88.3
	+	N	2	5	7
		%	6.7	16.7	11.7
$\chi 2$=2,456; p=0,082					
Total		N	30	30	60
		%	100.0	100.0	100.0

The comparison of postoperative complications indicate that there are statistically significant differences in occurrence of intra-abdominal infection and SSI-port site infections in term of lower frequency among patients underwent laparoscopic appendectomy ($p<0.05$).

Although, there was a lower number of postoperative ileus cases in group of patients who underwent laparoscopic appendectomy, there was no statistically significant difference.



There were no readmission/reoperation cases in this study.

DISCUSSION

Mariage M, et al. describe perforated appendicitis as a feature of complicated appendicitis (14). A recent analysis of three randomized-control trials by Quah GS, et al. showed that whilst open appendectomy is currently the more common procedure performed for complicated appendicitis due to a reported higher incidence of intra-abdominal abscess (IAA) formation with laparoscopic appendectomy, the latter demonstrates a statistically significant decrease in death and disability (15). Laparoscopic appendectomy is also associated with a shorter length of hospital stay and better outcomes when contrasted with open appendectomy. They also found similar statistics of IAA between both groups. The researchers subsequently recommended laparoscopic appendectomy for complicated appendicitis.

This is similar to our findings that showed statistically significant benefit of laparoscopic appendectomy over open appendectomy in terms of outcomes and postoperative morbidity. Incidence of IAA, SSI and length of postoperative stay were statistically significant lower in the laparoscopic appendectomy group.

Horvath P, et al. conducted a retrospective study on 1,762 patients comparing laparoscopic appendectomy to open appendectomy for perforated appendicitis (16). They found that while postoperative complications like SSIs only occurred in patients

who underwent open appendectomy, the occurrence of IAA in patients who underwent laparoscopic appendectomy was statistically significant with a p-value of 0.002. They also reported shorter hospital stay after laparoscopic appendectomy. In this study, it was advised that surgeons keep in mind the steps that can be taken to reduce the formation of IAA such as irrigations, handling of the stump, and use of endo bags (16).

In our study occurrence of IAA was not higher in patients who underwent laparoscopic appendectomy.

In a meta-analysis conducted by Athanasiou C, et al., it was demonstrated that, as repetitively evidenced in the literature, SSIs, length of hospital stay, and early tolerance of oral diet were all significantly lower after laparoscopic appendectomy (17). Like Quah GS, et al. (15), they found no statistically significant difference between incidences of IAA after both procedures. Thus, it was reported that laparoscopic appendectomy has better outcomes for morbidity (17).

Yu MC, et al. also produced results in their meta-analysis and systematic review favoring laparoscopic appendectomy over open appendectomy in complicated appendicitis. IAA was also seen to not increase with laparoscopic appendectomy in this study (18).

Wullstein C, et al. retrospectively analyzed laparoscopic appendectomy vs. open appendectomy for perforated appendicitis and found laparoscopic appendectomy better in terms of patient outcomes (19). Ball CG et al. recommended laparoscopic appendectomy as the procedure of choice for complicated appendicitis (20).

Mulita F, et al. retrospectively observed the outcomes of laparoscopic appendectomy and open appendectomy on patients suffering from both complicated appendicitis and UA and found that regardless of the type of appendicitis or the technique of appendectomy the incidence of IAA does not significantly vary. They advised the preference of laparoscopic appendectomy over open appendectomy because of the benefits that minimally invasive laparoscopy provides (21).

In our study, the statistically significant benefits of laparoscopic appendectomy over open appendectomy were reduced SSIs, reduced IAA and lower incidence of paralytic ileus, earlier discharge/shorter hospital stay.

Our study, in light of the literature, suggests that laparoscopic appendectomy is preferable over open appendectomy in terms of outcomes and postoperative morbidity. Nonetheless, the scope of this study does not facilitate a more in-depth analysis and further research is needed in order to impact policies.

CONCULSION

The present study revealed that the laparascopic appendectomy have more favorable outcomes than the open appendectomy. Therefore, in the light of current evidence and the literature review we can conclude that laparoscopic appendectomy can be safely adopted as the first line treatment of the perforated appendix.

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Complexity of Distinction between Psychotic and Obsessive-Compulsive Symptoms - Case Report

Kompleksnost distinkcije psihotičnih i opsesivno-kompulzivnih simptoma - prikaz slučaja

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ABSTRACT

Introduction: the intricate relationship between obsessive-compulsive and psychotic symptoms had been acknowledged since the early stages of psychiatric works. Recent meta-analysis suggests a prevalence of 24% of comorbidity of obsessive-compulsive disorder and psychotic disorders. Both disorders are characterized by disruptions in thoughts and behaviors, though the crucial distinction seems to lie in insight. Aim: to present complexity of distinction between psychotic and obsessive-compulsive symptoms. Case Report: we present a case of a 28-year-old female patient with positive family history for psychiatric illnesses. Through numerous examinations and check-ups, as well as two in-hospital admissions, the patient presents various symptoms of both psychotic and obsessive-compulsive kind in a complex and fluctuating clinical presentation. Due to the overlap of symptoms, an SSRI antidepressant was added to a treatment of antipsychotics and mood stabilizers, which lead to remission of both types of symptoms. Conclusion: the overlap of psychotic and obsessive-compulsive symptoms poses a difficulty for diagnosis and treatment, which highlights the requirement of an extensive and detailed approach.

Keywords: comorbidity, fluctuating clinical picture, overlapping symptomatology

SAŽETAK

Uvod: isprepletenost psihotične i opsesivno-kompulzivne simptomatologije je uočena još u ranom razvoju psihijatrije kao nauke. Nova meta-analiza pokazuje prevalencu od 24% komorbiditeta opsesivno-kompulzivnog poremećaja i psihotičnih poremećaja. Oba poremećaja su karakterizirana izmjenama psihičke funkcije mišljenja i ponašanja, ali krucijalna distinkcija leži u sposobnosti uvida. Cilj: prikazati složenost u razlikovanju psihotičnih i opsesivno-kompulzivnih simptoma. Prikaz slučaja: prezentujemo slučaj 28-godišnje pacijentice koja ima pozitivan psihijatrijski hereditet. Kroz veći broj kontrolnih pregleda i dvije hospitalizacije, pacijentica ispoljava širok spektar simptoma psihotičnog i opsesivno-kompulzivnog karaktera u kompleksnoj i fluktuirajućoj kliničkoj slici. Obzirom na preklapanje simptoma, dodat je SSRI antidepresiv u psihofarmakološki tretman koji se sastojao od antipsihotika i stabilizatora raspoloženja, što je dovelo do remisije obje vrste simptoma. Zaključak: preklapanje psihotičnih i opsesivno-kompulzivnih simptoma predstavlja poteškoću u dijagnostici i tretmanu, pri čemu se naglašava važnost detaljnog pristupa pacijentu.

Ključne riječi: komorbiditet, fluktuirajuća klinička slika, preklapanje simptomatologije

INTRODUCTION

It is now a widespread attitude that psychiatry is a spectrum of disorders and that it is often difficult to determine whether certain clinical presentations are comorbidities or different presentations of one disorder. The relationship between psychotic symptoms and obsessive symptoms has been recognized a long time ago, ever since the early 20th century, including works of Kraepelin and Bleuler who described both psychotic and obsessive-compulsive disorders. They emphasized the importance of a thorough distinction between these symptoms in order to establish an adequate diagnosis (1). The dominance of Freudian psychoanalysis among psychiatrists included a belief that obsessive-compulsive symptoms actually served as a defense mechanism against psychosis (2).

The main overlap between obsessive-compulsive and psychotic symptoms lies in disruptions in thoughts and behaviors. OCD is a disorder thoroughly explained through the synergy of obsessive thoughts and compulsive behaviors. On the other hand, psychotic disorders are characterized by the existence of delusional beliefs and delusional repetitive behaviors. It can often be very difficult to distinguish obsessions from delusions, and compulsions from delusional repetitive behaviors. The main difference appears to be insight (3).

