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October/December 2016.

KLINIČKI CENTAR UNIVERZITETA SARAJEVO

U SLUŽBI VAŠEG ZDRAVLJA

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

Bosna i Hercegovina je bila četvrta zemlja u Evropi koja je razvila Nacionalnu verziju HeartScore programa !

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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.

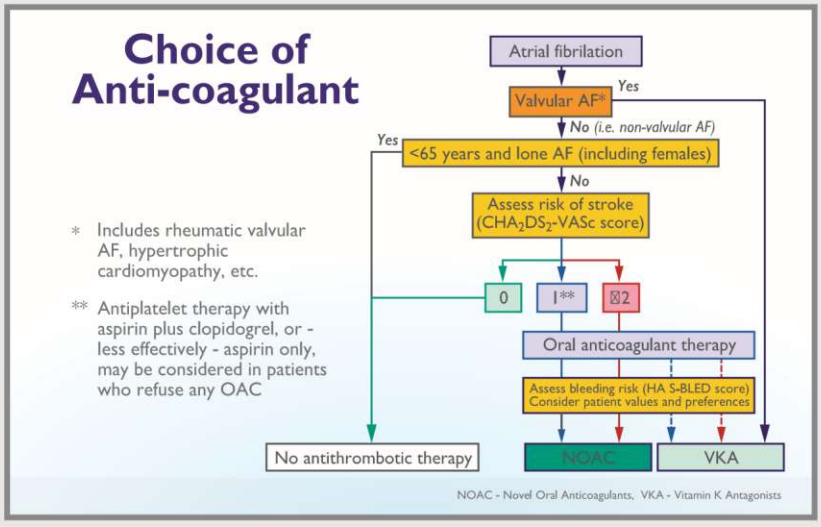
Major i non-major riziko fakori za procjenu tromboembolizma kod A Fib!

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 nuclide 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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Reliability of CA 125 in differentiation of benign tumors type endometrioma from malignant adnexal tumors

Pouzdanosti CA 125 u diferencijaciji benignih tumora tipa endometrioma od malignih adneksalnih tumora

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ABSTRACT

Ovarian cancer occurs in one or both ovaries, mostly in postmenopausal women. Despite the fact that it represents only about 4% of all malignant tumors in women, it is the most common cause of death among all cancers of the female genital organs. Endometriosis is characterized by ectopic endometrial localization in the organism of women, and localization beyond the inner surface of the uterus. It is mostly localized in the ovaries. Nowadays tumor marker CA-125 is used as a diagnostic tool in the diagnosis of ovarian diseases. It is also used for the differentiation of endometrial from non-endometrial benign ovarian cysts. The aim of this study is to demonstrate the degree of reliability of CA 125 for differentiating benign tumors type endometrioma from malignant adnexal tumors. Materials and methods: the study included the analysis of medical records of 120 patients with recorded tumor changes in the ovaries who were surgically treated at the Clinic of Gynecology and Obstetrics of the University Clinical Center Sarajevo and General Hospital "Prim. Dr. Abdulah Nakaš" in a three-year period. In the preoperative preparation, all patients were tested for level of tumor marker CA 125, and underwent additional subspecialist examinations including ultrasound, CT and MRI of the pelvis. The study included 120 subjects. Group "A" consists of patients with PHD verified malignant ovarian tumors, and group "B" consists of patients with PHD verified benign ovarian disease type endometrioma. Results: the average age was higher in patients with malignant diseases. The subjects in the subgroup under 40 years of age had an average of 34.13 ± 3.28 years in malignant disease and 31.23 ± 4.98 years in benign disease. In the subgroup of subjects aged over 40 examinees had an average of 57.83 ± 8.12 years in malignant disease and 49.96 ± 5.81 years in benign disease. Average value of CA 125 in women with ovarian malignancies amounted to 800.9 ± 116 U/mL, and in patients with benign diseases 112.1 ± 108 U/mL. There was a significant difference in the average values of CA 125 in the tested groups, and women with malignant diseases had statistically higher values of CA 125, F=20.59; p=0.001. Conclusion: the method of determining the CA-125 is a simple and accessible, making it easier to monitor operational, conservative or combined therapy of ovarian cancer.

Key words: tumor marker CA-125, endometriosis, ovarian tumor

SAŽETAK

Karcinom jajnika javlja se na jednom ili na oba jajnika, najčešće kod postmenopauzalnih žena. Uprkos tome što predstavlja samo oko 4% svih zloćudnih tumora kod žena, najčešći je uzrok smrti od karcinoma ženskih spolnih organa. Endometriozu karakteriše ektopična lokalizacija endometrijuma u organizmu žene, odnosno lokalizacija izvan unutrašnje površine maternice. Najčešće se lokalizuje na jajnicima. Danas se kao pomoćno dijagnostičko sredstvo u dijagnostici oboljenja jajnika koristi tumorski marker CA-125. On se koristi i za diferenciranje endometrioidnih od neendometrioidnih benignih cisti jajnika. Cilj ovog istraživanja je da pokaže stepen pouzdanosti CA 125 za diferencijaciju benignih tumora tipa endometrioma od malignih adneksalnih tumora. Materijali i metode: u studiju je uključena analiza medicinske dokumentacije 120 pacijentica sa evidentiranim tumorskim promjenama na jajnicima, koje su operisane na GAK Sarajevo i OBS "Prim. dr Abdulah Nakaš", u trogodišnjem periodu. Sve posmatrane pacijentice su u preoperativnoj pripremi imale laboratorijske nalaze nivoa tumor markera CA 125, kao i dodatne subspecijalističke pretrage: UZ, CT i MRI male zdjelice. Studijom je obuhvaćeno 120 ispitanica. Grupu "A" su činile pacijentice sa PHD verificiranim malignim oboljenjima jajnika, a grupu "B" pacijentice sa PHD verificiranim benignim oboljenjima jajnika tipa endometrioma. Rezultati: prosječna starost je bila veća kod ispitanica sa malignim oboljenjima. Ispitanice u podgrupi ispod 40 godina su imale prosječno 34,13±3,28 godina kod malignih oboljenja i 31,23±4,98 godina kod benignih oboljenja. U podgrupi iznad 40 godina ispitanice su imale prosječno 57,83±8,12 godina kod malignih oboljenja i 49,96±5,81 godina kod benignih oboljenja. Prosječne vrijednosti CA 125 kod ispitanica sa malignim oboljenjima jajnika su iznosile 800,9±116 U/mL, a kod ispitanica sa benignim oboljenjima 112,1±108 U/mL. Ustanovljena je statistički značajna razlika u prosječnim vrijednostima CA 125 u odnosu na ispitivane grupe, te su ispitanice sa malignim oboljenjima imale statistički veće vrijednosti CA 125, F=20.59; p=0.001. Zaključak: metoda određivanja CA-125 je jednostavna i dostupna, čime se olakšava praćenje operativne, konzervativne ili kombinovane terapije karcinoma jajnika.

Ključne riječi: tumor marker CA-125, endometrioza, tumor jajnika

INTRODUCTION

Ovarian cancer occurs in one or both ovaries, the most common in postmenopausal women. Despite representing only about 4% of all malignant tumors in women, it is the most common cause of death from cancer of the female genital organs (1). The first symptom of ovarian cancer is pain in the pelvis, which is constant and is getting worse over time. Vaginal bleeding (between periods or during sexual intercourse) is a common early symptom of ovarian cancer. More frequent urination, constipation, back pain, feeling of bloating and swelling of the abdomen, are also common symptoms. Symptoms of ovarian cancer are often insignificant and ignored by the patient and doctor (2,3).

Screening of ovarian cancer represents a shift in approaching that entity and it is the answer to devastating statistical indicators. The aim of each screening program should extract individuals from clinically healthy population in whom the likelihood of certain diseases is such as to justify further diagnostic procedures. In ovarian cancer screening, high specificity of the test is particularly significant, since a definitive diagnosis can be made on the basis of pathohistological findings, i.e. following the surgery. Although a number of different methods of early detection of ovarian cancer were proposed, according to these criteria determination of serum concentration of tumor markers proved acceptable, particularly CA-125 and ultrasound, and arguably the greatest progress was enabled by application of transvaginal color and pulsed Doppler (4,5,6).

Endometriosis is characterized by ectopic endometrial localization in the body of women, and localization beyond the inner surface of the uterus. Most often, it is localized in the ovaries. By frequency, this localization is seen in about 50% of cases. Endometriosis is a disease that occurs during full maturity, from puberty to menopause. It is most often diagnosed in women who have not given birth and who are older than 30 years. According to some authors, about 15% of endometriosis is detected in women younger than 30 years. The origin of endometriosis is not always the same, nor can its occurrence be easily explained. When endometriosis affects ovary, it destroys its tissue, creates adhesions that are common contact between the ovaries and fallopian tubes and cause infertility (7,8). Nowadays, tumor marker CA-125 is used as a diagnostic tool. It is noted that this antigen is elevated in cases of endometriosis. It correlates with the progression of the disease and the effect of therapy. However, the sensitivity of this test is quite low to be used for the detection of disease. It is also used for the differentiation of endometrioid from non-endometrioid benign ovarian cysts, especially in combination with transvaginal ultrasound (7-9). The goal of the research is to examine the degree of reliability of CA 125 for differentiation of benign type endometrioma from malignant adnexal tumors.

MATERIALS AND METHODS

This is a retrospective, observational and descriptive study. It involved analysis of the medical records of patients with registered tumor changes in the ovaries who were surgically treated at the Clinic of Gynecology and Obstetrics of the Clinical Center University of Sarajevo (CCUS) and General Hospital "Prim. Dr. Abdulah Nakaš", over a three-year period. All patients in the preoperative preparation had a laboratory level of a tumor marker CA 125, as well as additional subspecialist examinations including ultrasound, CT and MRI of pelvis. The study included 120 medical documentations (medical history) of which group "A" consisted of documentation of patients with PHD verified malignant tumors of ovarian cancer, and group "B" of patients with PHD verified benign ovarian disease type endometrioma. Depending on the age of the examinees, both groups contained two subgroups, specifically examinees older than 40 years and those under the age of 40.

The research was conducted at the Clinic of Gynecology and Obstetrics of the CCUS and at Gynecological-obstetric Department of the General Hospital "Prim. Dr. Abdulah Nakaš".

Research methods

Histopathology

Archived materials from the Clinic of Gynecology and Obstetrics of the CCUS and the General Hospital were histologically analyzed. Tissue taken for histopathological analysis was immersed for 24 hours in 10% formalin. After fixation and processing it was set into the paraffin. Paraffin blocks were cut into slices, at 3-5 microns thickness, and subsequently painted with standard Hemalaun-eosin method, and if required, additional methods (PAS, PAS diastasis, Mallory, Gomory) were included.

CA-125

Determination of CA 125 was carried out shortly after a brief centrifugation and separation of the serum from the clot in laboratories of the Department for Clinical Chemistry and Biochemistry of the CCUS and the Department of Medical Biochemistry Laboratory Diagnostics of the General Hospital "Prim. Dr. Abdulah Nakaš" by immunochemistry methods with appropriate automatic analyzers.

Ultrasound

In addition to clinical and laboratory evaluation, all patients underwent transvaginal ultrasonography of ovarian morphology and diagnosis of possible modifications to the same. Transvaginal ultrasound examination of the uterus and ovaries was performed through vagina with a special vaginal probe 12 cm long and 1.5-2 cm thick.

RESULTS

The study included 120 examinees divided into two groups based on the study inclusion criteria. The first group included all examinees with malignant disease, and the second group consisted of examinees with benign disease. The division into sub-groups was also made. Depending on the age of the subjects both groups had

two subgroups, specifically examinees older than 40 years and those under the age of 40.

Table 1 Distribution of examinees by groups.

		GROUPS		Total
		Malignant diseases	Benign diseases	
SUBGROUPS	Age < 40	30	30	60
	Age > 40	30	30	60
Total		60	60	120

ANOVA test showed a statistically significant difference in the average age of subjects from examined groups divided into subgroups. The average age was higher in patients with malignant diseases. The subjects in the subgroup under 40 years of age had an average of 34.13 ± 3.28 years in malignant diseases and 31.23 ± 4.98 years in benign disease. In the subgroup of over 40 years of age, the subjects had an average of 57.83 ± 8.12 years in malignant diseases and 49.96 ± 5.81 years in benign diseases.

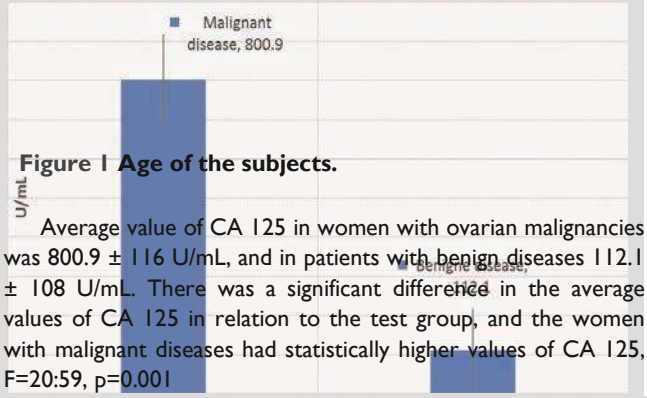

Figure 1 Age of the subjects.

Average value of CA 125 in women with ovarian malignancies was 800.9 ± 116 U/mL, and in patients with benign diseases 112.1 ± 108 U/mL. There was a significant difference in the average values of CA 125 in relation to the test group, and the women with malignant diseases had statistically higher values of CA 125, F=20:59, p=0.001

Table 2 Average value of CA 125 compared to the test group.

	X	SD	SEM	95% CI		Minimum	Maximum
				Lower	Upper		
Malignant disease	800.9	116	14.9	500.81	1101.04	14.50	6648.00
Benign disease	112.1	108	2.3	65.95	158.42	13.50	1111.00

Figure 2 Average value of CA 125 compared to the test group.

In patients with malignant ovarian disease, the average value of CA 125 was significantly higher in women over 40 years than in women under 40 years of age; F=17,790; p=0.001. In the group of patients with benign ovarian disease there was no statistically significant difference in the average values of CA 125 in relation to age subgroups, F=1.901, p=0.173.

Figure 3 Average value of CA 125 in relation to age subgroups of the examined groups.

Table 3 Average value of CA 125 in relation to age subgroups of the examined groups.

GROUPS		N	X	SEM	Minimum	Maximum	F	P
Malignant disease	Age < 40	30	281.63	54.57	23.20	873.9		
	Age > 40	30	1320.23	264.48	14.50	6648.0	14.790	0.000
Benign disease	Age < 40	30	143.81	44.01	13.80	1111.0		
	Age > 40	30	80.57	12.90	13.50	343.0	1.901	0.173

DISCUSSION

In the past several years, tumor marker CA 125 has an increasingly important place in the diagnosis and control of patients affected by ovarian cancer, as evidenced by the fact that in 1997 the European Group on Tumor Markers (EGTM) was established, which made recommendations for correct application of CA 125 for ovarian cancer (10,11).

This tumor marker is elevated in 90% of patients with ovarian cancer in the II, III or IV stage, and about 50% of patients with epithelial ovarian cancer stage I. The serum concentration of this marker was associated with the histological features of the malignant tissue, the clinical progression of the disease as well as with response to therapy applied (12).

Several different studies conducted on a large number of healthy subjects have shown that post-menopausal women have lower values of CA 125 in serum than before menopause. In some women there is a different distribution of CA 125 during the menstrual cycle. The literature has also shown the influence of some other factors to the level of CA 125 in serum. It has been confirmed that smoking lowers the value of CA 125 and that caffeine affects the value increase (13,14).

A whole series of benign diseases of different organ systems can cause a rise of tumor marker CA 125 levels. Diseases of the female genital tract that affect the increase in value include: ectopic pregnancy, endometriosis, myoma of the uterus, fallopian tube inflammation (salpingitis), tuboovarial abscess and Meigs' syndrome (ovarian fibroma, ascites, hydrothorax). The increase of CA 125 levels in serum of

other organ system diseases occurs in: cirrhosis of the liver, hepatitis, pancreatitis, diverticulosis of the colon, lung and pleura disease, dilatation of the heart muscle. Elevated levels of CA 125 are found at adenocarcinoma originating from different organ systems, especially when there are metastases in the body. Higher values (more than 35 U/mL) are found in adenocarcinoma of the breast, colon, pancreas, lung, endometrium, cervix and fallopian tubes (15,16).

Our study included 120 subjects divided into two groups based on the study inclusion criteria. The first group included all examinees with malignant disease, and the second group consisted of examinees with benign disease. The division into sub-groups was also made. Depending on the age of the examinees, both groups had two subgroups, specifically examinees older than 40 years and those under the age of 40. ANOVA test showed a statistically significant difference in the average age of patients from the examined groups divided into subgroups. The average age was higher in patients with malignant diseases. The subjects in the subgroup under 40 years of age had an average of 34.13 ± 3.28 years with malignant disease and 31.23 ± 4.98 years with benign disease. In the subgroup of over 40 examinees had an average of 57.83 ± 8.12 years with malignant diseases and 49.96 ± 5.81 years with benign disease.

Heintz APM (17) et al. in their work pointed out that less than 10% of patients with ovarian cancer were under the age of 40. The occurrence of ovarian cancer rises sharply above the age of 40. Between the age of 40-44, around 15/100 000 women are affected, from 70 to 74, around 57/100 000, which statistically coincides with our research.

Goran Vujić (18) in his doctoral dissertation entitled "The prognostic value of angiogenesis and DNA content of tumor cells in patients with serous ovarian cancer," states that the average age in the study group was 53.2 years (SD=13.71; SE=1,2). In the range of 65, the youngest patient was 19 and the oldest was 84 years of age. According to the 95% confidence interval, the largest number of patients were 50.6 to 55.7 years of age, which is consistent with our research.