Obsessions are understood to be thoughts which the patient recognizes as being their own. They are usually described to be of intrusive nature. The patient recognizes them as incorrect and inadequate, excessive and unreasonable, which leads to attempts of resisting them. Still, the patient has an intense fear the thoughts would become true and therefore the resistance is usually

unsuccessful. All of this leads to severe anxiety. Even though there are variants of OCD which include only obsessive thoughts, most clinical presentations include compulsive behaviors whose main goal is to temporarily neutralize intrusive, obsessive thoughts, images or impulses. The patients are aware of the futility of the actions, but still succumb to them due to the temporary relief of the pressure caused by intrusive thoughts; yet, the distress continues with progression of time.

Delusions, as seen in psychotic disorders, are recognized usually as thoughts of the patient's internal origin, with the exception of the phenomenon of thought inserting. Unlike obsessions, patients are convinced their delusions are truthful and they use them as a basis for integration of a whole belief system. Patients have no insight in their condition. Often, in cases of unpleasant delusions, patients can experience distress, which differs from distress caused by obsessions as that kind of distress derives from the insight that their obsessions are not valid and the inability to resist them. Unlike compulsions, delusional repetitive behaviors are not meant to invalidate delusions but rather to accompany them and achieve harmonization of delusions and delusional behaviors, which are perceived as appropriate, reasonable and justified (4).

AIM

The aim of this paper was to present complexity of distinction between psychotic and obsessive-compulsive symptoms.

CASE REPORT

A 28-years old female patient, living with her father and sister, was referred to Clinic of Psychiatry of the Clinical Centre University of Sarajevo due to persisting symptoms of obsessive-compulsive disorder (OCD) and psychotic symptoms. The patient had been in psychiatric treatment during the past three years, reported usage of olanzapine, paroxetine and alprazolam without any medical documentation as supporting evidence.

The patient reported positive family history for psychiatric illnesses as her sister had been treated for depression; her uncle was reportedly diagnosed with schizophrenia. She described her father as ,,showing symptoms of a psychiatric illness without being treated''. The patient's mother died three years ago which coincided with her first visit to a Psychiatrist.

On her first visit to a Psychiatrist at the Clinic of Psychiatry, the patient presented symptoms of impulsive actions and behavior, thoughts of hurting other people, thought echo, thought blocking, disruptions in sleep and focus. It was noticeable that the patient had a flattened affect. The patient reported feelings of anxiety due to the aforementioned symptoms and self-caused social isolation. All of these symptoms indicated a psychotic disorder which seemingly did not respond to treatment combination of olanzapine, paroxetine and alprazolam, which indicated a need for a change in psychopharmacotherapy. Olanzapine was discontinued, and the patient started with gradual discontinuation of paroxetine. Instead, low doses of clozapine, aripiprazole and oxcarbazepine were prescribed.

During the next three routine examinations in one-week intervals, doses of clozapine, aripiprazole and oxcarbazepine were gradually increased, and on the third check-up, a low dose of haloperidol was added. The patient presented a persistence of occasional thoughts of impulsive reactions and violence towards other people and a fear of hurting other people. On the other hand, symptoms of thought blocking were gradually but incompletely reduced, as well as troubles with focus on everyday activities, sleeping, appetite and overall mood. We could interpret this improvement as an effect of antipsychotic treatment, and better mood could be a result of decreased anxiety due to symptom reduction.

Two days after the last examination, the patient was admitted to Clinic of Psychiatry, Intensive Care Unit, due to worsening of symptoms which include occasional thought blocking, thoughts of anxiety and worrying about her own health which border on delusional, disruptions in sleep, appetite, will and social relationships, depressed mood and anxiety, all of this leading to her experiencing suicidal ideations without a defined plan.

During her hospitalization, the patient spoke of violent, intrusive, uncomfortable thoughts which she usually recognized as her own, but ones she could not resist from thinking, although she managed not to act in those violent ways towards other people. This could be interpreted as obsessive thoughts in OCD. Occasionally she perceived said thoughts to be ,,coming to her from her surroundings'', which could be interpreted as input of thoughts of the delusional kind which corresponds to a psychotic process. She had a fear of red color, associating the color with feelings and thoughts of violence and danger, avoided wearing clothes in that color out of fear it would cause intrusive thoughts of violence which she said were not her own, and had a fear of receiving energy of other people who, before her, wore the same hospital slippers as she did. It was difficult to distinguish whether fear of the red color was an obsession or a delusional belief, which would mean that not wearing red clothes would either be a compulsion or a behavior caused by a delusional belief. The patient herself was not sure where her fear of the red color originated from or whether it was justifiable or not. This could be interpreted as an overlap between obsessive-compulsive and psychotic symptoms. During this time, she was obsessively writing down everything she heard from doctors and medical staff, explaining that that was her way of trying to help herself, which showed that she had certain insight towards her illness and desperately wanted to get better. Routine laboratory examinations showed no deviations apart from hyperprolactinaemia which was interpreted as iatrogenic. Psychological tests showed obsessive ruminations which were affirmed in the course of a psychotic state including thought blocking, extreme anxiety and fear, slowed thought process, confusion, damaged attention and focus. Psychopharmacotherapy was titrated up to the patient's discharge from hospital treatment to doses of clozapine of 500 mg per day, aripiprazole 20 mg per day, and oxcarbazepine 600 mg per day. Haloperidol was discontinued. She was discharged in initial remission.

The patient regularly went to her routine check-ups with a fluctuating clinical presentation with persistent intrusive, uncomfortable and egodystonic thoughts which interrupted her overall functioning, caused her feelings of anxiety leading up to social phobia due to her fears of hurting other people. There appeared to be a reduction in symptoms which manifested as psychotic in the earlier period, and her insight was intact. This was interpreted as a positive effect of psychopharmacotherapy where doses of clozapine and aripiprazole were titrated, but her clinical presentation showed there was a need for treatment focused on the persistent symptoms which were now evaluated as obsessive.

A month after her last check-up, the patient was for the second time admitted to the Clinic of Psychiatry, Intensive care unit,

due to intrusive, obsessive thoughts of auto-and heterodestructivity. During this hospitalization, there was a fluctuating clinical presentation including a fear of „being possessed by the devil while smoking cigarettes" and fear of her cigarettes containing marijuana, which she ruminated upon after being told that information by a friend, which was interpreted as an overlap of obsessive-compulsive and psychotic symptoms. Psychotic symptoms were significant in the domain of the patient's affect which was flattened, and occasional disruptions in her perception including auditory hallucinations of „someone calling out her name". She also presented obsessive, intrusive thoughts of self-harm and hurting other people, and intrusive thoughts of speaking curses and foul language, thoughts of egodystonic and obscene sexual acts.

Routine laboratory examinations showed no deviations apart from hyperprolactinaemia which was interpreted as iatrogenic as an MRI was performed which showed no signs of pituitary microadenoma.

During her hospitalization, we introduced sertraline in therapy, and afterwards the patient reported a significant decrease in obsessive and intrusive thoughts. Sertraline was titrated up to dose of 150 mg per day. We also decreased the dose of clozapine to 75 mg per day and increased the dose of aripiprazole to 30 mg per day. With a significant reduction of both psychotic and obsessive-compulsive symptoms, the patient reached a remission of her illness and was subsequently discharged from the hospital.

The remission of the symptoms continued during her routine check-ups The patient regained her overall functionality, was able to socialize and find a job.

DISCUSSION

A recent meta-analysis showed that the estimated prevalence of comorbid OCD and psychosis was 12%, but that including both diagnosis and dimensional symptoms showed a prevalence of 24%. Insight is difficult to be assessed in some cases due to the fact the only proof we have of it is the patient's own words. Often patients cannot explain what they're experiencing, or the way th ey perceive their thoughts and behaviors. This can pose a difficulty in distinguishing obsessions from delusions, and compulsions from delusional repetitive behaviors. In other cases, there simply exists an overlap between the symptoms given the complex neurobiological nature of both disorders.

CONCLUSION

The intricate interplay between symptoms of psychotic disorders and OCD presents a difficulty in adequate psychiatric diagnosis and treatment. A comprehensive and thorough approach is needed in order to recognize the subtle, yet critical, distinctions between these two groups of symptoms, which is necessary in order to provide an adequate psychopharmacological treatment to the patient.