In our study, the average value of CA 125 in women with ovarian malignancies was 800.9 ± 116 U/mL, and in patients with benign diseases 112.1 ± 108 U/mL. There was a statistically significant difference in the average values of CA 125 in relation to the test group, and the women with malignant diseases had statistically higher values of CA 125, F=20:59, p=0.001. In patients with malignant ovarian disease, the average value of CA 125 was significantly higher in women over 40, than in women under 40 years of age, F=17.790, p=0.001. In the group of patients with benign ovarian disease, no statistically significant difference was found in the average values of CA 125 in relation to the age subgroups; F=1.901, p=0.173.

In over 80% of patients with CA 125 concentrations above 35 U/mL in serum, malignant ovarian tumor was detected. In relation to the stages of ovarian cancer, elevated levels (above 35 U/mL) were present in serum of 41% of all women in FIGO stage I, 85% in stage II, 93% in stage III and 97% in stage IV (19,20).

In a study entitled "The tumor marker CA 125 and adnexal inflammatory tumors," Branka Nikolić et al. stated that in 27 patients (55.1%) CA 125 values ranged from 38.8 U/mL to 794 U/ml, and in 30 patients CA 125 values were within normal limits. In the group in which 57 patients were examined and treated, the largest value of serum CA 125 (794.7 U/mL) was obtained in patients who, align

with inflammatory process, had histologically confirmed endometriosis. In the postoperative period and the therapy with danazol, CA 125 showed a downward trend. Values lower than 35 U/mL were obtained two months after the operation (21).

Srđan Đurđević et al. in their study "Diagnostic value of CA 125 in detection of recurrence and progression in stage III - IV of epithelial ovarian carcinoma" obtained the following results: in 60 patients who were surgically treated in stage III and IV of epithelial ovarian carcinoma, continuous determination of CA 125 in serum was performed over the next two years. Determination of CA 125 in serum for 2 postoperative years was reliable, but not absolutely safe diagnostic tool in detecting the disease progression in stages III and IV of epithelial ovarian carcinoma (sensitivity 79.3%, specificity 97.1%, positive predictive value of 91, 2%, negative predictive value of 92.4%, the accuracy of the test 92.1%). False-positive (0.7%) and false negative results (4.7%) of individual tests were present in 5.4% of all samples (10).

Ren P., et al. in a study under the title "High serum levels of follistatin in patients with ovarian cancer," stated that tumor marker CA 125 in malignant ovarian disease was increased, with the high sensitivity of 77.8% and specificity of 84% (22).

CONCLUSION

In our study, the average value of CA 125 in women with ovarian malignancies was 800.9 ± 116 U/mL, and in patients with benign diseases 112.1 ± 108 U/mL. There was a statistically significant difference in the average values of CA 125 in relation to the test group, and the women with malignant diseases had statistically higher values of Ca 125. The average value of CA 125 was significantly higher in women over 40, than in women under 40 years of age, in the group of patients with malignant diseases. In the group of patients with benign ovarian disease, no statistically significant difference in the average values of CA 125 in relation to age subgroups was found. We conclude that the method of determining the CA-125 is simple and accessible, making it easier to monitor operational, conservative or combined therapy of ovarian cancer.

Conflict of interest: none declared.

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International Prognostic Index remains a significant clinical tool in the treatment of Diffuse Large B-cell Lymphoma

Internacionalni prognostički indeks ostaje značajan klinički aparat u menadžmentu oboljelih od Difuznog velikostaničnog B ćelijskog limfoma

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ABSTRACT

Introduction: Difuse Large B-cell Lymphoma (DLBCL) is the most commonly represented subtype of Non-Hodgkin Lymphoma (NHL), accounting for 30% - 58% of newly diagnosed. Immunochemotherapy is considered a standard treatment in first line therapy. International Prognostic Index (IPI) which includes: age, level of serum lactate dehydrogenase (LDH), general condition of the patient, clinical stage and extranodal involvement, offers a possibility of recognizing patients with expected poor outcome. Aim: to prove predictive value of the International Prognostic Index in DLBCL patients in the era of immunochemotherapy in relation to achieving first complete remission and three-year survival. Material and methods: the conducted research is a retrospective analysis of DLBCL patients' treatment results in the era of immunochemotherapy. The research included 46 patients (32 women and 14 men) aged from 24 to 74 years, with median age 52 years, most of them diagnosed between 50 to 60 years of age. Results: results of the research indicated statistically significant influence of IPI>2 in achieving first complete remission in patients treated in first line by immunochemotherapy (p=0.028). 66% of the examinees with a high IPI score (3, 4, and 5) did not achieve complete remission in the first line of immunochemotherapy. Threeyear survival in participants who achieved complete remission in relation to primarily progressive disease and early relapse is significantly different (p< 0. 0005). IPI>2 was in correlation with three-year survival of the participants (p=0.0447). In the participant group with IPI>2, patients survive up to 30 month s (p=0.008; Kaplan Meier survival curve). Statistics: assessment of the significance of differences (X2 tests), Log Rank (Mantel-Cox) test, Kaplan-Meier curve of survival. Conclusion: although established in the era before immunochemotherapy, IPI remains the most important and the cheapest clinical tool in the management of DLBCL patients.

Key words: DLBCL, IPI, immunochemotherapy

SAŽETAK

Uvod: Difuzni velikostanični B limfom (DLBCL) je najzastupljeniji subtip Non-Hodgkin limfomi (NHL), čineći 30%-58% novodijagnosticiranih. Standardom liječenja u prvoj liniji liječenja smatra se imunohemoterapija: rituksimab (R)+(cyclophosphamid, doxorubicin, oncovin i prednisolone - CHOP). Internacionalni prognostički indeks (IPI) koji uključuje:starost, kondiciju prema ECOG skali, klinički stadij, nivo serumskog laktat dehidrogenaze (LDH) i ekstranodalno mjesto, pruža mogućnost prepoznavanja pacijenata kod kojih se očekje loš odgovor na standardni pristup liječenja. Konstruisan prije uvođenja imunoterapije IPI je pokazao snažnu prediktivnu vrijednost terapijskog uspjeha i predviđanja trogodišnjeg preživljavanja kod oboljelih od DLBCL. Cilj: provjeriti prediktivnu vrijednost Internacionalnog prognostičkog indeksa kod oboljelih od DLBCL-a u eri imunohemoterapije u odnosu na postizanje prve kompletne remisije i trogodišnje preživljavanje. Materijal i metode: provedeno istraživanje je retrospektivna analiza rezultata liječenja pacijenata sa DLBCL u eri imunohemoterapije. Istraživanje je obuhvatilo 46 pacijenta (32 žena i 14 muškaraca) starosne dobi od 24. do 74. godine, prosječne dobi 52 godina sa najviše oboljelih u dobi od 50 do 60 godina. Rezultati: rezultati istraživanja su pokazali statističku signifikantnost uticaja IPI>2 na postizanje prve kompletne remisije kod pacijenata liječenih u prvoj liniji imunohemoterapijom(p=0,028). 66% ispitanika sa visokim IPI scorom (3,4 i 5) nije postiglo kompletnu remisiju u prvoj liniji imunohemoterapije. Trogodišnje preživljavanje kod ispitanika koji su u prvoj liniji liječenja postigli kompletnu remisiju u odnosu na primarno progresivnu bolest i rani relaps je značajno različito (p< 0,0005). IPI>2 je bio u korelaciji sa trogodišnjim preživljavanjem ispitanika (p=0,0447). U grupi ispitanika sa IPI> 2 ispitanici preživljavaju maksimalno do 30 mjeseci (p= 0,008; Kaplan Meier krivulja preživljavanja). Statistika: procjena značajnosti razlika (X2 test), Log Rank (MantelCox) test, Kaplan-Meier krivulja preživljavanja. Zaključak: iako konstruisan u eri prije imunohepoterapije IPI ostaje najvažniji i najjeftiniji klinički aparat u menadžmentu oboljelih od DLBCL.

Ključne riječi: DLBCL, IPI, imunohemoterapija

INTRODUCTION

Non Hodgkin's Lymphoma is the fifth most common malignancy in men, and sixth in women. DLBCL is the most common subtype of NHL, accounting for 30% -58% of newly diagnosed and around 80% of all aggressive lymphoma in adults (1). In the United States of America the incidence amounts to 8.44 and in European Union accounts for 3-4 cases per 100.000 citizens per year (2,3). The newest DLBCL classification from 2008 is based on findings in the fields of morphology, immunophenotyping, molecular biology, genetics and clinical presentation (4). Therapeutic Protocol CHOP (cyclophosphamid, doxorubicin, oncovin, prednisolone), introduced in 1970, remains a standard first line therapy. In November 1997, Food and Drug Administration (FDA) approved immunotherapy, a monoclonal antibody directed toward CD20. Before the introduction of immunotherapy in DLBCL, the rate of overall survival ranged from 26% to 73% (5). By adding the immunotherapy to the standard therapy regime, 75% to 80% patients with DLBCL achieve complete remission (CR) (6). The advantage of immunotherapy in first line therapy has been proved both in older and younger patients (7,8,9). The role of autologus bone marrow transplantation (ABMT) in the therapy of chemosensitive relapse in DLBCL has been proved in multicentric study PARMA (10); patients under ABMT had significantly higher survival without disease and overall survival, as compared to those who were administered only second line therapy without ABMT (46% and 53% vs. 12% and 22%). Numerous studies followed, also proving the importance of ABMT (11,12). Relapsed/refractory disease has a bad prognosis. Implementation of allogeneic transplantation is an option if autologus transplantation proves to be unsuccessful, and the same patients are candidates for new therapeutic options that are in clinical trial phase (13). Prognostic factors in patients with DLBCL include characteristics and diseases of the patients and they are expressed in: clinical, immunophenotypical, cytogenetical and molecular features. Clinical prognostic factors are encompassed with International Prognostic Index (IPI), which is developed in 1993 as a result of collaboration work of 16 medical institutions in Europe, North America and Canada (5). IPI includes following risk factors: 1. age (<60 vs. >60 ages), 2. level of Lactate dehydrogenase (LDH) in serum (normal vs. elevated), 3. patients' condition according to ECOG scale (Eastern Cooperative Oncology Group) (0,1 vs. >1), 4. clinical stage according to An Arbor classification (I/II vs. III/IV) and 5. extranodal involvement (0.1 vs. >1). According to the risk factors, IPI differentiates four prognostic groups: low (0-1), low intermediate (2), high intermediate (3), high (4-5).

Aim of the research

To prove predictive value of IPI in patients with DLBCL in the era of immunochemotherapy in relation to achieving first complete remission and three-year survival.

MATERIALS AND METHODS

The research is a retrospective, clinical, comparative and descriptive study. The study included 46 participants: 14 male and 32 female patients, with age ranging from 24 to 74 years. The examinees were divided into two groups according to IPI: group A (IPI 0,1,2) and group B (IPI 3,4,5); with de novo diagnosed DLBCL; participants with immunohistochemically diagnosed nodal and extranodal DLBCL; age 18 and above, diagnosed for the first time and not treated; planned treatment with 4 + 4 cycles of R-CHOP, started or implemented; the study excluded: patients with transformed indolent lymphomas in DLBCL; patients that belonged to a group with borderline lymphomas. DLBCL diagnosis was established through immunohistochemical analysis of biopsied material. Homogeneous group of patients in relation to first line treatment was involved. In the first line treatment the patients were administered immunochemotherapy according to R-CHOP protocol (rituksimab first day 375mg/m2 iv + CHOP/ first day cyclophosphamid 750mg/m2 iv, doxorubicin 50mg/m2 iv, oncovin max. 2. mg/ iv, 1-5 day pronizon 100mg p.o.). Radiotherapy was applied in: bulky, extranodal involvement and residuum. Post-therapeutic restaging included repetition of earlier pathology tests and/or biopsy. The response was assessed based on conventional criteria (normalization of metabolic tests and absence of an earlier present tumor mass) and PET/CT was used when possible. Therapeutic response after first, second and third line of therapy and three-year survival of participants was monitored.

Statistical methods of processing obtained data

Nominal and ordinal variables in the research were analyzed with X2 test. Correlations (Spearman and Pearsons) were used for relation and direction of variables. Survival and differences in survival between certain groups were calculated with Log - Rank (Mantel-Cox) c2 test, and results were expressed with Kaplan-Meier curve and survival tables. Value α=0.05 was used for the statistical significance border.

RESULTS

The implemented research included 46 patients with de novo Diffuse large B-cell lymphoma, age ranging from 24 to 74 years, median age 52 years. The highest number of participants was in the 50-60 age range. *Results of clinical parameters by International Prognostic Index (IPI)*

Age category: in the examined sample, 14 male participants (36.8%) and 24 female patients were under 60 years of age. In the examined sample of patients over 60 years of age, female participants were dominant, specifically 8 patients or 100%.

Figure 1 Structure of examinees according to age category (≤ 60 years and > 60 years) N= 46 DLBCL.

Condition of examinees according to ECOG scale: in the implemented research, 25 (55%) participants had ECOG 0, 17 participants (37%) had ECOG 1, and 2 participants (4%) had ECOG 2 and 3.

Level of LDH serum: 25 (54%) participants had normal level of LDH in serum and 21 (46%) had elevated level of Lactate dehydrogenase (LDH).

Clinical stage: in the conducted research 19 (41%) of participants had clinical stage I, 10 (22%) participants had clinical stage II, 15 (33%) participants had clinical stage III and 2 (4%) participants had clinical stage IV.

More than one extranodal location affected by the disease: in the conducted research, 12 (26%) participants had nodal localization of the disease. Dissemination of the disease in one extranodal site had 14 (30%), in two 9 (20%), in three 8 (17%) and in four 3 (7%) participants.

Structure of the participants according to IPI risk groups in total sample N=46 DLBCL

In the conducted research 17 (37%) participants were in low, 14 (30%) in low intermediate, 10 (22%) in high intermediate, and 5 (11%) participants were in high risk group.

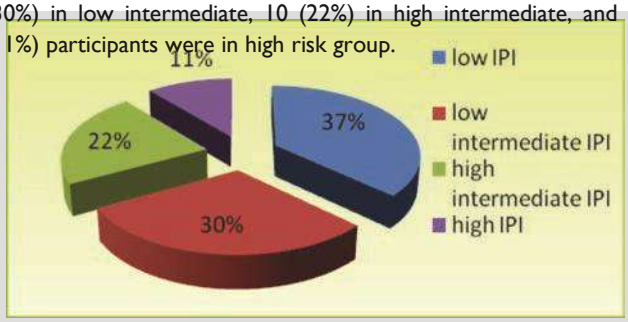

Figure 2 Structure of participants according to IPI risk groups N=46 DLBC, influence of IPI in relation to the first line therapy N=46 DLBCL.

Overall response of participants to the therapy: in the conducted research 24 (52%) participants achieved complete remission (CR) and 14 (30%) partial remission (PR). The overall response was: CR+PR= 38 (82%). Eight (18%) participants had primarily progressive disease (PD).

Influence of IPI >2 in achieving first complete remission

In the conducted research the first complete remission was achieved in 12 (71%) participants with low IPI, in 7 (50%) participants with low intermediate IPI, 4 (40%) participants with IPI high intermediate, and in 1 (20%) participant with high IPI.

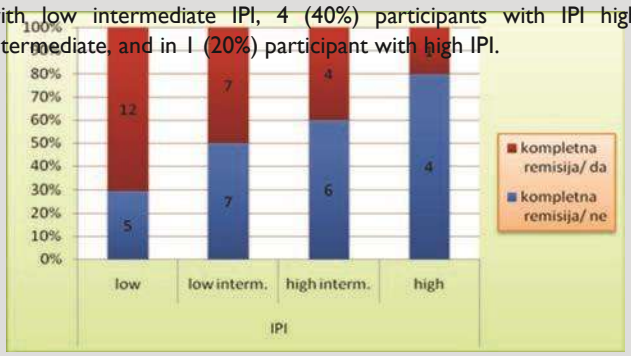

Figure 3 Influence of IPI >2 in achieving first complete remission in patients treated with first line immunochemotherapy in total sample N=46 DLBCL.

IPI is in correlation with achieving first complete remission. The correlation is negative and moderately strong (rho=-0,325). The achievement of first complete remission declines with the increase of IPI (p=0,028).

The proportion of participants in the total sample N=46 with IPI (low + low intermediate), in which a complete remission was present in positive predictive value (PPV). In the conducted research 31 participants had IPI (low + low intermediate), of whom 19 participants entered into complete remission, hence PPV (low + low intermediate) was 61%. The proportion of participants in the total sample N=46 with IPI (high intermediate + high) in which complete remission was absent in negative predictive value (NPV). In the conducted research 15 participants had IPI (high intermediate +high), of whom 10 participants did not enter complete remission, hence NPV IPI (high intermediate +high) was 66%.

Influence of IPI >2 on three-year survival

In the conducted research, 15 (88.2%) participants with low IPI survived three years after being diagnosed with DLBCL, 12 (85.7%) participants with low intermediate, 8 (80%) participants with high intermediate, whereas 2 (40%) participants with high IPI survived three years.

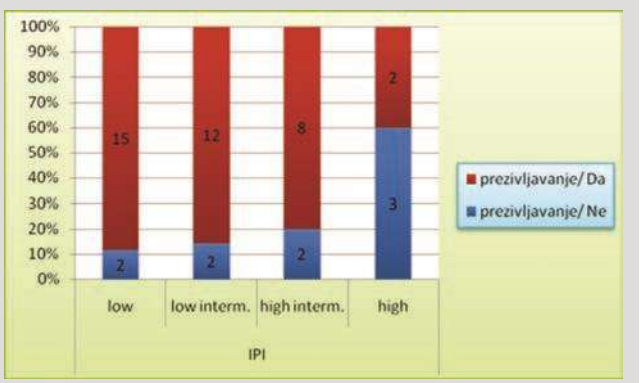

Figure 4 Influence of IPI >2 on three-year survival in the era of immunochemotherapy N= 46 DLBCL.

IPI is in correlation with three-year survival. The correlation is negative and moderately strong (rho=-0.482). Survival on the first line therapy moderately declines with the increase of IPI up to high IPI when it abruptly falls (p=0.047). The proportion of participants with IPI (low+low intermediate) who survived three years from the day of diagnosing the disease is positive predictive value (PPV). In the conducted research, 31 participants had IPI (low+low intermediate) of whom 27 survived three years; hence the PPV IPI (low+ low intermediate) is 87%. The proportion of participants with IPI (high intermediate +high) who did not survive three years from the day of diagnosing the disease is negative predictive value (NPV). In the conducted research 9 participants had IPI (high intermediate +high), of whom 3 participants did not survive three years; therefore the NPV IPI (high intermediate +high) is 33%.

Chance of survival in IPI<=2 is higher for 29% as compared to IPI>2, in other words in this population of participants the chance of survival ranges from 3-130% to the detriment of IPI<=. Average survival of participants with IPI <=2 is 52 months, or 95% CI (41-64 months), and it is longer than survival of participants with IPI >2 which amounts 18 months on average, or 95% CI (11-24 months). The presented differences in survival is statistically significant (p=0.008).

Kaplain Meier survival curve indicates that in the group IPI 0, 1, 2 (low + low intermediate) survivals of the participants are longer. In the group of patients with IPI 3, 4, 5 (high intermediate +high), the participants survive 30 months at most (Figure 1).

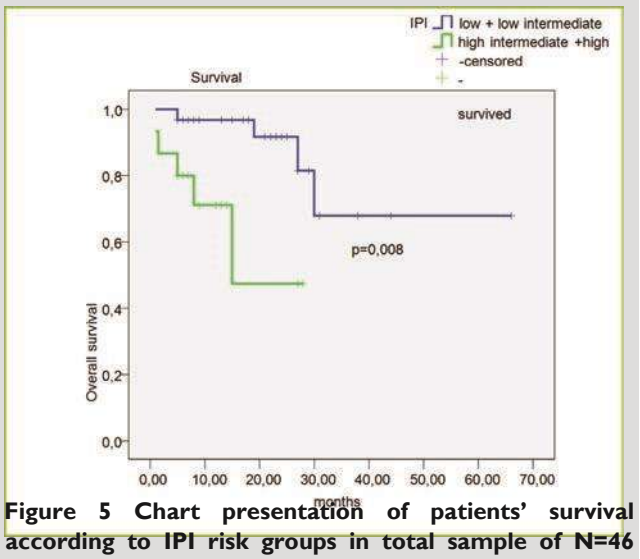

Figure 5 Chart presentation of patients' survival according to IPI risk groups in total sample of N=46 DLBC.

Response influence after the first line therapy on three-year survival

The participants who achieved first remission live on average 64 months, 95% CI (61-68 months). Participants with relapse live on average 23 months 95% CI (4-32 months). Examinees with primary progressive disease live on average 10.5 months, 95% CI (1-20 months).

Presented differences in survival of the participants categorized according to the progression of the disease are statistically significant (p<0.0005).

Multivariate analysis of independent variables on three-year survival

We examined the influence of independent variables (sex, age, ECOG, clinical stage, LDH, extranodal site) on three-year survival of examinees. Among the variables, LDH level proved statistically significant influence (normal versus elevated) p=0.03, OR=58.7, whereas sex, age, ECOG performance status, clinical stage, remained without statistically significant influence. If LDH level moves from normal into elevated, OR (chances for non-survival) increases by around 60 times (Table 1).

Table 1 Influence of independent variables (age, sex, ECOG, clinical stage, LDH, extranodal site) on threeyear survival in the total sample of N=46 DLBCL.

	ß	SE	Wald test	Df	P	Exp(ß)
Sex	-.806	.865	.868	1	.352	.447
Age	.087	.063	1.868	1	.172	1.090
ECOG	-.706	1.495	.223	1	.637	.494
Clinical stage	1.344	1.547	.756	1	.385	3.836
LDH	4.074	1.874	4.728	1	.030	58.792
Extranodal site	.073	.147	.246	1	.620	1.076

DISCUSSION

The study analyzed a correlation between predictive value of International prognostic Index and therapeutic response in 46 patients diagnosed with DLBCL de novo in the era of immunochemotherapy.

Median age was 52 years (from 24 to 74 years), 38 (82.6%) participants were younger, and 8 (17.4%) participants were over 60 years of age, but without confirmed significant influence of the age on the research results (p=0.172). The data of median age in this research to great extent differ from the data of the developed Western countries (14), where the highest number of diagnosed is in the age group of 65 years. However it is comparable to data obtained in researches conducted on examinees from non developed countries, including our country. The Uzurov-Dinić study, conducted at the Clinical Centre in Novi Sad, confirmed median of 54 years of age (15). In Brazil, the median age of the disease appearance was 43 years, in Egypt 47 years and in India 50 years (16,17,18). The explanation of this discrepancy of the median age in DLBCL occurrence has to be looked primarily in the exposure of probable risk factors in non developed countries, as well as in quality and availability of medical services for patients diagnose with this malignity. In this research, women were more represented than men (70%: 30%), which also did not have statistical significance on three-year survival of examinees (p=0.352). In the study of Gregorić, et al. from 2011, conducted at the Institute for Oncology in Ljubljana, the number of women was insignificantly higher than the number of men (55.3% vs. 44.7%) which can be explained by complex post-war epidemiological situation and demographic trends of population in Bosnia and Herzegovina and surrounding countries (19). In almost all relevant studies male sex was referred as dominant in DLBCL patients, but also as a factor that negatively influences on patients survival. The Carella study proved that male sex had unfavorable influence on fiveyear survival together with IPI (20). The same data were obtained in the study of Riihijärvi, et al. where female patients had significantly better four-year survival without progression of disease as compared to male patients (75% vs. 60%; p=0,013) (21). Also, the data of two separate, prospective studies conducted on the same participants should be taken into account. These studies confirmed that older male patients had faster clearance of rituximab, compared to female patients, which would explain negative influence of male sex on therapeutic outcome of DLCBL patients (22,23). In this study, 92% participants had ECOG performance status 0 and 1, while two (8.0%) participants had performance status 2 and 3. CR in the group with the performance status 1 achieved 83.1% participants, 72.4% participants with performance status 2, and 50% participants with ECOG performance status 3. It was established that the performance status

according to ECOG scale did not have statistically significant influence on threeyear survival of the participants (p=0.637). One of the most probable explanations of such research results could be obtained from the fact that the examinees in the presented research were relatively younger (50-60 years). Having in mind the fact that the scale in use was applied for quantification of general condition and the level of performance of everyday activities of patients with malign diseases, it is clear that the performance status in this case did not indicate a significant influence on three-year survival. The Abdelhamid's Study of DLBCL patients at Cairo University, confirmed that ECOG performance status had influence in achieving CR (p= 0.04) (17).

In this research, Cox regression analysis indicated independent statistically significant influence of the serum LDH level on three-year survival of the participants (p=0.03; OR= 58.7-95% CI 15.63-0.815). The participants with LDH level within normal reference values lived on average 8 months longer than the participants with higher level of serum LDH (p< 0. 0005). The obtained data correlates with the data obtained in the study of Sretenović, et al. (24,25). This study, without statistically significant influence, also proved infection of more than one extranodal location (p=0.620). Influence of extranodal location on response and three-year survival in DLBCL patients is very controversial, as it is exceptionally hard to define dissemination of the disease into extranodal location and primary extranodal site of DLBCL. It is because of this fact that Zhou, et al. (26) in their study mention the importance of dissemination disease location, and not the number of them, pointing out that patients with the disease affected on marrow bone, liver, lungs and CNS have higher risk and poorer prognosis. In the study of Ziepert, et al. (27) more than one extranodal location affected by the disease indicated a loss in its predictive value as compared to the Shipp, et al. (5) study. The authors pointed out that the oversight could appear between the clinicians, as in that period there was no unique consensus as to what was considered to be an extranodal location. The response of the patients in the conducted research was evaluated through achievement of the first complete remission and three-year survival. If we compare the obtained results with the study of Ship, et al. who initially suggested IPI as a predictor of achievement of first complete remission and five-year survival, we found that the participants in this research had a lower rate of complete remission achievement in all risk groups according to IPI (low: 87% vs. 71%; low intermediate: 67% vs. 50%; high intermediate: 55% vs. 40%; high: 44% vs. 20%). The discrepancy in the obtained data could be explained by the fact that in this research genetic profiling and immunophenotypic features of the participants were not taken into account. There is a possibility that the more aggressive subtypes of DLBCL were represented in patients included in this research. By comparison of two groups (IPI≤2 vs.IPI>2), a statistically significant difference in achieving the complete remission (p=0.028) was obtained. In this research, statistical significance of the participants' survival in relation to the response in the first line treatment (p<0.0005) was confirmed. That means that patients who had primarily progressive disease lived on average 10.5 months (95% CI: 1-20 months), whereas the participants who had relapse of the disease lived 23 months (95% CI; 14-32 months). The obtained results are comparable with the results of study of Coiffier, et al. (9) in which the median of the patients' survival who had a progression of the disease after the first line treatment was 1.2 years, whereas the patients who had primarily progressive disease lived on average 12.4 months (95% CI: .9-1.8; p<0.0001). IPI > 2 as a negative predictor of three-year survival as compared to patients with IPI≤2 was confirmed in this research (p=0.0047). The patients who were categorized as IPI≤2 had significantly longer three-year survival as compared to the participants with IPI>2 (OR=0.29 95% CI (0.03-1.30). In the research, patients in the low category according to the IPI had a rate of three-year survival of 88.2%, low intermediate 85.7%, high intermediate 80%, while patients with high risk had survival rate of 40%, which could be compared to the result of prospective study of Ziepert, et al. (27) where the low category had three-year survival of 91.4%, low intermediate 80.9%, high intermediate 65.1%, and high 59%. These results have confirmed additional value of IPI in the era of immunochemotherapy.

CONCLUSION

The achievement of the first complete remission declines with the increase of IPI (p=0.028). IPI is in correlation with three-year survival in relation to the response in the first line treatment. Survival related to a response in the first line treatment moderately declines with the increase of IPI up to high IPI when it abruptly falls (p=0.047). Average survival of patients with IPI<=2 is 52 months, or 95% CI (4164 months) and is longer than survival of the participants with IPI >2 which is on average 18 months or 95% CI (11-24 months). The indicated difference in survival is statistically significant (p=0.008).

Conflict of interest: none declared.

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Original article

Evaluation of diagnostic - therapeutical parameters of febrile neutropenia in children with acute leukemia

Evaluacija dijagnostičko - terapijskih parametara febrilnih neutropenija kod djece oboljele od akutnih leukemija

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ABSTRACT

Introduction: febrile neutropenias are emergency conditions which require necessary use of diagnostic-therapeutic procedures in children with acute leukemia during the treatment with cytostatics. Aim: to establish the value of diagnostic-therapeutic procedures which enable early recognition and adequate treatment of febrile neutropenias in order to prevent complications, primarily infections. Materials and methods: the study included 97 patients treated from acute leukemia at the Pediatric Clinic of the Clinical Center University of Sarajevo (CCUS) in the period from January 2010 to May 2015. Results: 80.4% of cases related to acute lymphoblast leukemia (ALL) and 19.5% to myeloid (AML). Male sex was dominant with 62.85%, and there were 42.3% of pre-school patients. Over three quarter of all acute leukemia (78.35%) related to ALL/L1 and ALL/L2. Out of the total number of patients (97) febrile neutropenia was present in 70 patients. Complications during febrile neutropenias related to infections were present in 47 (67.14%) patients while culture proven pathogens were found in 22 (31.43%) patients. Bacteremia/ sepsis was found in 7 patients, which was 10% of the total number of patients with febrile neutropenia or 14.89% of patients with infections, or 31.82% of all patients with positive cultures. Treatment in 41 patients consisted of the first line antibiotics administration (monotherapy), combination of the third generation of cephalosporin and aminoglycosides in 20 patients as well as modified therapy which included vancomycin, imipenem, parenteral antivirotis and antimycotics in 11 patients. Five/ multi-year survival without signs of illness was registered in 80.41% of our patients with mortality rate from AL at about 19.59% (out of 97 patients treated for ALL 19 died), ALL 12 (15.38%), and AML 7 (36.84%). Conclusion: based on the results of acute leukemia treatment it can be concluded that febrile neutropenias, as the most urgent conditions, should be recognized on time through clinical-diagnostic procedures and adequately treated in order to avoid more serious complications resulting in fatal outcome.

Key words: acute leukemia, febrile neutropenia, diagnosis and therapy, evaluation

SAŽETAK

Uvod: febrilne neutropenije predstavljaju hitno stanje koje zahtijeva ranu neophodnu primjenu dijagnostičko-terapijskih procedura kod djece oboljele od akutnih leukemija u toku tretmana citostaticima. Cilj rada: utvrditi vrijednost dijagnostičko-terapijskih procedura koje omogućavaju rano prepoznavanje i adekvatno liječenje febrilnih neutropenija u cilju sprečavanja komplikacija, prvenstveno infekcija. Materijali i metode: obuhvaćeno je 97 ispitanika tretiranih od akutnih leukemija na Pedijatrijskoj klinici Kliničkog centra Univerziteta u Sarajevu (KCUS) u period od januara 2010. do maja 2015. godine. Rezultati: akutnih limfatičkih leukemija je bilo 80,5%, a mijeloičnih 19,5%, muškog pola 62,85%, a predškolske dobi 42,3%. Više od tri četvrtine (78.35%) svih akutnih leukemija su bile tipa ALL/L1 i ALL/ L2. Od 97 pacijenata febrilne neutropenije smo imali kod 70 ispitanika. Komplikacije u toku febrilnih neutropenija u vidu infekcija smo imali kod 47 pacijenata (67,14%), a dokazane uzročnike u kulturama kod 22 pacijenta (31,43% pacijenata). Bakterijemiju/sepsu smo imali kod 7 pacijenata što je 10% svih pacijenata sa febrilnom neutropenijom, odnosno 14,89% svih pacijenata sa infekcijama ili 31,82% svih pozitivnih kultura. Tretman se sastojao od primjene monoterapije kod 41 pacijenta, kombinacije cefalosporina treće generacije i aminoglikozida kod 20 i modificirajuća terapija - vankomicin, imipenem, parenteralni antivirotici i antimikotici kod 11 pacijenata. Petogodišnje/ višegodišnje preživljavanje bez znakova bolesti kod naših pacijenata je iznosilo 80,41%, sa mortalitetom kod AL od 19,59% (od 97 tretiranih pacijenata sa ALL umrlih je bilo 19), ALL 12 (15,38%), AML 7 (36,84%). Zaključak: na osnovu rezultata tretmana akutnih leukemija može se zaključiti da febrilne neutropenije kao najurgentnije stanje treba na vrijeme prepoznati putem kliničko-dijagnostičkih procedura i adekvatno tretirati terapijom da ne bi došlo do težih komplikacija fatalnog ishoda.

Ključne riječi: akutna leukemija, febrilna neutropenija, dijagnoza i terapija, evaluacija

Evaluation of diagnostic - therapeutical parameters of febrile neutropenia in children with acute leukemia

INTRODUCTION

Pediatrics is medical field which deals with healthy and ill

children since birth until the end of adolescence. Important part of pediatrics dealing with malignancies of children (including leukemia) is pediatric oncology. Leukemia represents 30% of all malignancies of children age. The most common complication during the treatment of children with leukemia is febrile neutropenia. Neutropenia represents decrease in number of neutrophils in blood below 1,5 x109/L (1). If during the period of lowest number of neutrophil granulocytes (below 1x1x109/l) febrile state occurs over 38°C or if signs and symptoms of infection such as pharyngeal pain, cough, urinary problems, diarrhea, lesions in oral cavity, and infection of operative wounds occur we can suspect febrile neutropenia. The most frequent cause of infection is bacteria, fungi and viruses. The most frequent cause of bacterial infections is gram positive bacteria: Streptococcus pneumoniae, Streptococcus pyogenes (group A), Streptococcus viridans, Staphylococcus Aureus, and gram negative bacteria: Escherichia Coli, Salmonella, Proteus, Pseudomonas aeruginosa, Klebsiella and Bacteroides. In the last 20 years frequency of infections with gram positive bacteria has been in constant growth, because of the use of central venous catheter, use of antacids together with corticosteroid therapy and aggressive cytostatics leading to significant mucositis. Entry points of infection development in patients with neutropenia are blood (sepsis, bacteremia, fungemia), respiratory tract (upper respiratory tract: sinusitis, otitis, rhynopharyngitis and tonzillopharyngitis, laryngitis; lower respiratory tract: pneumonia, pleuritis), gastrointestinal tract (oral cavity: mucositis, oesophagitis, stomatitis, intestines: gastroenterocolitis, perineum cellulitis), skin (wounds, cellulitis), and urogenital tract (balanitis, vulvovaginitis, urinary tract infections). In febrile neutropenia increased body temperature is associated with infections in 50% of patient, and bacteremia is present in 20% of patients. According to number of neutrophils in blood, there are variations considering clinical aspect of patients. Patients with febrile neutropenia usually develop clinical aspect of infection. Body temperature in patients with neutropenia is usually increased (> 38.5°C or 38°C for more than one hour). In certain number of patients clinical aspect of infection does not have to occur, and increased body temperature can sometimes be the only sign. Diagnostic evaluation includes many aspects of evaluation such as anamnesis, physical examination, laboratory diagnostics, radiology diagnostics, and other imaging methods, even some invasive methods such as lumbar puncture, biopsy of lymph nodes or liver biopsy.