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Case report - pregnancy on a Caesarean Section Scar

Prikaz slučaja - trudnoća na ožiljku carskog reza

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ABSTRACT

Pregnancy on a previous caesarean section scar is a rare and potentially dangerous condition, where the fertilized egg is implanted in the myometrial defect of the previous scar. It is an ectopic pregnancy that accounts for 1% of all ectopic pregnancies, although the trend of increasing the number of caesarean sections leads to an increase in the number of newly discovered pregnancies on the scar. Exact management for a diagnosed pregnancy on a scar does not exist, and the treatment is based on a combination of surgical and medical treatment. This ectopic pregnancy is detected in the early weeks of pregnancy by ultrasound examination, with special attention in patients who have already had a cesarean section in the anamnesis. Clinical symptomatology varies from asymptomatic pregnancies with a positive pregnancy test to profuse vaginal bleeding accompanied by severe pain.

Keywords: scar pregnancy, Caesarean section, ectopic pregnancy.

SAŽETAK

Trudnoća na ožiljku predhodnog carskog reza je rijetko i potencijalno opasno stanje, gdje se oplođena jajna ćelija implantira na defektu miometrija ranijeg ožiljka. To je ektopična trudnoća koja čini 1% svih ektopičnih trudnoća, mada trend rasta broja carskih rezova dovodi u vezu i porast broja novootkrivenih trudnoća na ožiljku. Egzaktan menadžment za dijagnostikovanu trudnoću na ožiljku ne postoji, te je tretman zasnovan na kombinaciji hirurškog i medikamentoznog tretmana. Ova ektopična trudnoća se otkriva u ranim sedmicama trudnoće ultrazvučnim pregledom, sa posebnom pažnjom kod pacijentica koje su već imale carski rez u anamnezi. Klinički simptomatologija varira od asimptomatskih trudnoća sa pozitivnim testom na trudnoću, do obilnih vaginalnih krvarenja praćenih izrazitom bolnošću.

Ključne riječi: trudnoća na ožiljku, carski rez, ektopična trudnoća.

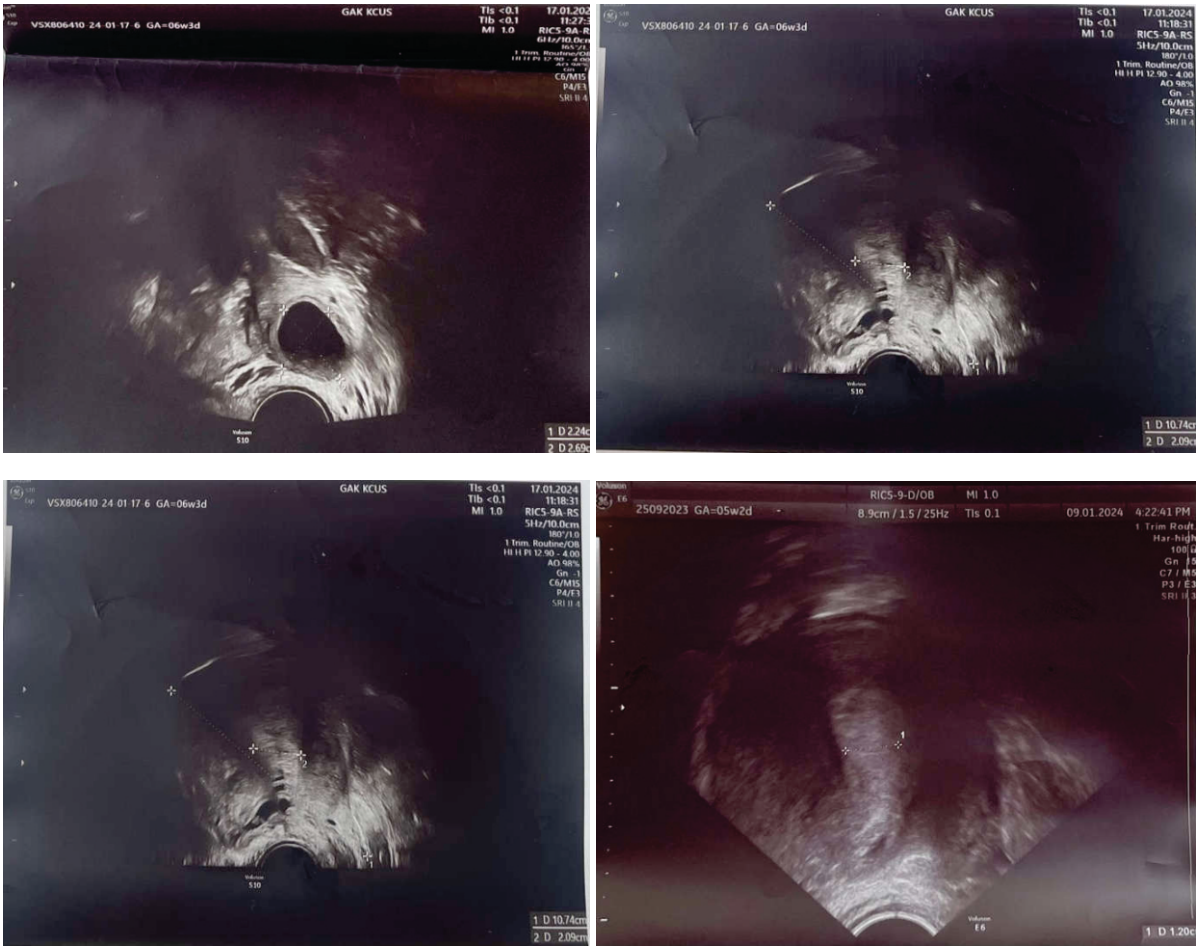
INTRODUCTION

The global increase in the number of caesarean sections is accompanied by an increased number of cases of early pregnancies on caesarean section scars. Looking at the period of 23 years, specifically from 2000 to date, the number of caesarean sections has doubled, and therefore the literature records a greater number of described cases of early pregnancies on the scars. Pregnancy on a caesarean section scar is an ectopic pregnancy, which results from the implantation of a fertilized ovum in the lower, most often isthmiocervical, part of the uterus, on a caesarean section scar. At the site of the cut surface of the uterus, a scar with a myometrial tissue defect is formed (1). The scar is most often located on the lower part of the front wall of the uterus, at the site of the initial incision. At that point, with a myometrial defect, there is incomplete healing of the tissue, which causes thinning or dehiscence of the remaining myometrium (2). Pregnancy on the scar can also be defined by the depth, i.e. the residual thickness of the myometrium in relation to the surrounding myometrium. We speak of a large defect when the thickness of the myometrium is 50-80% less than the surrounding myometrial tissue or when the residual thickness of the myometrium is less than 2.2 mm measured by TVUS (2,3). The first case of pregnancy on a scar was recorded in 1978. The incidence of scar pregnancies is increasing due to the increase in the number of primary cesarean sections and the decrease in vaginal deliveries after a previous cesarean section, and now accounts for 6.1% of all ectopic pregnancies (4). Guidelines on the exact treatment of pregnancy on a scar do not exist, and currently it is recommended to terminate the pregnancy in the first trimester, in order to reduce complications to a minimum (5). The diagnosis of pregnancy on the scar is based on the US examination in the first trimester of pregnancy. Clinically, it is asymptomatic and generally does not deviate from regular pregnancies. Sometimes mild, painless vaginal bleeding may occur in the clinical picture, or some patients may have pain in the lower abdomen. Differential diagnosis for any pregnancy in the first trimester, accompanied by pain, bleeding and a positive history of a previous caesarean section should exclude pregnancy due to a scar. The most common gestational age at which pregnancy on a scar is diagnosed is between the 5th and 16th weeks of pregnancy (6).