The Multinational Association for Supportive Care in Cancer risk index score (MASCC) is the way to evaluate the risk of originating febrile neutropenia. Based on the number of scores, patients with low risk receive oral antibiotic therapy, and patients with high risk intravenously antibiotics of wide spectrum (2). The use of antibiotic profilaxis in afebrile patients, except of the use of trimethoprim-sulfametoksazol in order to prevent Pneumocystis carinii, is not recommended because of the possible resistance of microorganism on antibiotic. Profilaxis with antifungal medication flukonasol and antiviral medicines acyclovir or ganciclovir guarantee successful alogene transplantation of hematophoetic stem cells. According to guidelines published by IDSA (Infectious Diseases Society of America) treatment of febrile neutropenia consists of: evaluation of patient, initial antibiotic therapy, use of antiviral medicines, transfusion of granulocytes, use of factors of granulocitopoesis, use of antimicrobic profilaxis at afebrile patients. Results of studies of European Organisation for research and treatment of cancer (EORTC) gave the advantage to antibiotic combination of cephalosporins of 3 and 4 generation with Amynoglicozids, but new studies about the effects of Imipenem and Meropenem reveal new possibilities of monotherapy in febrile episodes of neutropenic patients. Positive response on antibiotic therapy relate to a decrease of temperature below 38 0C, along with regression of other symptoms and signs of infection, if infection is clinically proved. Response on empiric therapy of antibiotic combination is expected after 72 to 96 hours since the beginning of therapy. If the response is negative antibiotic therapy is being modified based on bacteriology analysis and clinical findings. Death during the therapy is the source of constant fear during the treatment of ALL and although it is mostly caused by infection, it can also occur due to allergic reactions and thrombosis during the use of L-asparaginase, and nowadays it is considered unacceptable to be larger than 2% (3).

The aim of this paper was to establish the value and reliability of diagnostic-therapeutic parameters of febrile neutropenia in children with acute leukemia. The tasks of the study were: to show the frequency of febrile neutropenias in treatment of acute leukemia with cytostatics related to certain types of acute leukemia, sex, age, number of neutrophils and value of CRP; to evaluate diagnostic procedures related to complications of acute leukemia treatment mainly infections and results of taken and positive culture; elaboration of therapy, choice of antibiotics, the manner of antibiotic use along with conclusion after elaboration of the results.

Null hypothesis is that febrile does not represent the emergency condition which requires necessary use of diagnostic-therapeutic procedures in children with acute leukemia during the treatment with cytostatics. Alternate hypothesis is that febrile neutropenias are emergency conditions requiring necessary use of diagnostic-therapeutic procedures in children with acute leukemia during the treatment with cytostatics.

MATERIALS AND METHODS

The study included the total of 97 patients in the age since the birth to 18th years of age diagnosed with acute leukemia. The research had retrospective, descriptive and analitic aspect. The data was collected from the history of patients treated at the Department of Pediatric Hematooncology of the CCUS. The data related to the period from 1 January 2010 to 15 May 2016. The inclusion criteria were: diagnosed leukemia, complete anamnesis data, and trackable treatment results. Exclusion criteria were: incomplete anamnestic data, unknown treatment results, inadequate length of treatment and controls.

RESULTS

In the period from 1 January 2010 to 15 May 2016, a total of 99 children with leukemia were treated (40.6% of all children malignancies - 244 children) at the Department of Hematooncology of the Pediatric Clinic, CCUS. Acute leukemia was diagnosed in 97

patients, and chronic leukemia in 2 patients. Lymphoblastic or lymphatic acute leukemia occurred in 78 children (80.41%), or in 31.97% of all pediatric age malignancies. There was also 19 patients with acute myeloid leukemia (19.59%) or 7.79% of all pediatric age malignancies. Patients under treatment were from all parts of Bosnia and Herzegovina.

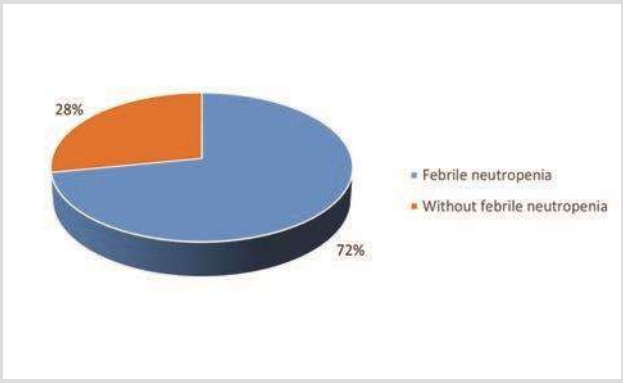

Figure 1 Presence of febrile neutropenia.

During the treatment these patients were hospitalized 5 times on average. Out of the total of 97 patients with acute leukemia there were 27 (27.8%) patients who did not have episodes of febrile neutropenia during any hospitalization stage (Figure 1). Out of the other 70 patients (72.7%), 39 (55.7%) had febrile neutropenia once, and 31 (44.3%) had febrile neutropenia multiple times (Figure 2).

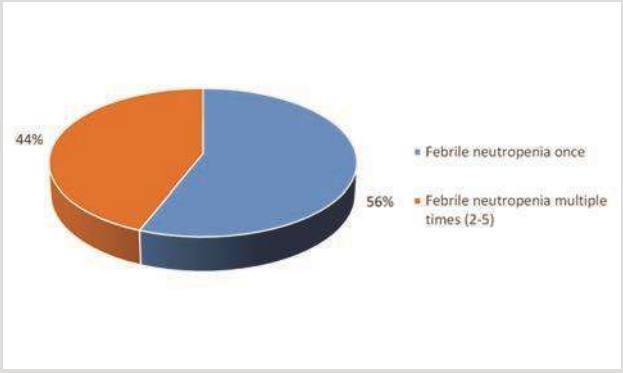

Figure 2 Frequency of febrile neutropenia.

Distribution of febrile neutropenia based on the level of neutropenia showed that the most frequent level of neutropenia occurred when the number of leukocytes was 500-1000 (37%) (Figure 3).

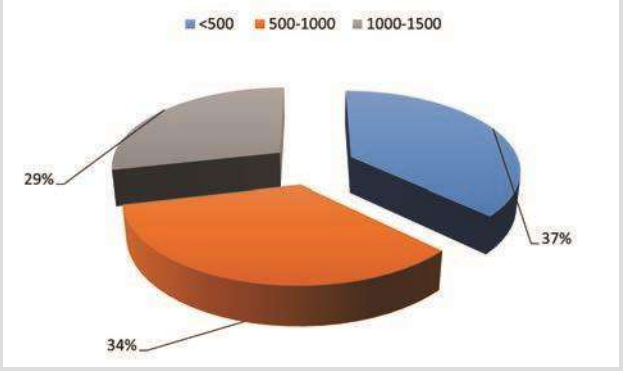

Figure 3 Distribution of febrile neutropenia based on the level of neutropenia/number of leukocytes.

The most frequent level of increased body temperature was 39-39.5 (Figure 4).

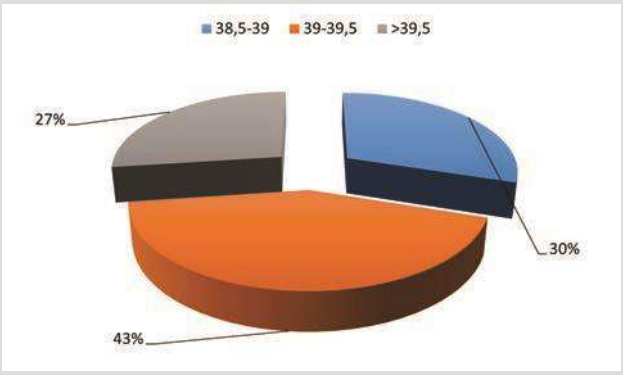

Figure 4 Distribution of febrile neutropenia based on the level of increased body temperature.

The most frequent value of C reactive protein (CRP) was over

Table 1 Value of CRP in patients.

Below 5	16	22.86%
5-50	23	32.86%
Over 50	31	44.28%
Total	70	100%

Out of 70 patients with febrile neutropenia 23 patients did not have any complications during febrile neutropenia, and other patients

Infection was present in 67.14% of cases (isolated positive culture

Table 2 Positive cultures during febrile neutropenia.

Positive cultures	Number of children	%
Hemocultures	7	31.82
Urine cultures	6	27.27
Coprocultures	3	13.64
Throat cultures	5	22.73
BAL	1	4.55%
Total	22	100%

py, antibiotic of the first line) (Figure 5), 66 were cured, and 12 died. Out of the total number of 19 patients with AML, 12 were cured and 7 died.

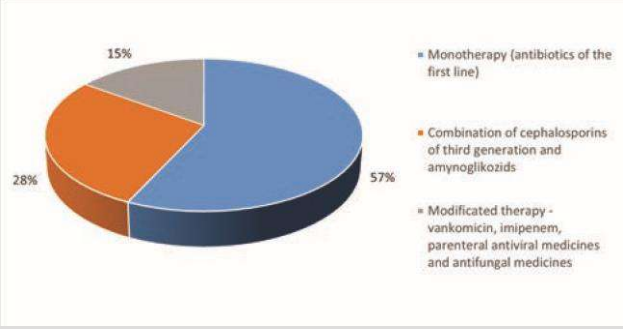

Figure 5 Treatment of febrile neutropenias.

Out of the total of 78 patients treated for ALL (57% as monothera-

(47) had one or multiple complications.

was found in 22 patients) (31.43%) (Table 2).

DISCUSSION

There was 80.4% of acute leukemia lymphatic or lymphoblastic type, and around 20% (19.5%) of acute leukemia of myeloid type, which is compatible with large epidemiologic studies in the world. Data related to larger incidence in male sex, in our case 62.85%, in the USA 1.2:1, is also quite compatible. We had more significant frequency of male sex with acute myeloid leukemia (78%). The largest incidence was registered in preschool children (42.3%). These results were expected and already described in the literature. The specific political and governmental situation in our country and the Federation of Bosnia and Herzegovina shows that our department is the main referral center in the entire area. Regarding the FAB classification the largest percentage related to ALL1 - 55.67%, ALL2 - 22.68%, and 78.35% of all acute leukemia related to ALL1 and ALL2. With the development of medicine and pediatric oncology, along with new diagnostic and therapeutic procedures, currently 5-year survival of these patients is over 80%. Mortality in AL was 19.59% (out of 97 treated patients 19 died). Total of 12 patients with ALL1 and ALL2 died (15.38%), and 7 with AML (36.84%). Globally, as stated in different literature, the survival is about 75-90%.

In our research febrile neutropenia during the treatment of ALL was present in 72.7% of children. Out of 70 patients with febrile neutropenia 23 (32.86%) did not have any complications during febrile neutropenia, and other 47 patients (67.1%) had one or more complications. Infection was present in 67 (14%) patients (isolated positive cultures were found in 22 patients (31.43%) out of 70 with febrile neutropenia). Hemocultures were positive in 7 patients, urine cultures in 6, nose and throat cultures in 5, coprocultures in 3 and BAL in 1 patient. Bacteremia/sepsis was present in 7 patients (14.89%). Medical staff is mostly afraid of G- bacteria and Streptococcus viridans (alfa hemolytic streptococc), which is proven to have significant penicillium resistance. In the last few years fungi infections are becoming more and more frequent (4). Spectrum of complications during the treatment of ALL was very wide starting from sepsis, bronchopneumonias, gastroenterocolitis, stomatitis, urinary tract infections, allergies on medicine, blood products, cytostatics; skin changes, TBC, Varicella virus, effusion of pericardium, effusion of pleura, Herpes labialis, pleuritis, mental changes, immunoodeficiencies, otitis acuta, dermatitis, macrohematuria, hematoma, cellulitis, subileus, holelytiasis, liver laesions, neuropathies, osteomyelitis, secondary malignancy, along with comorbidities such as diabetes, hypothireosis, which all indicate to the complexity of treatment. One complication was found in 11 patients, while 36 patients had more than one complication. Organs that were affected the most, except of blood, during febrile neutropenia were respiratory system, urinary tract, organs of digestive system, mucosis and skin.

Acute complications are being more and more researched through metabolic disorders, with following parameters of heart and brain hemostasis and obligatory multidisciplinary approach is highly recommended due to a better success during the treatment (5,6,7). There are indications that with following of liver protein synthesis during the treatment with L asparaginase genesis of febrile neutropenia could be predicted (following the level of antitrombin, fibrinogen) (4). Ewing S, et al. have found febrile episodes in 48% of children. Same authors found pneumonia in 35% of children, gastrointestinal tract infections in 7% of children, and urinary tract infections in 6% of children. The most frequent causes according to Jagarlamudi R, et al. are G+ bacteria (Staphylococcus Aureus and beta haemolytic streptococc) in 50% of children and G- bacteria in 30% of children, while fungi infections were found in 20% of children. Our therapy in all 70 cases of febrile neutropenia was supportive therapy. The total of 21 patients were taking antibiotics as monotherapy or antibiotics in combination with other antibiotics and antimicotics peroraly, 20 patients had monotherapy with antibiotic parenteraly, 18 patients had combined therapy most commonly with cephalosporins of third generation and aminoglycozids, while 11 patients used vancomycin, imipenem with occasional use of parenteral antiviral medicines and antifungal drugs. Antibiotic therapy is undoubtedly imperative, but groups of antibiotics that should be used are subject to constant discussions. According to Khuran, et al. it is necessary to define use of antibiotics more precisely based on resistance and use of new antibiotics (4).

American association for infections suggests monotherapy with ceftazidim or carbapenem - first line of antibiotics, combination of beta lactam antibiotics with aminoglycozids - second line of antibiotics, and use of vankomicin is suggested as a third line. National Comprehensive Cancer Network (NCCN) suggests monotherapy with carbapenem or cephalosporin with antipseudomonas activity (cefazidim, cefepim - in first line, in second line combination of aminoglycosids with antipseudomonas penicilin or antipseudomonas Cephalosporin, while third line represents antistafilococc antibiotic such as vancomicin or teicopen). German Association for Oncology and Hematology suggests aminoglycozids with azilaminopenicilin or cephalosporins 3rd or 4th generation or monotherapy with ceftazidim, cefepim, piperacilin or carbapenem.

Cytotoxic drugs have direct impact on bone marrow, and they lead to suppression of granulocyte colonies on the level of progenitory cells of bone marrow, damaging their DNA molecule directly. According to Kiralle, et al. the link between higher values of endocan (one of the newly discovered molecules in endotel cells) in serum and febrile neutropenia in newest studies is unreliable for diagnostics, and other indicators such as level of zinc in serum, as well as level of selen, retinol and tokoferol, with supplementation of antioxidans at the same time could possibly decrease the number of infections in patients with febrile neutropenia (8,9).

Phillips, et al. have opinion that predictive model should be developed with possibility to track many more parameters than it is the case at the moment (10). Risk from infection in patients can be predicted based on calculation of so called absolute number of neutrophils in blood (ANC - absolute neutrophil count). Practical Algorithms in Pediatric Hematology and Oncology 2003 defines leukopenia as neutropenia and/or leukopenia, but neutropenia is far more common and more important clinical problem.

Immunocompromised Host Society defines febrile neutropenia as a febrile state which is manifested by increased body temperature 38.5°C at one point or increase of body temperature over 38°C in time interval of 12 hours (some of the scientists take time interval of 4 hours), and neutropenia is defined as an absolute number of leukocytes below 0.5 x 109/L (<500/mm3) or if the number of neutrophil is <1000/mm3, and if further decrease of that number is expected in the next 24-48 hours below 0.5 x 109/L (<500 mm3).

Two most important question considering leukemia is its etiology and treatment. Etiology of leukemia has not been completely defined so far. Increased risk of leukemia is often connected with viruses, radiation and chemicals. Human T leukemia virus I (HTLV I) is one of the causes of leukemia. Mechanism of leukemogenesis is that virus is not completely defined. HTLV has some characteristics of both acute and chronical retroviruses. Acute retroviruses have gene which inducts transformation of cell. That is why for these viruses specific integration spot in genome of host is not necessary to achieve malign biological effect. Chronical retroviruses do not have these genes so transformation is a consequence of specific integration of virus in genome of host. In this case virus activates cell genes which leads to cell transformation. (11,12) Higher incidence of acute leukemia is associated with many congenital and attained diseases. The illness of stem hematopoetic cells evolutionary can become acute leukemia, that is way chronical myeloproliferative diseases and syndrome of myelodisplasia are often being called preleukemias. Ionizating radiation can most definitely cause acute and chronic leukemia (after atomic bomb explosion in Hiroshima and Nagasaki incidence of leukemia was 30 times bigger in radiated people than in those who were not affected by the bomb in any way). The higher incidence of leukemia was noticed in patients treated for ankylosing spondylitis. Leukemia has higher incidence in radiologists too, in persons who are in direct contact with benzene and benzene products, especially toluol, and also sometimes due to the treatment with drugs such as chloarmefenikol, fenilbutazon, sulfonamid and citostatics.

Besides clinical and hematological remission, there is more and more talk about remission on the cell level. That is why for estimation of treatment success of acute leukemia so called Minimal residual disease - MRD is being determined. Finding of high level of MRD (>103, namely finding of >1 leukemic cell on 1000 analysed cells at any point of measurement is connected with a risk of relapse. For estimating MRD-a cytogenetic methods and molecular analysis PCR (polymerase chain reaction) are being used. PCR is very important method for discovering MRD because it can reveal very small number of malign cells in bone marrow when the patient is in complete morphologic remission (<5% of malign cells in bone marrow with physiological finding of peripheral blood). Efficiency of AL treatment is being estimated by following leukemic cells disappearing from bone marrow during the use of therapeutic protocols (13,14,15).

Conflict of interest: none declared.

CONCLUSION

During cytostatic treatment of acute leukemia febrile neutropenia appeared in 72% of our patients, most commonly during neutropenia bellow 500 (37%), febrile state over 39 degrees (43%) and CRP over 50 (44%). We experienced complications in 47 patients (67%) while positive causers were proven in 22 patients (31%). Febrile neutropenia is one of the most urgent states in the treatment of children suffering from acute leukemia. With fast recognition, emergent diagnostics and energetic antibiotic treatment it is possible to prevent infections and possible lethal outcome thereof.

E. Hasanbegović

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Original article

Frequency of risk factors and presence of mitral regurgitation among patients with myocardial infarction according to its localization

Učestalost faktora rizika i prisustvo mitralne regurgitacije kod pacijenata nakon infarkta miokarda u odnosu na njegovu lokalizaciju

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ABSTRACT

Main risk factors for myocardial infarction are actually main risk factors for the atherosclerosis. Risk factors can be unchangeable (age, sex, family heritage, genetic disorders) or changeable (dyslipidemia, hypertension, smoking, diabetes mellitus, C-reactive protein, body mass index, physical inactivity, stress, postmenopausal estrogen deficiency, lipoprotein(a), excessive trans fatty acids intake, infection caused by Chlamidia pneumoniae). Mitral regurgitation is a frequent complication of the acute myocardial infarction. The aim of this study was to detect frequency of risk factors and presence of mitral regurgitation regarding localization of myocardial infarction. The study was carried out at the Clinical Centre University of Sarajevo. It included 80 examinees diagnosed with myocardial infarction and admitted at intensive and semiintensive care unit of the Clinic of Heart Disease, Blood Vessels and Rheumatism, in the period from August 2015 to March 2016. Examinees were divided into two groups based on localization of the myocardial infarction - antero-septo-lateral (ASL) and infero-posterior (IP) localization. Analyzing the presence of risk factors within the groups, the most represented risk factors in ASL-group were hypertension (60%) and hypercholesterolemia (57.5%), and hypertension (80%) and smoking (77.5%) in the IP group. Analysis of the groups shows that women smokers and women with diabetes are significantly more represented in the IP group ($p<0.05$). A total of 66 patients (82.5%) even developed mitral regurgitation as a complication of the myocardial infarction, of which 28 (70%) in the ASL group, and 38 (95%) in the IP group. Our study mostly included one-vessel coronary arterial disease with 68.7%. Conclusion: patients who smoke and have diabetes are more likely to develop infero-posterior than antero-septo-lateral myocardial infarction, which leads to more frequent developing of mitral regurgitation as a complication, due to occlusion of right coronary artery and ischemic rupture of the posterior papillary muscle.

Key words: risk factors, myocardial infarction, localization, mitral regurgitation

SAŽETAK

Glavni faktori rizika za infarkt miokarda su, zapravo, glavni riziko faktori za nastanak ateroskleroze. Faktori rizika mogu biti nepromjenjivi (dob, spol, naslijeđe, h+genetički poremećaji) ili promjenjivi (dislipidemija, hipertenzija, pušenje, dijabetes, C-reaktivni protein, indeks tjelesne mase, fizička neaktivnost, stres, postemenopauzalni deficit estrogena, lipoprotein, povećan unos trans masnih kiselina, infekcija bakterijom Chlamidia pneumoniae). Mitralna regurgitacija je česta komplikacija akutnog infarkta miokarda. Cilj ove studije je da ispitamo učestalost faktora rizika i prisustvo mitralne regurgitacije kod pacijenata nakon infarkta miokardau u odnosu na njegovu lokalizaciju. Ova studija je sprovedena na Kliničkom centru Univerziteta u Sarajevu. Uključivala je 80 ispitanika sa prethodnom dijagnozom infarkat miokarda primljenih na odjel intenzivne i polu-intenzivne njege na Klinici za bolesti srca, krvnih žila i reumatologiju, u period od augusta 2015. do marta 2016. godine. Ispitanici su podijeljeni u dvije grupe u odnosu na lokalizaciju infarkta miokarda - antero-septolateralna (ASL) i inferoposteriorna (IP) lokalizacija. Analizom prisutnosti faktora rizika u okviru grupa, najzastupljeniji faktori rizika u ASL grupi su bili hipertenzija (60%) i hiperholesterolemija (57,5%) dok su u IP grupi najzastupljeniji bili hipertenzija (80%) i pušenje (77,5%). Analiza među grupama je pokazala da su žene koje puše i žene koje imaju dijabetes signifikantno više zastupljene u IP grupi ($p<0,05$). Čak 66 (82,5%) ispitanika su razvili mitralnu regurgitaciju kao komplikaciju infarkta miokarda, od kojih je 28 (70%) bilo u ASL grupi, odnosno 38 (95%) u IP grupi. U našj studiji, najzastupljenija je bila jednosudovna koronarna arterijska bolest sa 68,7%. Zaključak: ljudi koji puše i imaju dijabetes će češće razviti inferoposteriorni nego anteroseptolateralni infarkt mikarda, što vodi većoj učestalosti razvijanja mitralne regurgitacije, usljed okluzije desne koronarne arterije i ishemične rupture stražnjeg papilarnog mišića.

Ključne riječi: faktori rizika, infarkt miokarda, lokalizacija, mitralna regurgitacija

INTRODUCTION

Acute coronary syndrome (ACS) refers to a spectrum of clinical presentations ranging from those for ST-segment elevation myocardial infarction (STEMI) to presentations found in non-ST-segment elevation myocardial infarction (NSTEMI) or in unstable angina. It is almost always associated with rupture of an atherosclerotic plaque and partial or complete thrombosis of the infarct-related artery. Therefore, main risk factors for myocardial infarction are actually main risk factors for the atherosclerosis.

Risk factors are certain diseases, pathological states, characteristics or habits, which are favorable, or lead to the development/occurrence of the certain disease and complications thereof. Presence of the risk factors does not mean that illness must occur, and, on the contrary, absence of the risk factors is not a warranty that it will not.

Risk factors can be unchangeable (age, sex, family heritage, genetic disorders) or changeable (dyslipidemia, hypertension, smoking, diabetes mellitus, C-reactive protein, body mass index, physical inactivity, stress, postmenopausal estrogen deficiency, lipoprotein, excessive trans fatty acids intake, infection caused by Chlamidia pneumoniae).

Many epidemiological studies have shown that age is a dominant risk factor for the coronary diseases. Arterial wall thickness is linearly increasing 3 times between 20 and 90 years of life, even in the absence of the atherosclerotic plaques (1). Approximately 10% of the myocardial infarction happen to the people younger than 40 years, and 45% to those younger than 65 (2).

Men are mostly affected with ACS, although this difference is progressively decreasing with older age. Women develop atherosclerotic changes approximately 10 years later than the men. It is explained with favorable influence of the estrogen to the lipoproteins, because estrogen increases HDL values, and decreases LDL and Lp(a), decreases oxidation of the LDL-particles, fibrinogen and homocistein. On the other hand, postmenopausal risk for the coronary disease in women is not significantly lower than in equally old men. Estrogen inhibits atherosclerosis or clinically significant coronary disease with direct effect on the arterial wall (3).

Dyslipidemia is mostly explored risk factor. There is a linkage between level of LDL cholesterol and increased frequency of the atherosclerosis. Low HDL-cholesterol level is also proved to be linked with increased frequency and intensity of the atherosclerosis. Correction of lipid status is prevention and treatment for atherosclerosis and its consequences, at the same time. Hyperlipidemia treatment decreases cardiovascular mortality for 30-40%, and decreases frequency of the non-fatal cardiovascular incidents (4).

Arterial hypertension, with Hyperlipidemia, is the most important risk factor for atherosclerotic plaques development. Hypertension is connected increased frequency of clinical manifestation of the atherosclerosis, such as myocardial infarction and cerebrovascular insult (5). More than 50% of the patients with IM, and even 2/3rd of the patients with apoplectic insult have had hypertension. In the moment of the firstly diagnosed hypertension, more than 60% already have certain atherosclerotic changes. Systolic pressure above 135 mmHg and diastolic pressure above 85 mmHg are already established as a high cardiovascular risk factor.

Tobacco smoking is one of the most important factors for the increase of the atherosclerosis frequency and development of its main consequences, especially peripheral arterial disease. It is especially emphasized when smoking is combined with other risk factors. Risk for coronary atherosclerosis is proportionate to the number of the smoked cigarettes per day and number of the years person smoked. After quitting smoking, the risk is significantly decreasing in the following 2-3 years, but it still remains higher that in non-smokers, up to 10 years. However, quitting is undeniable one of the most important protective measures in prevention of the early death from cardiovascular diseases.

Diabetes mellitus is a very important risk factor. Frequency and intensity/severity of atherosclerosis is significantly higher in patients with diabetes, especially type 2. Even three quarters of diabetic patients' deaths are caused by atherosclerosis, especially ischemic disease, myocardial infarction, ischemic stroke. Coronary disease mortality rate in diabetic patients is almost 10 times higher than in patients who do not suffer from diabetes. Diabetic patients also have unfavorable long-term prognosis after myocardial infarction, including higher risk for re-infarction, congestive heart failure and death (6).

Obesity is spread worldwide with more than one billion overweight people and more that 300 million who are clinically obese. Obesity is considered to be chronic disease which leads to the massive, chronic noncommunicable diseases, such as atherosclerosis, type 2 diabetes, nonalcoholic liver steatosis, cancer and osteoarthritis. Excessive fat tissue increases atherosclerosis, lowers insulin resistance and promotes progression of type 2 diabetes with cytokine and bioactive substance secretion (7).

Insufficient physical activity or physical inactivity are major risk factors. Regular physical activity lowers blood pressure, improves glucose tolerance and positively affects blood coagulation, increases HDL level, decreases triglycerides in blood (2).

Psychosocial and behavior patterns are also considered as risk factors. Socio-economic status, education level, incomes are affecting health status in a way that those persons with lower determinants are 3 times more likely to have coronary disease than those with higher, mostly because they smoke more, consume more alcohol and eat unhealthier (8).

Genetic predisposition is very important, but unfortunately, unchangeable risk factor for even 50% developed atherosclerosis (9).

Elevation of plasma fibrinogen increases blood viscosity and platelet aggregation and several epidemiological studies imply its relation with coronary diseases and stroke (10). Increased homocysteine blood level doubles the risk of infarction, regardless the sex.

Mitral regurgitation is a frequent complication of the acute myocardial infarction. Ischemic mitral regurgitation that follows myocardial infarction is proven to be poorer prognostic factor and it is related to higher mortality rate. It is a result of the multifactorial processes on the mitral valve level which cause systolic blood return/ recurrence from left ventricle to the left atrium.

The aim of this study was to detect frequency of risk factors and presence of mitral regurgitation in respect of the myocardial infarction localization.

MATERIALS AND METHODS

This study was conducted at the Clinical Centre University of

Sarajevo. It included 80 examinees diagnosed with myocardial infarction and admitted at the Intensive and Semi-intensive Care Unit of the Clinic of Heart Diseases, Blood Vessels and Rheumatism, in the period from August 2015 to March 2016.

Examinees were divided into two groups based on the myocardial infarction localization:

1. 40 patients of both sexes, diagnosed with the antero-septo-lateral myocardial infarction (ASL group);
2. 40 patients of both sexes, diagnosed with the infero-posterior myocardial infarction (IP group).

Inclusion criteria were as follows:

- Patients hospitalized at the Clinic of Heart Diseases, Blood Vessels and Rheumatism in the period from August 2015 to March 2016;
- Patients with verified diagnose of the antero-septo-lateral or infero-posterior myocardial infarction, based on clinical examination and parameters established by a cardiologist (clinical manifestation, ECG, biochemical markers, Color Doppler ultrasound);
- Patients who underwent coronary catheterization;
- Existence of the discharge letter and necessary laboratory findings, anamnesis, i.e. patients with complete data history.

This retrospective study collected data from patients' histories: age, sex, smoking defined as minimum of 5 cigarettes in previous month, hypertension defined as previously diagnosed hypertension by the family medicine doctor, usage of antihypertensive medication and average values of systolic blood pressure above 140 mmHg and diastolic above 90 mmHg after third measuring in the hospital, hypertriglyceridemia defined with triglyceride serum values above 1,7 mmol/L, hypercholesterolemia defined with total cholesterol values above 5,0 mmol/L, diabetes defined as serume glucose level above 11,1 mmol/L, documented history of type 2 diabetes and/or use of antidiabetic medications. Color Doppler 3D echocardiographic findings verified the existence and quantification of the mitral regurgitation using several parameters: vena contracta width (VCW), regurgitation volume (RVol), fraction (RF) and effective regurgitant orifice area (EROA).

Statistical analyses

Statistical analyses were realized using statistical package IBM Statistics SPSS (v. 21.0, SPSS Inc., Chicago, Illinois, USA). Values were expressed as mean, standard deviation (SD), standard error of the mean (SEM). Comparison between mean values of groups was performed by Student's t-test. Analysis of associations between outcome and categorized risk factors was done with the chi-square test. P values less than 0.05 were considered statistically significant.

RESULTS

The study included 80 patients diagnosed with myocardial infarction, specifically 57 (71.3%) male and 23 (28.8%) female patients. Average age in total sample was 60.5±12.7 years, with the youngest patient aged 29 and the oldest 85.

Patients were divided into two groups of 40 patients of both sexes, based on the myocardial infarction localization. The first group consisted of patients diagnosed with antero-septo-lateral (ASL) myocardial infarction, and the second group of patients diagnosed with infero-posterior myocardial infarction. The ASL-group included 28 (70%) male patients, with equal representation of those who were younger and older than 59 years; and 12 (30%) female patients, of which 7 (58.3%) were younger than 59 years ($p>0.05$). The IP group included 29 (72.5%) male patients and 11 (27.5%) female patients. In both groups insignificant number of patients was older than 59 years ($p>0.05$). There was statistically significant difference between the sex in both groups ($p<0.05$).

Table 1 Presence of the risk factors in patients with myocardial infaction regarding its localization.

		ASL		IP		TOTAL
Smoking $X^2=4,528$; $p=0,032$	N	22	N	31	N	53
	%	55.0	%	77.5	%	66.3
Diabetes $X^2=7,040$; $p=0,015$	N	7	N	18	N	25
	%	17.5	%	45.0	%	31.3
Hypertension $X^2=3,810$; $p=0,087$	N	24	N	32	N	56
	%	60.0	%	80.0	%	70.0
Hypertriglyceridemia $X^2=0$;$p=1$	N	21	N	21	N	42
	%	52.5	%	52.5	%	52.5
Hypercholesterolemia $X^2=1,529$; $p=0,216$	N	23	N	17	N	40
	%	57.5	%	43.6	%	50.0

Analyzing the presence of risk factors within the groups, the most represented risk factors in the ASL group were hypertension (60%) and hypercholesterolemia (57.5%), and hypertension (80%) and smoking (77.5%) in the IP group. The least represented risk factor in the ASL group was diabetes (17.5%), and hypercholesterolemia (43.6%) in the IP group. There was statistically significant difference between the ASL and IP group regarding diabetes, which was more represented in the IP group patients ($p<0.05$) (Table 1).

Table 2 **Presence of risk factors in patients with myocardial infaction in relation to sex (M-male, F-female) and localization.**

		ASL			IP			TOTAL
		M	F		M	F		
Smoking	N	18	4	N	22	9	N	53
	%	64.3	33.3	%	75.9	81.8	%	66.3
Diabetes	N	3	4	N	10	8	N	25
	%	10.7	33.3	%	34.5	87.5	%	31.3
Hypertension	N	16	8	N	23	9	N	56
	%	57.1	66.7	%	79.3	81.8	%	70.0
Hypertriglyceridemia	N	14	7	N	14	7	N	42
	%	50.0	58.3	%	48.3	63.6	%	52.5
Hypercholesterolemia	N	16	7	N	13	4	N	40
	%	57.1	58.3	%	44.8	36.4	%	50.0

In the ASL group, the most represented risk factors among men were smoking (64.3%), hypertension (57.1%) and hypercholesterolemia (57.1%), and among women the most represented risk factors were hypertension (66.7%), hypertriglyceridemia (58.3%) and hypercholesterolemia (58.3%). In the IP group, men were mostly hypertensive (79.3%) and smokers (75.9%), as well as women (81.8%). Analysis of the groups showed that women smokers and diabetic were more represented in the IP group, which was statistically significant ($p<0.05$) (Table 2).

Table 3 **Frequency of mitral regurgitation (MR) in relation to the myocardial infarction localization ($X^2=8.658$; $p=0.003$).**

		ASL	IP	Total
Presence of the MR	N	28	38	66
	%	70.0	95.0	82.5
Absence of the MR	N	12	2	14
	%	30.0	5.0	17.5
Total	N	40	40	80
	%	100.0	100.0	100.0

Our study mostly included one-vessel coronary arterial disease (CAD), with 68.7%, followed by three vessels CAD with 17.5% and, finally two-vessels CAD with 13.7% of the total number of patients with myocardial infarction.

In the one-vessel CAD, LAD was mostly occluded with 96.4% in the ASL group, and RCA in the IP group (59.3%), which was statistically significant based on the myocardial infarction localization ($p<0.05$).

In the two-vessels CAD, LAD and CX were mostly occluded in the ASL group (57.1%), and LAD and RCA in the IP group (100.0%), which was statistically significant between the groups, ($p<0.05$), and which also made LAD and RCA occlusion the most represented in two-vessels CAD in our study (45.5%).

In this study, 66 patients (82.5%) developed mitral regurgitation (MR) as a complication of the myocardial infarction, of which 28 (70%) in the ASL group, and 38 (95%) in the IP group.

Analysis of the mitral regurgitation (MR) presence regarding the localization of the myocardial infarction showed that MR was significantly more common in the IP group of patients (95.0%) and than in the ASL group (70.0%) ($p<0.05$) (Table 3).

MR was more represented in women (91.3%) than in men (78.9%), without significant difference, regardless of the myocardial infarction localization ($p>0.05$). Average age of patients who developed MR was 62,5±12 years, which was significantly higher than the average age of the patients who did not develop MR, which was 51.4±12.3 years ($p<0.05$).

Mitral regurgitation was also significantly more common in patients older than 59 years (93%) compared to those who were younger than 59 (70.3%) ($p<0.05$).

I grade MR was mostly represented with 43.9%. Comparing the two groups, I grade was mostly represented in the ASL group (50.0%) and II grade in the IP group (44.7%), which was statistically significant in respect to the localization ($p<0.05$).

DISCUSSION

Cardiovascular risk factors are characteristics or symptoms significantly linked with increased incidence, prevalence, morbidity and mortality of certain cardiovascular diseases. Their significance was firstly described in Framingham study reports, and nowadays, risk factors are used to identify individuals with increased risk for developing certain condition or illness, apart from healthy population (11).