CASE REPORT

The patient reported due to absence of menstruation and determination of pregnancy. In the gynecological anamnesis, she mentioned two births, by caesarean section, myomectomy and appendectomy. She denied having abortions. At the time of examination, she was not bleeding and was generally in good condition. From the diagnostic findings of TVUS: uterus in AVF, endometrium approx. 12 mm, visible initial gestational bladder with a visible yolk sac of approx. 2.2 mm diameter in the projection of the scar, without a clearly visible embryonic echo (corresponding to amenorrhea (5+2)). The left ovary next to the uterus is 36 x 27

mm with the corpus luteum, while the right ovary distal to the uterus is 20 x 12 mm. There was no free fluid in the cavum Douglasii. Finding of Beta HCG 9259.10 (increasing). Considering the location of the pregnancy, all potential complications and the outcome of the pregnancy were explained to the patient, and with her consent, she was referred to an surgical council, with a proposal for curettage of the uterus and termination of the pregnancy. The Council approved the proposed procedure. The procedure was performed under TIV anesthesia, after disinfection of the operative field, the cervix was visualized with a speculum, and a uterine probe was introduced under ultrasound control, which determined the position and depth of the uterus and verified the existence of the fetus at the site of the scar (6+2 n.g.). With Hegars, the cervical canal was dilated up to number 6. After dilating the cervical canal, a vacuum was entered with an aspirator and a vacuum aspiration was performed. US checked the uterine cavum, which remained empty after the intervention, with no signs of implant tissue. The patient was discharged home the day after the intervention, in good general condition. She reported for a follow-up examination after 10 days, and she did not report any vaginal bleeding, the US findings confirmed that the uterine cavum was empty.



Figures 1, 2, 3, 4 **Transvaginal ultrasound image of the cavum of the uterus with an implanted embryo sac at the site of the previous caesarean section scar**.

DISCUSSION

There is insufficient information about the etiology of pregnancy at the site of the caesarean section scar. From the pathological aspect, its development is conditioned by the myometrial defect and the vascular network at the site of the defect (1,2). Wang J, et al in their study emphasized the importance and association of cesarean scar defects and preoperative factors. Perioperative factors include: the size of the incision on the uterus, indication for CS, length of labor, dilatation of the cervix before SC, closure technique, existing adhesions, and uterus in retroversion (7).

In a comparative study, Osser OV, et al talk about the relationship between residual myometrial tissue after vaginal delivery and caesarean section. The thickness of the residual myometrial tissue after a natural, vaginal delivery is approximately 11.6 mm, while the thickness of the same after a cesarean section varies from 8.3 mm, 6.7 mm, and even 4.7 mm, which again depends on the number of previous cesarean sections (8). This leads to a connection between the number of caesarean sections and a decrease in the thickness of the residual myometrial tissue on the scar, and therefore due to tissue defects to a potential increase in the number of pregnancies on the scar. Factors that determine the optimal choice of treatment

include the type of pregnancy at the scar, residual myometrial tissue, gestational age, serum Beta HCG level, presence or absence of fetal cardiac activity, hemodynamic stability, expertise of endoscopic methods teams, and the patient's desire for pregnancy and willingness to expose to risks. The decision to continue the treatment of pregnancy on the scar when it comes to pregnancies from IVF procedures, with long-term treated infertility should be viewed multidisciplinary and the best decision for the patient's life should be made (9).

A UK national cohort study pooled 86 early pregnancy assessments (EPAUs) and reported treatment outcomes for 92 patients with scar pregnancies. Success rate of conservative treatment 43%, 46% success rate for medical treatment and 96% for surgical treatment. The corresponding complication rates were 71% with conservative treatment, 60% with medical treatment, and 36% with surgical treatment (10). The non-surgical method of solving a pregnancy on a scar includes the following methods: the use of methotrexate, direct local embryocidal injection directly into the embryonic sac with continuous aspiration of the contents, and embolization of the uterine arteries. Methotrexate is given in uncomplicated cases with a gestational age of up to 8 n.g., when the Beta HCG level is less than < 5000 iu/ml (1). Surgical treatment includes: LPSC, HSC, laparotomy and curettage. The most common treatment modality for pregnancy on a scar is a combination of medicinal and surgical methods, with the consent, wishes and current condition of the patient.

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Conservative Treatment of Lateral Malleolar Fracture in 54-year Old Female with Bioactive Collagen Peptides

Konzervativni tretman preloma lateralnog maleola kod 54-godišnje žene uz bioaktivne kolagene peptide

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ABSTRACT

Introduction: isolated malleolus fractures are among the most common injuries that orthopedic surgeons encounter. Conservative treatment has shown excellent outcomes. Case report: this case report presented a case of a 54-year obese post-menopausal woman with left lateral malleolus fracture. She was treated conservatively with bioactive collagen peptides supplementation. Compared to the usual protocols recovery time was shortened, as the cast was removed 31 days after the injury, and she was able to walk with full weight-bearing 46 days after the injury. Conclusion: further studies are required to investigate benefits of collagen supplementation in fracture healing.

Keywords: malleolus, fracture, conservative, collagen, post-menopausal

SAŽETAK

Uvod: izolirani prelomi maleola su među najčešćim povredama s kojima se ortopedi susreću. Konzervativno liječenje je pokazalo odlične rezultate. Prikaz slučaja: u ovom prikazu prikazan je slučaj gojazne žene stare 54 godine u postmenopauzi sa prelomom lijevog lateralnog malleola. Liječena je konzervativno uz suplementaciju bioaktivnim kolagenaim peptidima. U odnosu na uobičajene protokole vrijeme oporavka je skraćeno, jer je gips skinut 31 dan nakon povrede, a 46 dana nakon povrede mogla je hodati uz puno opterećenje. Zaključak: potrebne su daljnje studije kako bi se istražile prednosti dodatka kolagena u zacjeljivanju preloma.

Ključne riječi: maleol, prelom, konzervativno, kolagen, postmenopauza

INTRODUCTION

Isolated lateral malleolus fracture represents one of the most common injuries. According to Weber classification, there are theree types of these fractures: type A - infrasyndesmotic fractures, type B - trans-syndesmotic, type C - suprasyndesmotic (1-4). In most cases, type A fracture can be treated conservatively. Type B fractures may or may not require open reduction and internal fixation (ORIF), depending on their stability. Type C fractures are inherently unstable and in most cases they require ORIF. When treated conservatively, cast is applied after the swelling has subsided and it is worn for minimum of 6 weeks until the bone has healed sufficiently. During this time, muscle atrophy and bone density loss occurs due to inactivity. Accelerating bone healing progress is therefore important to mobilize patient as soon as possible and to progress to full weight-bearing on injured leg. Recent studies have shown benefits of using bioactive collagen peptides in preventing osteoporosis in post-menopausal women, as well as the accelerated bone healing processes (5-9).

CASE REPORT

A 54-year-old female patient reported to the General Hospital Konjic Emergency Center after an injury to her left ankle, which had occured the night before. It was noted that patient was obese (BMI >30) and also in post-menopause. The left ankle was swollen and showed clinical signs of possible lateral malleolus fracture. X-ray was taken and it showed Weber A type of fracture in left lateral malleolus (Figure 1). According to the established protocol, conservative treatment was indicated and ankle splint was applied. Patient was given instructions and alongside thromboprofilaxis and painkillers she was prescribed bioactive collagen peptides (5g) and calcium-lactate (1.14 g) in the form of the single daily dose of powder. Afterwards she was sent home and instructed to report for the follow-up after 10 days.

Figure 1 **Initial X-ray of the left ankle showing Weber A type of lateral malleolus fracture.**

At follow-up 10 days after the injury, significant reduction of swelling was noticed. Also, patient reported that she tripped and fell, a day before the follow-up. Therefore, X-ray was taken (Figure 2). Slight dislocation of the fragment was noted and cast was applied. Patient was instructed to walk with crutches without wieght-bearing and continue using daily dose of bioactive collagen peptides (5g) and calcium-lactate (1.14 g), as well as the other previously prescribed medication.

Figure 2 **Left ankle X-ray 10 days after the injury.**

Next follow-up was scheduled two weeks after the last appointment, 24 days after the injury. Patient reported that she was feeling well and had no pain or any discomfort. Control X-ray was taken and it showed significant signs of fracture healing (Figure 3). Patient was instructed to continue previously prescribed medication and walk with cruthes without weight-bearing on injured leg.