In our study, cardiovascular risks were present in a significant number. In a general sample, there were more men than women in both groups, which confirm the thesis that males present a risk factor regardless of the other risk factors presence. Atherosclerotic changes, especially of coronary and peripheral blood vessels, happen approximately 15 years later in women. Coronary atherosclerosis' mortality rate between 35 and 44 years is 5.2 times higher in men then in women (12). Beside sex, significant risk factors between these two groups are smoking, hypertension and hypercholesterolemia.

The most represented risk factors in the group of patients with antero-septo-lateral localization of the myocardial infarction were hypertension (60%) and hypercholesterolemia (57.5%), among men smokers (64.3%) and among women with hypertension (66.7%).

On the other hand, most represented risk factors in the group of patients with infero-posterior localization of the myocardial infarction was hypertension (80%) and smoking (77.5%), with hypertension as a main risk factors for both sexes (79.3%; 81.8%).

Van der Meer et al. analysis of the risk factors and progression of atherosclerosis shows that age, smoking, total cholesterol and hypertension present strong independent predictors for development of polivascular atherosclerotic disease (13).

There was statistically significant difference between the ASL and IP group regarding diabetes, which was more represented in the IP group patients ($p<0.05$).

International REACH study showed similar results to ours, namely that type 2 diabetes was represented in smaller percentage in patients with coronary disease.

Arterial hypertension is the main risk factor of the cardiovascular morbidity and mortality in developed countries. More than 50% of patients who suffered myocardial infarction and even two third of the patients with cerebrovascular stroke suffer from hypertension (14). In our study, hypertension was slightly more represented in the IP group.

Smoking is a major risk factor and it could be completely diminished. Consequences of smoking on the cardiovascular system could be devastating, and statistic reports are very significant. Smoking doubles the risk for developing polivascular atherosclerotic disease, and as a risk factor causes 350 000 of deaths per year in the USA, which is more than combined effect of the drug, medication and other abuses (15).

Smoking in our study was significantly more represented in the IP group than in the ASL group ($p<0.05$), and it was main risk factor in women with IP localization of the myocardial infarction.

EUROASPIRE I study was carried out in the period from 1995 to 1996. It included 3569 examinees with coronary disease, and EUROASPIRE II study was carried out from 1999 to 2000 and included 3379 examinees. The aim of the study was identifying and following risk factors for the development of the cardiovascular diseases in order to determine the best preventive strategy. Results of the second study showed that incidence of the obese and hypertensive patients was higher, as well as the smokers (16).

Results of our study showed that smoking and diabetes were more represented in the group of patients with IP localization of the myocardial infarction, with statistical significance. Hypertriglyceridemia and male sex were equally represented in both groups as risk factors. Insignificantly, hypertension was more represented in the IP group, and hypercholesterolemia in the ASL group.

Hypertension, hyperglycemia, smoking and Hyperlipidemia are

all modifiable risk factors. Assessment of the risk factors for development and outspread of the atherosclerosis are basic methods for the risk assessment in order of defining and determining preventive measures of the lifestyle changes and therapeutically interventions, therefore, reducing the frequency of the atherosclerotic complications, such as myocardial infarction.

This research determined the most occluded blood vessels in the patients with the myocardial infarction in relation to the localization of the infarction. Our patients mostly had one-vessel coronary arterial disease (CAD) with 68.7%. In the ASL group the mostly occluded was left anterior descending artery (LAD) with 96.4%, and in the IP group the right coronary artery (RCA) with 59.3%, with statistically significant difference between the groups.

Two-vessels coronary arterial disease was represented with 13.7%, with mostly occluded left anterior descending artery (LAD) and circumflex coronary artery (CX) with 57.1% in the ASL group, and left anterior descending artery (LAD) and right coronary artery (RCA) with 100.0% in the IP group of two-vessels CAD ($p<0.05$).

Three-vessel coronary arterial disease was represented with 17.5% in this study sample.

Mild mitral regurgitation is commonly found in acute coronary syndrome. Ischemic mitral regurgitation is more present in the cases of myocardial infarction, rather than cases with angina pectoris, where mitral regurgitation fades away following decrease of acute ischemia itself.

In this study, mitral regurgitation was diagnosed in 66 (82.5%) patients after myocardial infarction. This incidence was interpreted in a way that even the mildest grades of the mitral regurgitation were diagnosed and adopted in this study. In large number of patients "functional" ischemia was noted, where papillary muscles, chords and mitral cuspises remained normal. Therefore, it is very important that doctor right after myocardial infarction have an insight in the patient's previous medical history, and other diagnostic procedures, such as electrocardiography and angiography, because these procedures exclude structural mitral regurgitation and confirm secondary, ischemic MR (17).

MR was present in 38 (95%) patients with the infero-posterial localization of the IM, in relation to 28 (70%) patients with anterosepto-lateral localization of the myocardial infarction, with statistical significance ($p<0.05$).

The most common cause of the MR incidence in patients with IP localization of the myocardial infarction is the occlusion of the right coronary artery which is dominant in this type of infarction. Right coronary artery is the only blood vessel which vascularizes postero-medial papillary muscle. Furthermore, ischemia of this muscle progress in the rupture of the muscle which as a consequence has mitral regurgitation. Antero-septal papillary muscle has double vascularization, from the left anterior descending artery and circumflex artery, and, therefore, it is more difficult to develop ischemia and rupture of this papillary muscle, which would lead to the mitral regurgitation in patients with anterosepto-lateral myocardial infarction (18).

The most represented was Grade I of the mitral regurgitation with 43.9%, followed by Grade II with 42.4%. The least represented was Grade IV with 1.5% of patients. Grade II and III were more represented in the IP group of patients, with statistical significance.

In 2003 Toshiro, et al. from Kagoshime, Japan, published a research about incidence of mitral regurgitation in 103 patients with myocardial infarction (61 with anterior and 42 with posterior IM) and 20 patients in the control group without IM. Incidence of the significant mitral regurgitation was higher in patients with inferior IM 16/42 (38%) rather than anterior IM 6/61 (10%), ($p<0.001$). This study conclusion was that higher incidence and severe grades of the MR are associated with the severe geometrical changes in mitral valve apparatus with great shift of posterior papillary muscle, caused by infero-basal localized remodeling of the left ventricular (19).

CONCLUSION

The analysis of the risk factors frequency, in relation to the myocardial infarction localization, established that smoking and diabetes were more represented in the group of patients with infero-posterior localization of the myocardial infarction, with statistical significance. Hypertriglyceridemia and male sex were equally represented in both groups as risk factors. Insignificantly, hypertension was more represented in the IP group, and hypercholesterolemia in the ASL group. Also, analysis of the groups showed that women smokers and diabetic were more represented in the IP group, with statistical significance. Mitral regurgitation was significantly more common in the IP group of patients than in the ASL group. Average age of the patients who developed MR was 62.5±12 years, which was significantly higher than the average age of the patients who did not develop MR, which were 51.4±12.3 years. Mitral regurgitation was also significantly more common in patients older than 59 years (93%) compared to those who were younger than 59 (70.3%) ($p<0.05$). In general, patients who are smokers and have diabetes are more likely to develop infero-posterior than antero-septo-lateral myocardial infarction, which make them more likely to develop mitral regurgitation as a complication, due to the occlusion of right coronary artery and ischemic rupture of the posterior papillary muscle.

Conflict of interest: none declared.

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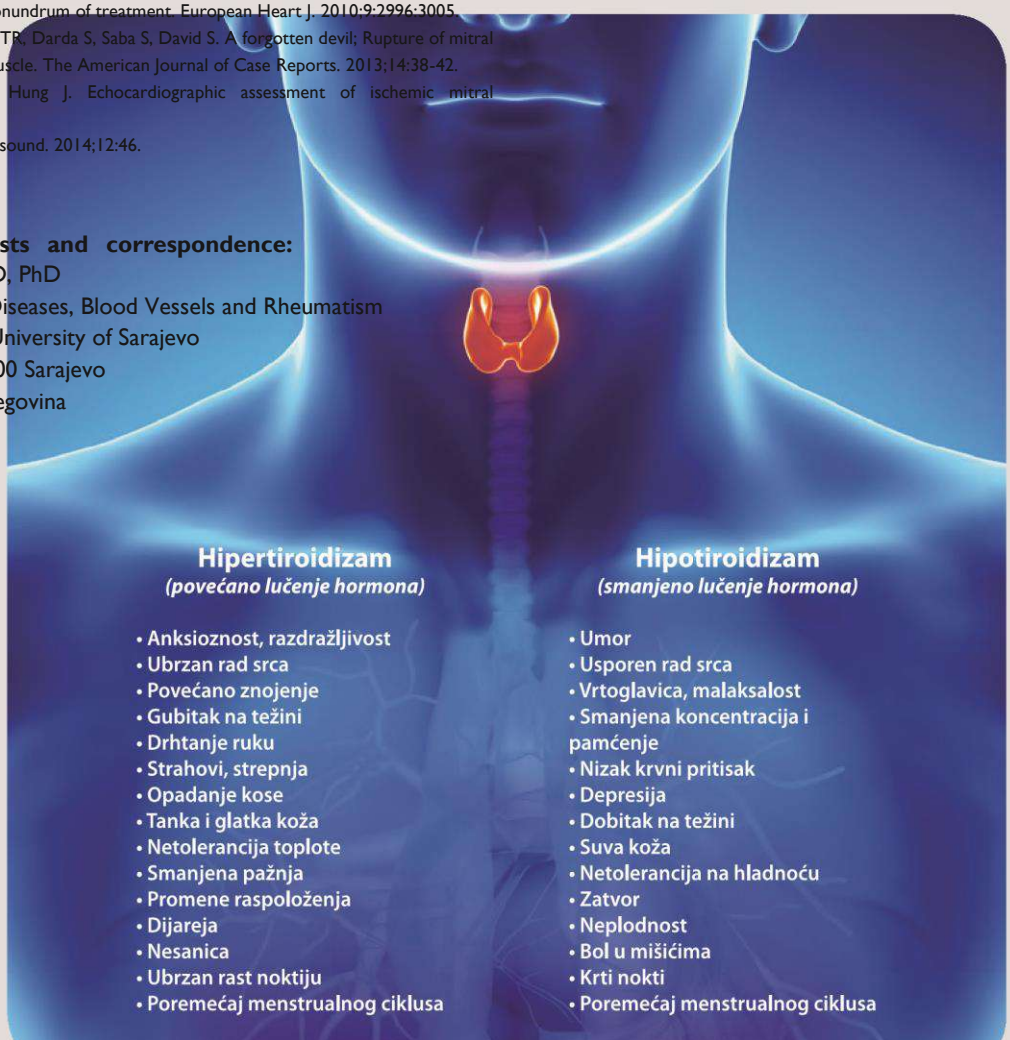

Medical Journal (2016) **Vol. 22, No 4**, 183 - 187 **Original article** **Platelet-rich Plasma in the treatment of gonarthrosis**

ABSTRACT

Aim: degenerative knee diseases, the most common of which is arthrosis, represent a serious therapeutic problem. In addition to its incidence, its rapid evolution also represents a particular challenge in the treatment. Gonarthrosis is the second most common reason for appointments with orthopedist due to the "back pain" syndrome. It is estimated that 12% of the world population aged over 25 years have clinical signs and symptoms of knee arthrosis, while more than 80% of persons aged over 75 show symptoms of gonarthrosis. This paper presents the results of degenerative knee diseases (gonarthrosis) treatment with the Platelet-rich Plasma method in the Hospital for Surgical and Internal Medicine "Stetik" in Banja Luka. Materials and methods: in the period from 1st February 2011 to 30 June 2015, we applied the Platelet-rich Plasma method, according to our protocol (3 administrations every 7 days), in the treatment of 217 female patients aged between 48 and 79 years, with clinical manifestations of unilateral knee arthrosis of the 2nd grade of the Kellgren-Lawrence Grading Scale. Results: analysis of the Platelet-rich Plasma PRP method results in the treatment of the second grade gonarthrosis, using the WOMAC index evaluation, showed that for 84.3% of patients the results were excellent, for 11.5% of them the results were good, while for 4.2% of patients the results were poor. Conclusion: according to the results obtained through this study, it is evident that the treatment of degenerative knee diseases using the Platelet-rich Plasma (PRP) method has good initial results and it should be considered as a method of choice in terms of the gonarthrosis treatment. In addition to the promising results obtained in this study, it should be noted that a lot has to be done to further examine full effects of the PRP and its elements and to set up a defined indication area, with standardized protocols of the number and incidence of the Platelet-rich Plasma administrations.

Key words: Platelet-rich Plasma, gonarthrosis, WOMAC

SAŽETAK

Cilj: degenerativna oboljenja koljena od kojih je najčešća artoza predstavljaju ozbiljan terapeutski problem. Učestalost i brz evolutivni tok su poseban izazov u liječenju ove bolesti. GA je drugi najčešći razlog dolaska na pregled kod ortopeda nakon sindroma „bolnih leđa". Procijenjeno je da 12% svjetske populacije u dobi> 25 godina imaju kliničke znakove i simptome artroze koljena, a preko 80% osoba starijih od 75 ima simptome GA. U radu prikazujemo rezultate liječenja degenerativnih oboljenja koljena (gonartoze) metodom „Plazme obogaćene trombocitima" u Bolnici iz hirurških i internističkih oblasti „Stetik" u Banjaluci. Materijali i metode: u periodu 01.02.2011. do 30.06.2015. godine metodom „Plazme obogaćene trombocitima",po našem protokolu od 3 aplikacije svakih 7 dana liječili smo 217 osoba ženskog pola starosti od 48-79 godina sa kliničkim manifestacijama unilateralne artroze koljena II stepena klasifikacije po Kellgren Lawrencu. Rezultati: na osnovu analize rezultata primjene ove metode liječenja (PRP) u liječenju gonartroze II stepena, a koristeći evaluaciju putem WOMAC indexa, kod 84,3 % oboljelih smo imali odlične rezultate, kod 11,5 % oboljelih imali smo dobre rezulate, a kod 4,2 % oboljelih smo imali loše rezultate. Zaključak: prema rezultatima koje smo dobili u ovom radu potpuno je vidljivo da liječenje degenerativnih oboljenja koljena metodom Plazme obogaćene trombocitima (PRP) ima dobre početne rezultate i treba je uzeti kao jednu od metoda izbora u liječenju gonartroze. Pored obećavajućih rezultata dobijenih u ovom radu treba biti iskren i reći da je potrebno još puno rada na ispitivanju potpunog dejstva PRP i njenih elemenata kao i na postavljanju jasnog indikacionog područja uz standardizovanje protokola broja i učestalosti apliciranja plazme obogaćene trombocitima.

Ključne riječi: plazma obogaćena trombocitima, gonartroza, WOMAC

INTRODUCTION

Degenerative joint diseases are the most common type of joint diseases in orthopedic surgery and damage in the knee joint is usually defined as gonarthrosis (Latin: Gonarthrosis, English: knee arthritis). In the knee joint, three bones get into contact, namely the thignbone (Latin: femur), the shinbone (Latin: tibia) and the kneecap or kneepan (Latin: patella) (Figure 1). These three bones are covered with cartilage in places of contact. Cartilage is a type of connective tissue containing a solid intercellular substance and cartilage cells. Cartilage cells, called chondrocytes, are located in cavities (lacunae) of the intercellular substance and surrounded by a markedly basophilic membrane. Chondrocytes have a round or oval shape. The cytoplasm contains developed rough endoplasmic reticulum, mitochondria and the Golgi apparatus. They produce secrete components of the matrix, namely molecules of proteoglycans and collagen. The intercel-

Plazma obogaćena trombocitima u liječenju gonartroza

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lular substance of cartilage is an amorphous mass which bases are proteoglycans, structural glycoproteins and collagen fibers. In hyaline and elastic cartilage, collagen fibers built of type II collagen are found, while fibrocartilage contains collagen fibers built of type I collagen. Proteoglycans are linked into proteoglycan chains by hyaluronic acid and they contain glycosaminoglycans such as chondroitin-4-sulfate, chondroitin-6-sulfate and keratan sulfate. Glycoprotein hydronectine is a binding agent of chondrocytes, together with collagen. It has the consistency of rubber or tire and it can be cut and folded. Functional characteristics of cartilage come from intercellular substance, especially its fibrous component. Cartilage tissue does not contain blood vessels, so it is fed from connective tissue surrounding the cartilage - perichondrium and synovial fluid. Cartilage has no nerve endings; therefore it is not innervated (1).

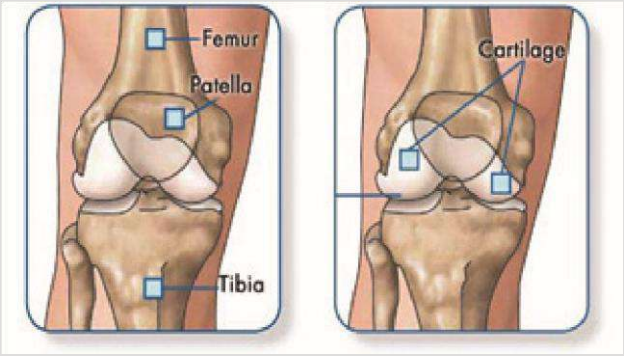

Figure 1 Scheme of the knee.

Changes in the knee cartilage in young people occur due to injuries, while in the elderly they occur as a result of degenerative cartilage changes (spending). Risk factors for gonarthrosis include age, injuries, anatomical abnormalities, heritage, high values of bone density, hypermobility of joints, obesity, and muscle weakness. Gonarthrosis (GA) or osteoarthritis (OA) begins as a lack or loss of the cartilage surface, with further subchondral progress into epth, eventually leading to complete loss of cartilage, with an exposed bone. The main symptoms of gonarthrosis are pain in the knee, limited range of motion and swelling (2).