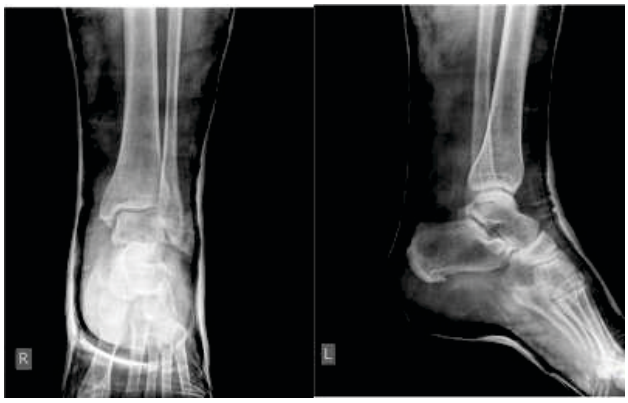

Figure 3 **Left ankle X-ray 24 days after the injury**.

After a week, patient checked in for follow-up. X-ray was taken and it showed completely healed fracture (Figure 4). Cast was removed and patient was instructed to continue using crutches and use limited weight-bearing up to 15 kg on the left leg, while also continuing using daily dose of bioactive collagen peptides (5g) and calcium-lactate (1.14 g).

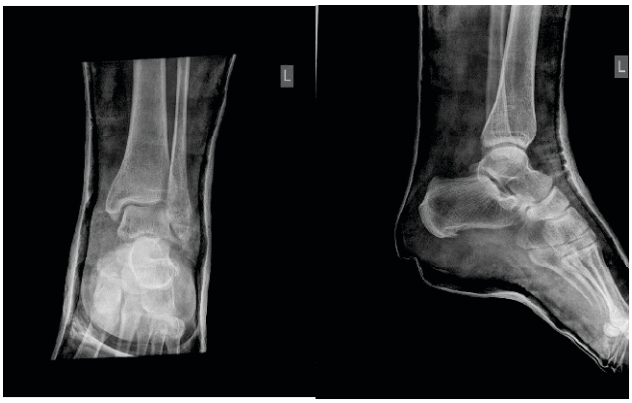

Figure 4 **Left ankle X-ray 31 days after the injury.**

At the follow-up examination, 6 days after the previous follow-up and 37 days after the injury, patient reported no pain or discomfort while walking with crutches. Weight-bearing limit was increased to 30 kg and continued use of daily dose of bioactive collagen peptides (5 g) and calcium-lactate (1.14 g) was prescribed.

Follow-up occured 9 days after the previous one, 46 days after the injury, where patient reported no discomfort or pain. Movement in the left ankle was painless and she was able to walk without using crutches. As a precautionary measure patient was instructed to use crutches with full weight-bearing for ten days and to gradually stop using them. She was also adviesd to continue using daily dose of bioactive collagen peptides (5g) and calcium-lactate (1.14 g) for period of total three months after the injury. Orthopedic treatment and rehabilitation were declared successful and no follow-up was scheduled.

DISCUSSION

Isolated stable lateral malleolus fractures are very common and are usually have good prognosis when treated non-operatively (4,10,11). Recent studies have shown significant benefits of using collagen peptides, especially in post-menopausal women, in regards to the bone mass density and reduced joint pain (7-9,12). Study published in 2022 by Seelemann CA, et al., has provided empirical evidence that collagen molecules denature as a result of fracture (13). Other recent studies have shown evidence of accelerated bone healing following bone fracture with collagen supplementation (5,6).

CONCLUSION

The patient was successfully treated conservatively after isolated left lateral malleolus fracture while using collagen supplementation. X-rays and clinical examination have shown accelerated bone healing and shortened rehabilitation time compared to the usual protocols. Further studies are required to investigate benefits of collagen supplementation in fracture treatment.

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Bilateral Total Hip Arthroplasty in 21 -Year Old Male with Developmental Dysplasia of the Hip

Bilateralna ugradnja totalne endoproteze kuka kod 21-godišnjeg muškarca sa urođenom displazijom kukova

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ABSTRACT

Introduction: developmental dysplasia of hip (DDH) is the main cause of total hip arthroplasties in younger patients. Case report: a 21-year old male presented with bilateral DDH of which the left side was classified as Crowe IV. The patient was treated with bilateral total hip replacement on Clinic of Orthopedics and Traumatology at Clinical Center University of Sarajevo in two separate acts eight months apart. Conclusion: postoperative follow-up showed that choice of treatment was correct and successful and allowed patient to have improved quality of life.

Keywords: Developmental dysplasia of hip, total hip replacement, Crowe IV, bilateral

SAŽETAK

Uvod: urođena displazija kuka (DDH) glavni je uzrok ugradnje totalne endoproteze kuka kod mlađih pacijenata. Prikaz slučaja: 21-godišnji muškarac javio se zbog bilateralne DDH od čega je lijeva strana klasificirana kao Crowe IV. Pacijent je tretiran obostrano ugradnjom totalne endoproteze kuka na Klinici za ortopediju i traumatologiju Kliničkog centra Univerziteta u Sarajevu u dva odvojena akta u razmaku od osam mjeseci. Zaključak: postoperativno praćenje pokazalo je da je izbor tretmana bio ispravan i uspješan, te je omogućio pacijentu da poboljšan kvalitet života.

Ključne riječi: urođena displazija kuka, endoproteza kuka, Crowe IV, obostrano

INTRODUCTION

Developmental dysplasia of hip (DDH) is complex disorder and it encompasses wide range of problems with hips including neonatal instability, acetabular or femoral dysplasia, hip subluxation and dislocation (1). It represents the most common cause of total hip replacement in younger people. Patients with DDH are usually diagnosed early on and proper treatment is administered. However in some cases, patients aren't treated in time and develop complications later in adulthood. It is estimated that DDH is the main cause of total hip replacement in young people (2). Nowadays, clinical screenings and imaging studies are conducted in newborns with risk factors for hip abnormalities (3). Usually classification systems by Crowe and Hartofildakidis are used for DDH (4). While the Crowe classification radiologically quantifies the degree of proximal displacement of the as a ratio of the size of the normal femoral head, the Hartofilakidis classification additionally describes anatomical deformities using intraoperative findings and correlates them with preoperative plain radiographs (4-6).

CASE REPORT

A 21-year-old male reported to the CCUS Orthopedics and Traumatology Clinic due to severely limited ability to walk. DDH in patient was confirmed several years ago, but patient wasn't treated for it at an early age. X-rays showed DDH in both hips, with left hip being stage IV according to Crowe classification (Figure 1). Due to the severity, surgical treatment was suggested, and the patient agreed to the implantation of a total endoprosthesis (TEP) in both hips. It was decided to implant TEP in right hip first, and after a period of time and sufficient recovery to plan implantation of TEP in left hip. Upon admission of the patient to the department, preoperative preparation was carried out, and the patient underwent operative treatment.

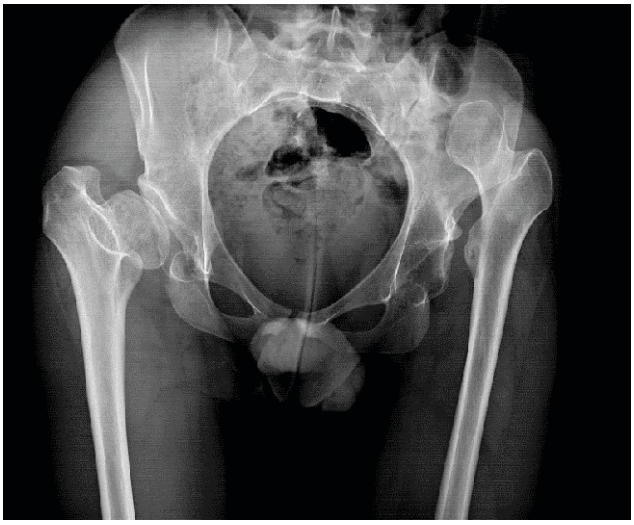

Figure 1 **Preoperative pelvis radiographic image.**

The operation was performed under general endotracheal anesthesia. The patient was placed in a dorsal decubitus position, and the lateral approach to the right hip was chosen as the surgical approach. Upon access to the neck of the femur, head was shown and sawed off. The head was removed, and then the acetabulum was accessed, which was then prepared for the acetabular component, after which it was placed with medical cement. Then the femur was accessed, and the canal was prepared for the stem, which was placed with medical cement. Intraoperatively, the size of the head of the endoprosthesis was determined, which was then placed on the stem. After the endoprosthesis was repositioned, clinical stability tests were performed, which showed that the placed prosthesis was stable. The wound was closed in layers with the placement of aspiration drainage. The operative course was smooth, as was the awakening from anesthesia, and the patient was transferred to the ward. The control X-ray showed the correct position of the endoprosthesis (Figure 2).

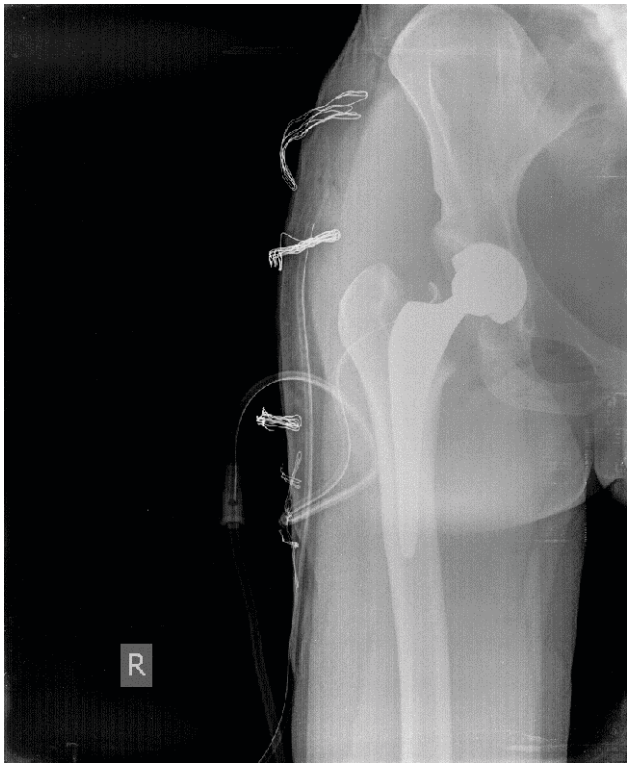

Figure 2 **Postoperative pelvis radiographic image.**

On the first postoperative day, the patient was included in a physical rehabilitation program. Aspiration drainage was removed on the second postoperative day. Because of the dysplasia and luxation of the left hip physical rehabilitation was limited.

On the seventh postoperative day, the patient was discharged from the KCUS Orthopedics and Traumatology Clinic for home treatment. During the control examination, on the fifteenth postoperative day, it was determined that the wound had healed properly, and that there were no signs of edema or inflammation, and the sutures were removed. Patient was directed to report to his local hospital for further treatment and also for spa physical treatment.

Follow-up examination at KCUS was made eight months after the first operation and X-ray of the pelvis was performed, which showed the proper position of the endoprosthesis and complete healing of the bone (Figure 3). Reduction of pain as well as the increased mobility was noted. It was deemed that healing and rehabilitation were complete and implantation of TEP in left hip was suggested, to which patient agreed. As before, upon the admission of the patient to the department, preoperative preparation was carried out, and the patient underwent operative treatment.

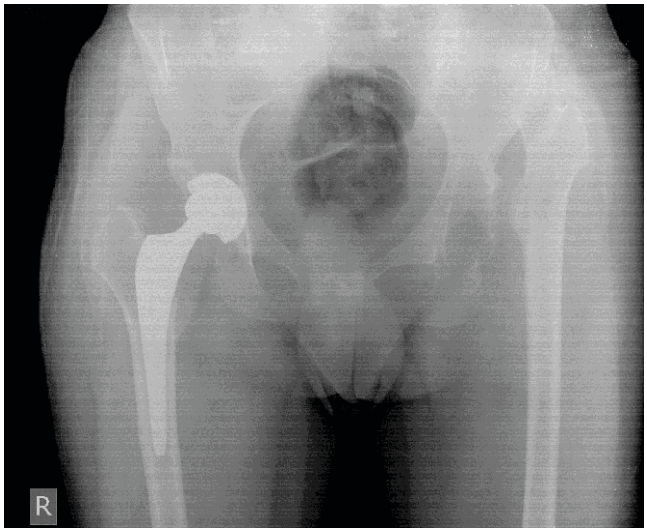

Figure 3 **Pelvis radiographic image at follow-up eight months after the first surgery.**

The operation was performed under general endotracheal anesthesia. The patient was placed in a dorsal decubitus position, and the lateral approach to the left hip was chosen as the surgical approach. Upon access to the neck of the femur, head was presented and sawed off. The head was then removed. Due to the elongation of left femur compared to the right, after careful consideration and measurements, it was decided to perform osteotomy of the left femur, so as to achieve similar length of both femurs. Afterwards anatomical position of the left acetabulum was accessed, and then it was prepared for the acetabular component, after which it was placed with medical cement. Then the femur was accessed, and the canal was prepared for the stem, which was placed with medical cement. Intraoperatively, the size of the head of the endoprosthesis was determined, which was then placed on the stem. After the endoprosthesis was repositioned, clinical stability tests were performed, which showed that the placed prosthesis was stable. The wound was closed in layers with the placement of aspiration drainage. The operative course was uneventful, as was the awakening from anesthesia, and the patient was transferred to the ward. The control X-ray showed the correct position of the endoprosthesis (Figure 4).

Figure 4 **Postoperative TEP radiographic image.**

On the first postoperative day, the patient was included in a physical rehabilitation program. Aspiration drainage was removed on the second postoperative day. Patient was instructed to use limited-weight bearing on the left leg and use crutches.

On the seventh postoperative day, the patient was discharged from the CCUS Orthopedics and Traumatology Clinic for home treatment. During the control examination, on the fifteenth postoperative day, it was determined that the wound had healed properly, and that there were no signs of edema or inflammation, and the sutures were removed.

Six weeks following the second surgery patient was sent to spa for further physical therapy and rehabilitation.

Six months after the second surgery, patient's gait was not satisfactory, and it was noted that left leg was 1 cm shorter than the right leg. Patient was prescribed shoe insole with elevation of 1 cm for the left leg.

The rehabilitation was successfully completed at a follow-up a year after the operation. It was noted that patient's gait was satisfactory, and that the patient was able to walk without discomfort and without using crutches.

DISCUSSION

Most of the DDH cases can be treated conservatively, however in 2.6% to 9.1% of cases total hip replacement is required (2). Systemic review by Shahbazi P, et al., conducted in 2023 has shown the Crowe IV DDH has significantly increased risk of dislocation following total hip arthroplasty (7). While DDH has shown to have higher revision rates compared to the patients with total hip arthroplasty suffering from osteoarthritis, dislocation rate was similar, although additional evidence may be required to prove this (8). Other studies have shown that the Studies by Greber EM,

et al., in 2017 and Qian H, et al., in 2023 have shown that treatment of Crowe IV DDH with true acetabulum reconstruction and possible osteotomy, which were performed in this patient, has shown to have better outcome (9,10). Longterm study by Fahlbusch H, et al., has shown that total hip arthroplasty in patients suffering from DDH can be challenging and is associated with higher risk of complications (11). Most notably, increasing number of patients with Crowe type IV DDH seem to be more sensitive to postoperative leg length discrepancy (12).

CONCLUSION

The patient was successfully implanted with a total hip endoprosthesis in both hips in the space of eight months apart.. There were no complications reported. Postoperative follow-up indicated the correct selection and success of the treatment, and led to an improvement in the patient's quality of life.

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Case Report: Minimally Invasive and Hybrid Coronary Revascularization - A Reliable Alternative to Traditional Coronary Surgery

Prikaz slučaja: minimalno invazivna i hibridna koronarna revaskularizacija - pouzdana alternativa tradicionalnoj koronarnoj hirurgiji

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ABSTRACT

Introduction: traditional coronary artery bypass grafting (CABG) is the gold standard for treating multivessel coronary artery disease (CAD) but is associated with significant surgical trauma and extended recovery. Minimally invasive coronary surgery (MiCS) and hybrid coronary revascularization (HCR) offer less invasive alternatives with reduced trauma, infection risk, blood loss, and faster recovery. Case report: this case study describes a 60-year-old male with triple-vessel disease requiring surgical intervention for significant lesions on the left anterior descending (LAD) and left coronary arteries. Using a minimally invasive approach through a left anterior thoracotomy, a LIMA -LAD direct bypass and Y graft (LIMA-VMS-Ramus Intermedius) were performed. The patient recovered uneventfully, with stable hemodynamics and satisfactory wound healing, and was discharged on postoperative day four. Conclusion: this case demonstrates the safety and efficacy of MiCS and HCR, highlighting their potential to become standard coronary surgery techniques, pending further research on long-term outcomes and cost-effectiveness.