The diagnosis is usually established based on medical history dominated by pain going down the stairs, which occurs a few months prior to doctor's appointment, with limited range of motion, especially when it comes to bending. The pain eventually becomes intense even at rest, while pain during the night is also common. Long-term pain may result in limping. Clinical examination reveals a swelling in the knee (with symptoms of reactive synovitis), with audible crepitus, and varus or valgus deformity. Palpation causes a dominant pain on the inner side, in the area of the medial collateral ligament and muscle insertion of the so-called goose foot (Latin: pes anserinus). Quite often an examination reveals a limited range of motion (bending the knee further than 90 degrees causes intense pain). In diagnostics, standard radiographs of the knee are usually sufficient. Using them, we can classify gonarthrosis (3).

Nowadays, the Kellgren and Lawrence system for classification of degenerative knee diseases is commonly used. This classification has 5 grades. It was published in 1957 and since 1961 it has been applied by the World Health Organization (WHO) (Figure 2) (4).

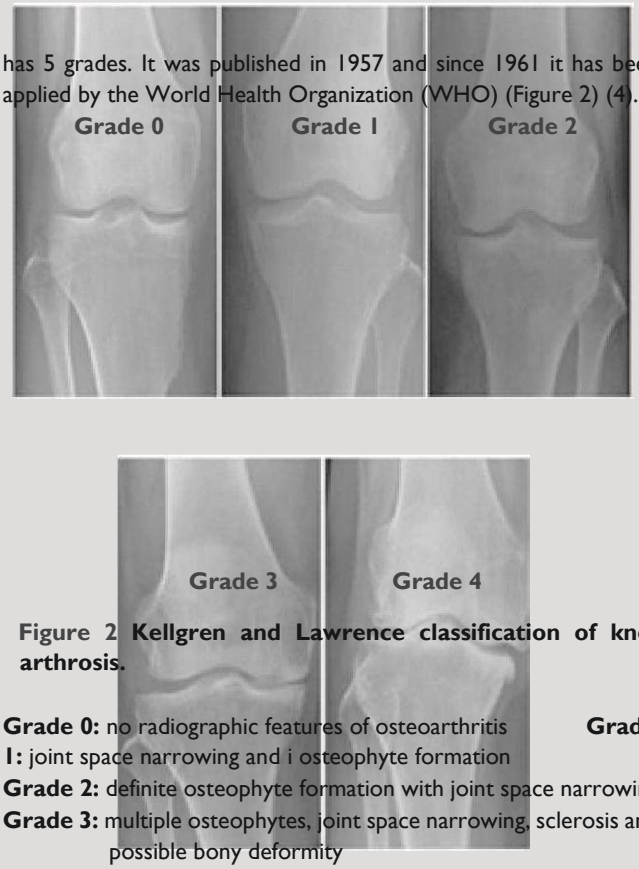

Figure 2 Kellgren and Lawrence classification of knee arthrosis.

Grade 0: no radiographic features of osteoarthritis **Grade 1:** joint space narrowing and i osteophyte formation
Grade 2: definite osteophyte formation with joint space narrowing
Grade 3: multiple osteophytes, joint space narrowing, sclerosis and possible bony deformity
Grade 4: large osteophytes, complete loss of joint space, bony deformity, sclerosis

Additional diagnostic methods include computed tomography (CT), magnetic resonance (MR) and diagnostic arthroscopy.

Both non-operative and operative procedures are used in the treatment of gonarthrosis. When it comes to non-operative procedures, the following are recommended: weight loss, analgesics - acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) - oral and local administration, preparations of glucosamine, chondroitin and gelatin, intraarticular corticosteroid administration, intraarticular administration of hyaluronic acid preparations, and all accepted methods of physical therapy. With regard to surgical treatment, the following are involved: arthroscopic "cleaning-up" procedure of damaged joint surfaces (shawing) with bone foraging at the site of cartilage damage, transplantation of in vitro produced cartilage based on cells of the patient, corrective osteotomy for the correction of varus or valgus deformity (5).

In addition to these methods, and as a result of the relatively poor results obtained through the treatment of gonarthrosis by means of

the previously mentioned methods, regenerative medicine and the use of preparations of the patient's own blood in the treatment of

certain diseases has become increasingly present in the past 15 years.

The first data on the Platelet-rich Plasma administration date back to 1960s, while its routine administration was described in the early 1970s. With the improvement of regenerative medicine during 1990s, the PRP treatment cases were described for soft tissue injuries and healing of skin defects (Margolis et al. 2001).

At the beginning of the 21st century, PRP was used for the first time in the treatment of the knee injuries after arthroscopic surgery (Sánchez et al. 2003), for tendon treatment (Sánchez et al. 2007), for muscle injuries (Sánchez et al. 2005), for arthrosis of the knee (Sánchez et al. 2008) and arthrosis of the hip (Sánchez et al. 2011), as well as for treatment of cartilage diseases (Kon, et al. 2010) (6).

PRP works through growth factors which play a key role in initiating and controlling the complex process of rehabilitation of injuries and diseases. Many of these factors are released in platelets and activated in case of injury or disease. When an injury or disease occurs, growth factors are released, including PDGF – platelet derived growth factor, TGF-transforming growth factor, IGF - insulin growth factor, bFGF - fibroblast growth factor, and VEGF - vascular endothelial growth factor. The release of growth factors (in PRP, their number increases up to 25 times compared with whole blood) initiates the rehabilitation process of injuries and diseases. The process goes from the proliferation and differentiation of various cell types, such as fibroblasts and chondroblastoma, leading to the formation of matrices that produce collagen and proteoglycan, with angiogenesis stimulation. This process is different from the natural immune response to injury or disease, in which the process is regulated by neutrophilic leukocytes, protease and antimicrobial peptides. By introducing PRP, where the platelet count is 2 to 10 times higher than whole blood, the neutrophilic process is blocked, while the natural healing process begins with the formation of new cells and blood vessels, with painful inflammation being inhibited. Hyperplasia does not occur in PRP and no cases of carcinogenesis, hyperplasia or tumor growth have been recorded. Cells in PRP stimulate expression of normal genes and their recovery, causing normal, but accelerated healing. Platelets make up to 6% of the cells in whole blood and up to 94% in PRP. The amount of blood collected for PRP is 10 to 100 ml of whole blood in a syringe, with or without an anticoagulant.

Centrifugation at a speed of 500 to 14,000 rpm lasts between 3 and 15 minutes. Some authors and pharmaceutical companies add 10% calcium chloride and/or thrombin to PRP (so-called activators). There are over 30 commercial systems to produce PRP. Growth factors are starting to get released after 10 minutes and are being released continuously for 7 to 10 days. Therefore, PRP is most effective in cases of fresh injuries in the early stage of rehabilitation (7,8,9).

The classification of Platelet-rich Plasma which is most widely used is based on the presence or absence of cells (mainly white blood cells) and fibrin (10).

A frequently used PAW (platelets, activators, white blood cells) classification provides an absolute white blood cell count and platelet count, as well as information about whether activators are used or not. This classification is similar to the classification by Mishra et al. that we use in our work. Mishra and Pavelko, together with colleagues from Stanford University in the United States of America, published the first-in-human study on the use of PRP in 2006. In this study, they presented their results of the treatment of chronic elbow tendinosis (so-called tennis elbow), with a two-year follow up (reported 93% reduction in pain). They also published the PRP classification that we have used in our work (Figure 3).

Table 1 Mishra et al. PRP classification.

Type	Platelet concentration	White blood cell count	Activator
1	A) 5 or more times higher compared with whole blood B) Up to 5 times higher compared with whole blood	increased	without an activator
2	A) 5 or more times higher compared with whole blood B) Up to 5 times higher compared with whole blood	increased	with an activator
3	A) 5 or more times higher compared with whole blood B) Up to 5 times higher compared with whole blood	minimal or without white blood cells	without an activator
4	A) 5 or more times higher compared with whole blood B) Up to 5 times higher compared with whole blood	minimal or without white blood cells	with an activator

MATERIALS AND METHODS

In the period from 1 July 2011 to 30 June 2015, 217 women aged between 48 and 79 years were treated at the "Stetik" Hospital in Banja Luka for osteoarthritis with clinical manifestations of the disease in one knee only. In all patients, manifestations of the disease occurred at least 6 months before their appointment at the hospital, with previously conducted NSAIDs treatment methods and physical therapy lasting at least 10 days. The diagnosis was usually established based on a medical history, clinical presentation, and X-ray imaging. The patients were informed about the type of treatment and asked to fill in the WOMAC index form (11). Afterwards, the preparation and administration of Platelet-rich Plasma was applied. After antiseptic preparation, patients' blood was collected from the cubital vein, by performing venipuncture. The amount of blood varied between 10 and 60 ml. Anticoagulant was not added in any of the cases. After collecting blood, centrifugation in a centrifuge manufactured by Hettich, at a speed between 600 and 5,000 rpm, was done for 5 to 12 minutes. Three blood segments were produced after the centrifugation; the first or so-called poor-quality plasma (pale yellow) on the top in the amount of 0.5 to 4 ml, highquality plasma (ochre to pale purple) underneath in the amount of 1 to 4 ml, and the remaining blood elements (red) that were not used. High-quality plasma was administered. Platelet count in whole blood obtained through PRP was measured using the equipment manufactured by Hemolab, Germany. After the PRP preparation was finalized, we prepared areas for the PRP administration into the knee. Usually, medial parapatellar area is used, where PRP is administered using a disposable hypodermic needle (12). Since PRP is lipemic a few hours after a meal, all administrations were done in the morning, before breakfast. For the purpose of a valid comparison of results, our paper only covers patients who underwent the PRP

administration 3 times at 7-day intervals (one administration per week).

RESULTS

In the period from 1 February 2011 to 30 June 2015, 217 female gonarthrosis patients with an X-ray 2nd grade arthrosis, based on the Kellgren and Lawrence classification, were treated at the "Stetik" Hospital in Banja Luka. There was no history of significant trauma for at least 5 years before the treatment was initiated. The patients' average age was 61.3 (48-79). Problems with the right knee were experienced by 74 patients, while 143 of them experienced problems with the left knee.

The mean amount of blood collected from the patients was 24.8 ml (10 to 60). The amount of produced PRP was 3.4 ml (1.4 to 5.6) using 10 ml of whole blood, with a mean value of platelets in whole blood of 206,000 ml (138 to 269), and of 690,000 platelets per ml (324 to 989) in the platelet-rich plasma. According to the Mishra et al. classification, our produced PRP was 1B in all cases.

White blood cell count in whole blood on the average amounted to 6.7 (3.6 to 9.3), while in the platelet-rich plasma it amounted to 12.6 (8.3 to 16.7). The number of erythrocytes in all patients was under $0.4x10^{12}$/L.

Results of the treatment were assessed through the WOMAC (Western Ontario and McMaster Universities Osteoarthritis) index, before the first administration and at the follow-up visit after three months, as well as 12 months after the last Platelet-rich Plasma administration.

The questionnaire includes the following parameters (filled in by the patient):

1. Pain - during walking, using stairs, in bed, at rest, under load (maximum 20 points)
2. Stiffness - in the morning, during the day (maximum 8 points)
3. Physical function - going down stairs, going up stairs, rising from sitting, standing, bending towards the floor, walking on an even surface, getting in/out of a car, shopping, putting on socks, taking off socks, lying in bed, rising from bed, getting in/out of bath, sitting, getting on/off toilet, heavy household duties, light household duties (maximum 68 points).

Patients assign points in the range between 0 and 4, where 0 - without pain, 1 - mild pain, 2 - considerable pain, 3 - severe pain, and 4 - extremely severe pain.

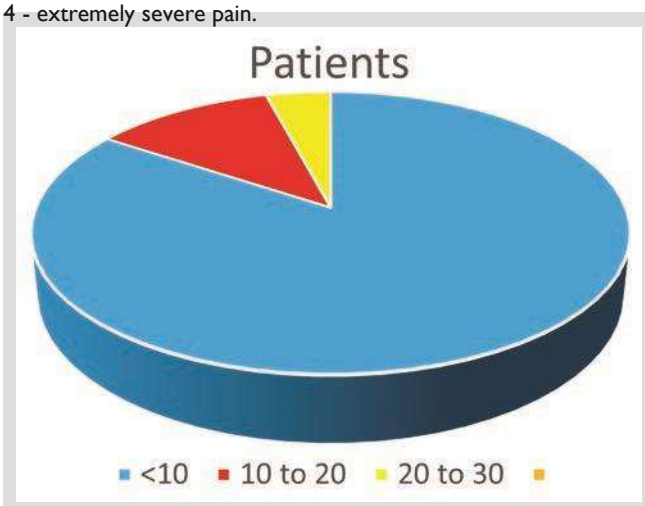

Figure 1 WOMAC index results based on total number of patients.

In 183 patients (or 84.3%) the WOMAC index value was below 10 after the therapeutic procedure described above, with an excellent subjective recovery (without pain in the knee even without the use of analgesics, subjectively without stiffness in the morning or during the

day, and without hindrance in performing normal daily duties).

In 25 patients (11.5%) the WOMAC index value was between 10 and 20, with dominant restriction of certain functional activities (going down the stairs, getting in a car) and morning stiffness.

In 9 patients (4.2%) the WOMAC index value was above 30, with dominant pain while moving, morning stiffness and difficulties while performing certain functions, such as going down the stairs, getting in/out of car, and difficulties while performing difficult household tasks, etc.

Table 2 Results based on the WOMAC Index – average score by questions.

WOMAC	Before PRP administration	3 months after PRP administration	12 months after PRP administration
Pain 20	13.8 (12 - 16)	6.1 (1-9)	4.2 (1-7)
Stiffness 8	5.2 (2 - 7)	2.4 (0-5)	1.2 (0-3)
Function 68	40 (20 – 65)	13.1 (3-40)	11 (2-20)
Total 96	60 (55 – 89)	21.6 (2-38)	16.4 (2 – 30)

DISCUSSION

Follow-up of the WOMAC index in patients with gonarthrosis after three administrations of Platelet-rich Plasma indicates an improvement of 64% after three months in comparison with the results recorded before starting the treatment, and an improvement of 73% after one year. It is almost impossible to carry out a comparison of our results with the available medical literature; bearing in mind the fact that searching the universal browser Google for the term Platelet-rich Plasma results in 843,000 search results, and in only 1,230 results in our language, in addition to the fact that this term exists in only 398 citations on Medscape. It is clear that there are no completed studies yet with which our results could be compared. In a study by Smith et al. entitled "Intra-articular Intra-articular Autologous Conditioned Plasma Injections", published in the American Journal of Sports Medicine in February 2015, an improvement of the WOMAC index by 78% was recorded in 78 patients, which corresponds to our results (13). A study by Meheux et al. entitled "Efficacy of Intra-articular PlateletRich Plasma Injections in Knee Osteoarthritis", published in the journal Arthroscopy in 2016, found a significant improvement in functional ability of the knee in a one-year follow-up, with significantly better results in comparison with the treatment using hyaluronic acid, and an improvement of over 60% in results in comparison with the results recorded at the beginning of the treatment (14). Treatment of degenerative diseases of the bones and joints represents a huge challenge faced by an

orthopedic surgeon. In certain cases, in spite of all modern methods being applied, results are not satisfactory; therefore, new or relatively new methods are being applied as an attempt to improve the segment of gonarthrosis treatment. In our five-year work, we have achieved promising initial results through the administration of Plateletrich Plasma method, with both subjective and objective improvements in patients; however, a complete mechanism of action and protocols for use have not been defined yet. From the biological perspective, characteristics of platelets represent a crucial step, but many other parameters also have to be taken into account, such as the number and composition of growth factors and other factors stimulating cell regeneration, the amount of plasma derived from whole blood, the

method of preparation and centrifugation, addition of activators (yes or no), and anticoagulants (yes or no). In addition to these biological parameters, the practical aspect of the PRP preparation must be considered as well, namely the size of centrifuge, centrifuging duration, price, and ergonomics of the preparation process, and final volume of the product and its form (liquid, gel, solid matter).

Conflict of interest: none declared.

CONCLUSION

Based on our five-year work, we can say that regenerative medicine with the Platelet-rich Plasma method nowadays has an important place in the treatment of bone and joint diseases, but it is necessary to further examine the concentrations and effects of all parameters contained in the PRP, while setting the standard in terms of the number, frequency and indications in treatment through the PRP administrations. This requires multi-annual prospective studies which would lead to complete results based on generally accepted scientific principles.

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Medical Journal (2016) **Vol. 22, No 4**, 188 - 191

Original article

Evaluation of the results Snodgrass procedure tubularized incised plate (TIP) in hypospadias surgery- our results for the period of 2010-2015

ABSTRACT

Objective: to present our results using the tubularized incised plate (TIP) urethroplasty (Snodgrass procedure) for repair of hypospadias. Materials and methods: the study was retrospective and included 46 patients with hypospadias who underwent Snodgrass surgery procedure at the Clinic of Pediatric Surgery of the Clinical Center University of Sarajevo in the period from 1 January 2010 to 31 Decembar 2015. Results: the surgery was performed on 46 children with hypospadias by Snodgrass procedure. All reconstructions had been done as the primary urethroplasty. According to the classification: 3/46 (6.5%) patients with subglandular hypospadias, 11/46 (23.9%) with coronal, 28/46 (60.9%) with distal penile and 4/46 (8.7%) with a mean penile hypospadias were operated. Chordectomy was performed in 36/46 (78.3%) patients. Average age of the patients was 2.3 years, taking into account that the youngest patient was 12 months old and the oldest was 14 years. In 29/46 (63%) patients neouretra was covered by the dorsal dartos flap, while in 3/46 (6.5%) patients neouretra was covered by the ventral dartos flap. Spongioplasty was performed in 14/46 (30.5%) patients. Period spent with the catheter was 7 days. Fistulas occurred in 6/46 (13.0%) patients. Conclusion: snodgrass urethroplasty provides satisfactory cosmetic and functional results.