Keywords: minimally invasive surgery, hybrid coronary revascularization, LIMA bypass

SAŽETAK

Uvod: tradicionalna operacija koronarne arterijske premosnice (CABG) predstavlja zlatni standard u liječenju višestrukih lezija koronarnih arterija (CAD), ali je povezana sa značajnom hirurškom traumom i produženim oporavkom. Minimalno invazivna hirurška metoda i hibridna koronarna revaskularizacija nude manje invazivne alternative sa smanjenom traumom, rizikom od infekcije, gubitkom krvi i bržim oporavkom. Prikaz slučaja: ovaj prikaz slučaja opisuje 60-godišnjeg muškarca s trosudovnom koronarnom bolešću koja zahtijeva hiruršku intervenciju zbog značajnih lezija na prednjoj silaznoj grani (LAD) i lijevim koronarnim arterijama. Korištenjem minimalno invazivnog pristupa kroz lijevu prednju torakotomiju, izvedena je direktna premosnica LIMA-LAD i Y graft (LIMA-VMS-Ramus Intermedius). Pacijent se oporavio bez komplikacija, sa stabilnom hemodinamikom i zadovoljavajućim zarastanjem rane, te je otpušten četvrtog postoperativnog dana. Zaključak: ovaj slučaj pokazuje sigurnost i efikasnost minimalno invazivne hirurške metode i hibridne koronarne revaskularizacije ističući njihov potencijal da postanu standardne tehnike koronarne hirurgije, uz potrebu za daljnjim istraživanjima dugoročnih rezultata i isplativosti.

Ključne riječi: minimalno invazivna hirurgija, hibridna koronarna revaskularizacija, LIMA premosnica

INTRODUCTION

Coronary artery disease (CAD) remains a leading cause of morbidity and mortality worldwide, necessitating effective revascularization strategies to restore adequate blood flow to the heart. Traditional coronary artery bypass grafting (CABG) has long been the gold standard for treating multivessel CAD, offering significant survival benefits and symptom relief (1). However, CABG is associated with substantial surgical trauma, prolonged recovery times, and higher risks of complications, particularly in high-risk patient populations. Despite improvements in surgical outcomes over the years, the fundamental technique of CABG has remained largely unchanged, highlighting the need for innovative approaches to coronary revascularization (2,3).

Minimally invasive coronary surgery (MiCS) and hybrid coronary revascularization (HCR) have emerged as promising

alternatives to traditional coronary artery bypass grafting (CABG). These approaches offer several advantages, such as reduced surgical trauma, lower risks of infection, decreased blood loss, and shorter hospital stays, making them attractive options for patients requiring coronary revascularization. MiCS encompasses which involve performing coronary revascularization through minimal incisions, often avoiding the need for a full sternotomy. These techniques have been linked to expedited recovery and enhanced patient outcomes, making them viable alternatives to conventional CABG (4).

Hybrid coronary revascularization (HCR) combines surgical and percutaneous methods to address multivessel coronary artery disease, integrating CABG using the left internal mammary artery (LIMA) for the left anterior descending (LAD) artery with percutaneous coronary intervention (PCI) for non-LAD vessels. This approach aims to capitalize on the long-term patency and survival advantages of LIMA grafts while minimizing invasiveness (5). HCR has demonstrated lower in-hospital major morbidity, lower blood transfusion use, and shorter postoperative length of stay compared to traditional CABG, further supporting its potential as a reliable alternative (6).

Despite these advancements, several challenges remain in the field of coronary revascularization. Technical challenges such as heavily calcified lesions, bifurcation lesions, and multivessel disease complicate percutaneous coronary intervention procedures (7). Clinical challenges include patient selection, particularly in determining which patients will optimally benefit from PCI, and managing acute coronary syndrome where timely intervention is critical (8). Logistical challenges such as operational inefficiencies and the need for specialized training and hybrid operating rooms further complicate the implementation of HCR programs (6).

CASE REPORT

A 60-year-old male presented with a history of triple-vessel coronary artery disease and a previous infero-postero-lateral myocardial infarction (seven months before surgery) which had been managed with percutaneous coronary intervention (pPCI) and deployment of a drug-eluting stent (DES) in the right coronary artery (RCA) (Figure 1). Cardiac catheterization revealed a normal left main artery, while the left anterior descending artery (LAD) exhibited diffuse atherosclerosis with significant stenoses of 70% in the proximal segment and 80% in the mid-segment. The circumflex artery showed atherosclerotic changes without significant stenosis, whereas the intermediate branch displayed an 80% stenosis in the proximal segment. The RCA was partially obstructed by a soft tissue plaque sub-occluding the proximal segment, where a 4.0 x 18 mm DES was successfully implanted, achieving excellent angiographic results despite slightly slower flow.

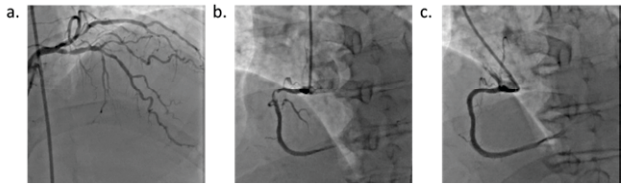

Figure 1 **Percutaneous Coronary Intervention Technique Using DES Stent. a. LAD and R. Intermedius; b. RCA proximal sub-occlusion; c. RCA-PCI DES Stent at proximal RCA.**

Additional vascular assessments through Doppler studies identified mild atherosclerosis in the carotid arteries without significant stenosis and normal parameters in the iliac-femoral segment bilaterally. The patient's cardiovascular condition was further complicated by ischemic cardiomyopathy with atrial fibrillation (AF) and grade II arterial hypertension, necessitating ongoing monitoring and management.

The pre-surgical examination confirmed the patient was in good general condition, with normal skin, mucosal coloration, vital signs, and unremarkable cardiovascular, respiratory, abdominal, and peripheral findings including hematological and biochemical parameters. This MiCS procedure was deemed as safe and appropriate because the right artery was already stented, ensuring minimal risk.

Method

Minimally Invasive Coronary Surgery (MiCS)

MiCS was performed using techniques such as minimally invasive coronary artery bypass grafting (MICS-CABG) Figure 2. These procedures involved coronary revascularization through minimal incisions avoiding the need for a full sternotomy. The procedure included LAST OPCAB Mix-CABG: Lima-LAD; Y graft: Lima-VSM-R. Intermedius. The procedure was conducted through a left small anterior lateral thoracotomy (LAST), A Lima-LAD direct bypass was performed alongside a Y graft (Lima-VMS-Ramus Intermedius). Heart was approached through a small anterior lateral thoracotomy in the fourth intercostal space. The left internal mammary artery (LIMA) was harvested using the standard surgical technique. Maquet ACROBAT Octopus stabilizer is utilized for local stabilization of the heart wall. The left pleural space was drained using the standard procedure, and the pericardial sac was emptied into the left pleural space through a posterior pericardiotomy. The left internal mammary artery (LIMA) was harvested using a standard technique, and heart wall stabilization was achieved using a Maquet ACROBAT Octopus stabilizer. Procedures were conducted under general anesthesia, with postoperative monitoring in the intensive care unit.

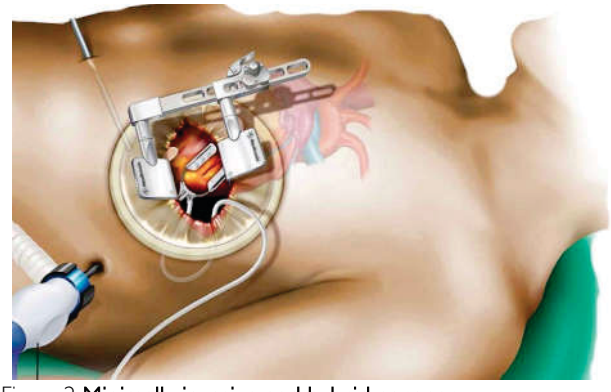

Figure 2 **Minimally invasive and hybrid coronary revascularization (9).**

Results

The surgery proceeded without complications, and the patient was successfully extubated the following morning. Postoperatively, the patient was conscious, oriented, communicative, afebrile, eupneic, and hemodynamically stable. The mini thoracotomy wound was dry, and all surgical sites displayed primary healing.

Surgical wounds healed appropriately, laboratory results were within acceptable ranges for the early postoperative phase, and the thoracotomy site showed no signs of inflammation (Figure 3). Electrocardiogram (ECG) indicated sinus rhythm at approximately 71 bpm, PQ 0.12 seconds, QS complexes in D2, D3, aVF, and V4-V6, with negative T waves in D1, aVL, and V2, and flattened T waves from V4-V6. ECG demonstrated satisfactory left ventricular systolic function, with mitral regurgitation graded 1-2+ (Figure 3). There was no evidence of pulmonary embolism or pleural effusion. A chest X-ray revealed minor basal left-sided opacification. No blood transfusions were necessary. The patient was discharged on the fourth postoperative day in stable condition with recommendations for a hygienic-dietary regimen, cardiac rehabilitation, and respiratory physiotherapy.

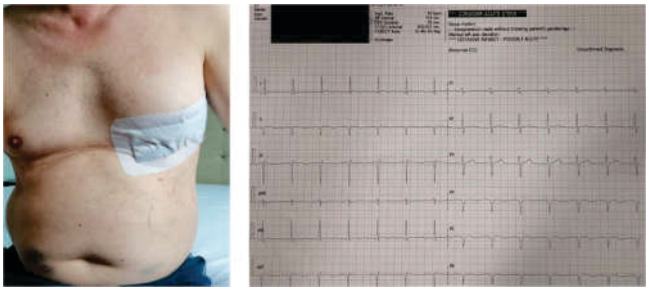

Figure 3 **Post-Surgery Outcomes. Left: Patient recovery following surgery. Right: Post-surgery ECG results.**

Table 1 provides a comparative overview of echocardiographic findings from preoperative assessment and postoperative follow-up. The preoperative findings indicate moderately reduced LV systolic function with segmental hypokinesia and an aneurysm in the basal part of the inferior wall. A mild diastolic dysfunction and mild mitral/tricuspid regurgitation are also noted.

Table 1 **Comparison of preoperative and postoperative echocardiograms.**

Parameter	Preoperative	Postoperative
LVIDd (mm)	46	46
LVIDs (mm)	34	32
LA (mm)	40	41
RVOT (mm)	N/A	32
IVSd (mm)	17	17
LVPWd (mm)	13	11
TAPSE (mm)	21	22
EFLV (%)	40%	47%
Segmental myocardial motility	Hypokinesia of the inferior wall, aneurysm	Mild hypokinesia
Mitral regurgitation	MR 1-2+	MR 1+
Tricuspid regurgitation	TR 1+	TR 1+
Pericardial effusion	None observed	None observed
Pleural effusion	N/A	Present on the left side

In general, the surgery improved left atrial size, myocardial motility, mitral regurgitation, and left ventricular posterior wall thickness. Postoperatively, the follow-up shows stable LV dimensions (LVIDd 46 mm, LVIDs 32 mm) with a slight reduction in TAPSE (19 mm) and the presence of a mild pleural effusion on the left side. LV systolic function remains moderately reduced. The clinical condition of patient was stable, with good tolerance to exertion. The surgery was uneventful and the patient remained hemodynamically stable with no post-surgical complications. Continuous monitoring of cardiac function was recommended, along with further follow-up.

DISCUSSION

Minimally invasive coronary surgery (MiCS) and hybrid coronary revascularization (HCR) offer several advantages over traditional coronary artery bypass grafting (CABG). These techniques involve performing coronary revascularization through minimal incisions, often avoiding the need for a full sternotomy. HCR combines minimally invasive CABG of the left anterior descending (LAD) artery with percutaneous coronary intervention (PCI) of non-LAD vessels. This hybrid approach leverages the long-term patency of left internal mammary artery (LIMA) grafts while reducing procedural invasiveness (6).

In response to these challenges, this study aims to evaluate the efficacy, safety, and short - and long-term outcomes of MiCS and HCR compared to traditional CABG. We employed innovative techniques such as MICS and HCR, to assess their potential in reducing surgical trauma, improving recovery times, and enhancing patient outcomes. The methodology involved a comprehensive analysis of patient demographics, baseline clinical characteristics, intraoperative and postoperative outcomes, and long-term clinical outcomes.

The results of the case study indicate that MiCS and HCR are associated with several short-term benefits, including decreased surgical trauma, lower infection risks, reduced blood loss, and shorter hospital stays, leading to expedited recovery and enhanced patient outcomes. Additionally, MiCS through a small thoracotomy allows for complete revascularization with favourable graft patency, low perioperative mortality, decreased need for blood transfusion, lower surgical site infection rates, and earlier return to full physical function (10).

This study demonstrates that minimally invasive and hybrid coronary revascularization techniques are reliable alternatives to traditional coronary surgery. These techniques offer substantial benefits, including reduced surgical trauma, lower infection risks, decreased blood loss, shorter hospital stays, and quicker recovery. The findings have significant implications for clinical practice, suggesting that MiCS and HCR should be considered viable options for patients with multivessel coronary artery disease, particularly those at high surgical risk. Further research is needed to evaluate long-term outcomes and cost-effectiveness, and to identify optimal patient populations for these less invasive procedures.

Intraoperative and Short-term Outcomes

MiCS and HCR demonstrated reduced operative times and lower rates of complications in comparison to traditional CABG. The minimally invasive approaches led to decreased need for blood transfusions, shorter hospital stays, and faster return to physical activity. Patients undergoing HCR experienced a lower incidence of in-hospital blood transfusions compared to off-pump CABG (11). These techniques were also linked to fewer surgical site infections and expedited functional recovery (10).

Long-term Outcomes

The long-term graft patency and survival outcomes of MiCS and HCR were comparable to those of traditional CABG. MiCS achieved excellent long-term survival rates, with freedom from major adverse events and angina reaching 87.0% at 5 years and 70.5% at 15 years (12). Similarly, HCR demonstrated reduced rates of myocardial infarction and target vessel revascularization during long-term follow-up (13).

Comparative Analysis with Traditional CABG

Traditional CABG remains the standard treatment for complex coronary artery disease (1). However, MiCS and HCR provide viable alternatives, particularly for high-risk patients or those requiring multivessel revascularization. These approaches reduce surgical trauma and recovery time, offering significant benefits in terms of patient satisfaction and quality of life. Patients reported less postoperative pain, quicker recovery, and improved physical and mental health following MiCS and HCR compared to traditional CABG (6).

Advancements in Technology

Technological innovations, including robotic and endoscopic approaches, have further enhanced the feasibility and safety of minimally invasive techniques (14). These advancements have also contributed to reduced operative times and improved outcomes, despite the technical challenges and learning curve associated with MiCS-CABG (15).

Clinical Implications

Study findings indicate that MiCS and HCR are reliable alternatives to traditional CABG, with substantial short- and long-term benefits. These minimally invasive techniques reduce the physical and psychological burden of surgery while achieving comparable clinical outcomes. Future research should focus on optimizing patient selection criteria and assessing the cost-effectiveness of these approaches. MiCS, has been associated with reduced surgical trauma, lower infection risks, decreased blood loss, shorter hospital stays, and faster recovery (16).

CONCLUSION

MiCS and HCR represent significant advancements in coronary revascularization, offering effective, less invasive alternatives to traditional CABG. These techniques minimize surgical trauma, reduce recovery time, and improve overall patient outcomes. With continued advancements in surgical technologies, MiCS and HCR have the potential to become standard practices for coronary artery disease management, especially for high-risk populations. Further studies are necessary to evaluate long-term outcomes and to refine strategies for broader clinical adoption.

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