Key words: hypospadias, surgery, Snodgrass urethroplasty

SAŽETAK

Cilj: prikazali smo naše rezultate pomoću Snodgrass procedure tubularizacije incidirane ploče (TIP) u rekonstrukciji hipospadije. Materijali i metode: studija je retrospektivna, obuhvatila je 46 pacijenata sa hipospadijom koji su operisani Snodgrass procedurom na Klinici za dječiju hirurgiju Kliničkog centra Univerziteta u Sarajevu u periodu od 01.01.2010. do 31.12.2015 godine. Rezultati: operisano je 46 djece sa hipospadijom Snodgrass procedurom. Sve rekonstrukcije su učinjene kao primarna uretroplastika. Prema klasifikaciji: operisana su 3/46 pacijenata (6.5%) sa subglandularnom hipospadijom, 11/46 (23.9%) sa koronalnom, 28/46 (60.9%) sa distalnom penilnom i 4/46(8.7%) pacijenta sa srednje penilnom hipospadijom. Hordektomija je rađena kod 36/46 (78.3%) pacijenata. Prosječna dob pacijenata iznosi 2.3 godine, s tim što je najmlađi pacijent imao 12 mjeseci, a najstariji 14 godina. Kod 29/46 (63%) pacijenata neuretra je pokrivena sa dorzalnim dartos flapom, dok je kod 3/46 (6.5%) pacijenata neouretra je pokrivena sa ventralnim dartos flapom. Spongioplastika je rađena kod 14/46 (30.5%) pacijenata. Vrijeme provedeno sa kateterom iznosilo je 7 dana. Fistule su zabilježene kod 6/46 (13.0%) pacijenata. Zaključak: snodgrass uretroplastika pruža zadovoljavajuće kozmetske i funkcionalne rezultate.

Ključne rječi: hipospadija, hirurgija, Snodgrass uretroplastika

INTRODUCTION

Hypospadias is a relatively common male genital deformity affecting about 0.3–0.4% of the population worldwide and its incidence is increasing (1,2).

Hypospadias (in Greek, hypo means "under" and spadon, means "rent") is a congenital defect of the penis with incomplete development of the anterior urethra resulting in meatus opening on under surface proximal to the tip of glans. In this condition, the urethral opening is sited anywhere along the underside of the penis from the glans to the perineum. It is one of the most common congenital anomaly of male genital system associated with significant physical and psychological trauma not only to the affected child but to the parents as well. In India, about 75.000 children are born every year with hypospadias, distal penile hypospadias (DPH) accounting for about 80- 85% of these cases (3).

In 1994, Snodgrass WT described his technique of tubularized incised plate urethroplasty, which is a relatively straightforward onestage procedure (4). It has become the standard technique used by many urologists for distal hypospadias correction (5,6).

The aim of hypospadias repair, for which over 300 different techniques are described, is to create a functional neourethra, correct any curvature, and produce a cosmetically normal penile appearance, with a slit-like meatus at the tip of the penis (7,8,9).

Evaluacija rezultata Snodgrass procedure tubularizacije incidirane ploče (TIP) u hirurgiji hipospadije-naši rezultati za period 2010-2015

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Surgical techniques have improved dramatically over the last 30 years or so, with the more modern terminalizing techniques providing successful function and an appearance which more closely matches the normal population (10). Reconstructing a functioning phallus that allows a boy to void as a "pointer" instead of a "squatter" and later to become a sexually active can be one of the most gratifying moments for the operating surgeon. Snodgrass introduced the concept of tubularized incised plate (TIP) urethroplasty repair with excellent short-term results and cosmesis almost replacing all other hypospadias repair and simplifying decision making (11).

In this paper, we describe our experience with Snodgrass TIP urethroplasty.

MATERIALS AND METHODS

The study was retrospective and included 46 patients with hypospadias who underwent Snodgrass surgery procedure (TIP urethroplasty) at the Clinic of Pediatric Surgery of the Clinical Center University of Sarajevo. All children in the age group 1-14 years presented to the department with hypospadias from Januar 2010 to Decembar 2015 were included in the study.

Operative procedure: the TIP urethroplasty technique was used in all cases as described by Snodgrass in 1994. A circumscribing skin incision was made 2 mm proximal to the meatus. The penile skin was degloved down to the penoscrotal junction. Full tuminescence of the corpora cavernosa was achieved using normal saline, to simulate penile erection for assessing chordee and curvature of penis. The urethral plate was tubularized over a feeding tube catheter (depending on the child's age) with a continuous absorbable suture to create the neourethra. The glandular wings were approximated by suture, and the distal ends were fixed to the underlying neourethra at 5 and 7 o'clock with the same type of suture. After the completion of repair, a urethral stent was fixed to the glans penis and the catheter was left for 7 days postoperatively.

RESULTS

A total of 46 cases of hypospadias included in the study underwent repair by TIP urethroplasty procedure. The age of the study participants ranged from 1 to 14 years. About 84.7% of the patients were under 5 years of age, and barely few (4.4%) were over 10 years of age. All cases were carefully examined for associated congenital anomalies (Table 1).

Table 1 Distribution of associated congenital anomalies (N = 46).

Associated congenital anomalies	No.of cases	Percentage (%)
Inguinal hernia	2	4.4
Undescended testis	3	6.5
ASD	1	2.2
No asociated congenital anomaly	40	86.9

Average age of the patients was 2.3 years, taking into account that the youngest patient was 12 months old and the oldest was 14 (Table 2).

Table 2 Demographic caracteristics.

Age pts	Number (%)
1 age	9 (19.5%)
2 age	17 (36.9%)
3 age	6 (13.0%)
4 age	7 (15.2%)
5 age	1 (2.2%)
6 age	1 (2.2%)
7 age	1 (2.2%)
9 age	2 (4.4%)
13 age	1 (2.2%)
14 age	1 (2.2%)

The positions of the urethral meatus are shown in Figure 1.

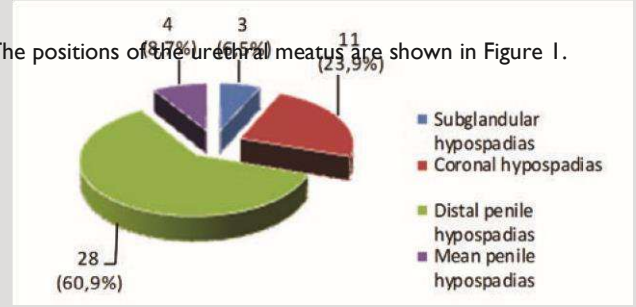

Figure 1 Type of hypospadias.

Chordectomy was performed in 36/46 (78.3%) patients (Figure 2).

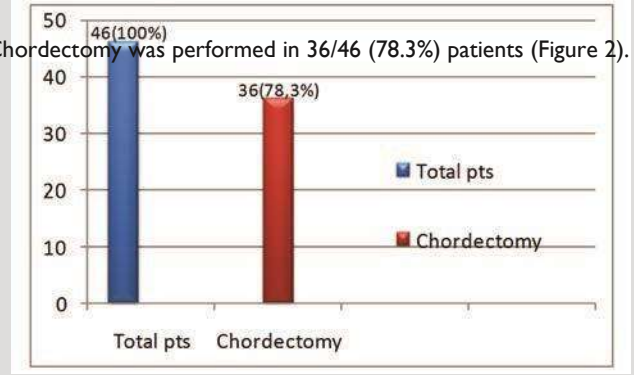

Figure 2 Chordectomy.

In 29/46 (63%) patients neouretra was covered by the dorsal dartos flap, while in 3/46 (6.5%) patients neouretra was covered by the ventral dartos flap. Spongioplasty was performed in 14/46 (30.5%) patients (Figure 3).

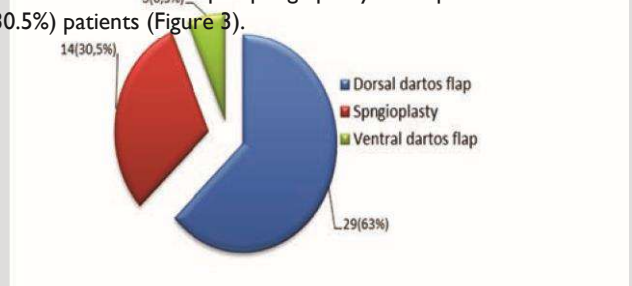

Figure 3 Types of covered neouretra.

Complications occurred in patients at a rate of 19.6% (Figure 4). Fistulas occurred in 6/46 (13.0%) patients.

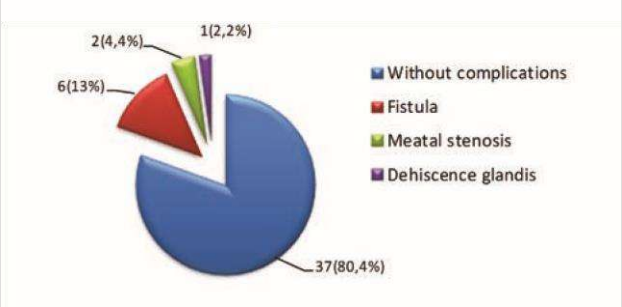

Figure 4 Complications.

DISCUSSION

Snodgrass TIP urethroplasty has become procedure of the choice for distal penile hypospadias (DPH) in modern era. Most of the cases of DPH are either without chordee or with skin chordee which is relieved by degloving of penile skin.

Hypospadias is one of the common congenital anomaly. It is associated with other anomalies as well. The most common anomalies associated with hypospadias are undescended testes and inguinal hernia. We observed inguinal hernia (2 cases), undescended testes (3 cases) and atrial (ASD) defect (1 case) with hypospadias. Khuri et al. (1981) found 9% incidence of undescended testes in patients with hypospadias (12).

Since it was introduced in 1994, Snodgrass urethroplasty has been the adopted procedure for distal hypospadias correction by many urologists. Its versatility, together with the normally appearing meatus, has made it the preferred technique (4,13,14).

The most feared complications after tubularized incised plate urethroplasty procedure are the urethrocutaneous fistula and meatal stenosis (14,15,16).

The primary objective of all hypospadias repair is to attain a functional neo-urethra with a near normal appearing penis. The repair of hypospadias has been a challenge to the surgeons for over a century. In 1994, a new method for distal hypospadias repair was described in which tubularization of the urethral plate without skin flaps was facilitated by midline plate incision. It was noted subsequently that the tubularized incised plate (TIP) technique simplified decision making in distal hypospadias surgery because the operation was successful regardless of various meatal and urethral plate configurations encountered by Snodgrass. The TIP urethroplasty is currently a popular technique for hypospadias repair (4,15).

The midline incision renders a narrow and shallow urethral plate wide enough for easy tubularization. Moreover, it provides a vertically oriented and cosmetically normal neo-meatus (5,7). The urethral plate is divided into two epithelial strips that are approximated ventrally to form the floor of neourethra, while the roof and sometimes the side walls are formed by the increased raw area that heals by re-epithelialization of relaxing incision without obvious scarring allowing the incised edges to remain separated (17,18,19,20,21).

Fistula formation was seen in 6 cases (13.0%). In a literature review of 54 case series, the median fistula rate was 5% (mean = 5.9%), ranging from 0 to 16% (22,23,24).

The Hospital for Sick Children experience included 48 children who underwent TIP urethroplasty from 1996 to 2000, representing the early part of our experience with this technique (25).

The fistula rate was 4%. Several factors may influence fistula formation: surgical technique, delicate tissue handling, patient age, type of hypospadias defect, surgeon experience, waterproof urethroplasty coverage, and concomitant foreskin reconstruction, among others (13).

In our study we had two cases of meatal stenosis (4,4%). Other authors have reported similar complication rate from 0-16% (22,23,24).

On the other hand, other series have shown a surprisingly high rate of meatal stenosis, ranging from 6 to 20% (26,27,28,29).

This has been a controversial topic and considered to be possibly related to the surgical technique (i.e., carrying the urethral plate incisions far too distal), as the drawings from the original technique implied that the urethral tubularization should include all the extension of the incisions to the tip of the glans. The high rates of meatal stenosis may reflect strict adherence to this description by Snodgrass. On the other hand, Snodgrass has reported meatal stenosis rates below 1% and has demonstrated with calibration and urethroscopy that the neourethra lumen after TIP repair is adequate and allows introduction of a 10-Fr feeding tube (15).

He has also shown that re-epitheliazation occurs by second intention after incision of the urethral plate.These findings support the thinking that urethral strictures or meatal stenosis should not occur after TIP repair for distal hypospadias, as long as the surgeon does not tubularize the incisions in the urethral plate too distally into the glans (30).

Turialis, et al. recommended limited degloving of the penile skin in order to limit the need for a large covering layer of the neourethra, whereas Selami and Warren performed complete degloving of the penile skin to provide full erection and prevent postoperative torsion or chordee (31).

CONCLUSION

A shorter urethral plate incision, use of a dorsal dartos flap to cover the neourethra, and more extensive skin degloving in Snodgrass urethroplasty reduce the rate of complications. In our experience, Snodgrass TIP urethroplasty is technically simple, easy to learn, single stage procedure with excellent functional and cosmetic outcomes for DPH. It has simplified the algorithm for distal penile hypospadias.

Conflict of interest: none declared.

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The treatment of burn injury correlated with percentage of affected area, potential complications and associated diseases

ABSTRACT

Introduction: the burn injury is potentially devastating state, which can involve many organic systems. Unavoidable burn wound contamination, which is the front door to sepsis, is a life threatening for a patient. The adequate operative and conservative treatment, indicated after appropriate assessment of each individual case, affects the prognosis in terms of reducing morbidity and mortality. Because of expected answer of all organic systems to the burn injury, a multidisciplinary approach to the treatment is medically justified. Materials and methods: we evaluated etiologic factor, occurrence of complications, associated diseases and modalities of treatment in 62 patients hospitalized at the Clinic of Reconstructive and Plastic Surgery of the Clinical Center University of Sarajevo, in the period from 1 January 2013 to 1 January 2016. Statistical analysis was conducted by SPSS ver. 13.0.program. X-square test with Yates' correction for continuity (Yates' chi-squared test) for correction of small values, t-test and one-way analysis of variance (ANOVA) were used for the assessment of differences between the tested groups. Results: the flame was the most common etiologic factor in our tested sample, 41 cases (66.2%), while smaller percentages related to two other evaluated etiologic factors, boiling liquids in 11 cases (17.7%) and contacts with hot objects in 10 cases (16.1%). Conservative treatment was applied in 29 cases (46.8%), while operative treatment was indicated in 33 cases (52.3%). X-square test did not prove clear correlation between the selection of the treatment modality and etiologic factor. Burns covering less than 30% of the total body surface area were indication for operative treatment in 27 cases (81.8%). Burns covering over 30% of the total body surface area represented indication for the operative treatment in 6 cases (18.2%). X-square test did not evaluate the clear correlation between the treatment modality and the total body surface area. Out of the total number of patients complications related to burn injury were evaluated in 20 cases (32.3%). After indication for surgical treatment complication were notified in 11 cases (32.3%). There was a difference in the number by X-square and ANOVA test. Complications occurred in higher percentages in associated diseases (14 cases, 92.3%) and in burns of higher degree, IIb and III degree (11 cases; 91.7%). We proved the colonization of burn wound by swabs in 41 cases (66.1%), by Gram-positive staphylococci (Staphylococcus aureus; Staphylococcus epidermidis) and Gram-negative microorganisms (Pseudomonas aeruginosa, MRSA, Enterobacter cloacae). Conclusion: the modality of treatment depends on degree of burns and etiologic factor. During burn injury assessment type of etiologic factor, length of exposure, comorbidities (associated diseases) and age of patient have to be taken into account. Correctly indicated operative treatment in terms of excisions and free skin transplantation has beneficial effects on morbidity and mortality. Conservative therapy with application of local chemotherapeutics also has beneficial effects on reducing colonization of burn wound by virulent pathogens, which can result in conversion of superficial burns to deep burns. The complexity of burn injury requires a multidisciplinary approach.

Key words: burn injury, modality of treatment, complication, associated diasease

SAŽETAK

Uvod: opekotinska povreda je potencijalno vrlo devastirajuće traumatsko stanje, koje involvira više organskih sistema. Neizbježna kontaminacija opekotinske rane, koja predstavlja ulazna vrata za septička stanja, životno ugrožava pacijenta. Adekvatan konzervativni i operativni tretman, indiciran procjenom svakog pojedinačnog slučaja, utječe na prognozu opekotinske povrede u smislu reduciranja morbiditeta i mortaliteta. Zbog očekivajućeg odgovora svih organskih sistema, multidisciplinarni pristup u liječenju opekotinske povrede je medicinski opravdan. Materijali i metode: evaluirali smo etiološke faktore, komplikacije, udružene bolesti i modalitete tretmana 62 pacijenta sa opekotinskom povredom,

of complication in relation to the treatment modality. That was confirmed

hospitalizirana na Klinici za rekonstruktivnu i plastičnu hirurgiju Kliničkog centra Univerziteta u

Tretman opekotinske povrede koreliran sa procentom zahvaćene površine, potencijalnim komplikacijama i udruženim bolestima

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Sarajevu u periodu od 01.01.2013. do 01.01.2016. godine. Statistička obrada podataka vršena je putem MS Excel programa. Detaljna statistička analiza provedena je putem SPSS ver.13.0 programa. Xsquare test uz Yates-ovu korekciju malih vrijednosti, t-test i jednosmjerna analiza varijanse (ANOVA) korišteni su za procjenu razlika ispitivanih grupa. Rezultati: plamen je najčešći etiološki faktor opekotinske povrede u našem ispitivanom uzorku, 41 slučaj (66.2%), dok su u manjim procentima bila zastupljena druga dva etiološka faktora u našim ispitivanim skupinama, vrele tekućine u 11 slučajeva (17.7%) i kontakt sa vrelim predmetima, 10 slučajeva (16.1%). Konzervativno je tretirano 29 pacijenata (46.8%) dok je hirurski tretman bio indiciran u 33 slučaja (53.2%). U našim ispitivanim skupinama nije dokazana jasna korelacija između selekcije modaliteta tretmana sa etiološkim faktorom putem X-square testa. Kod opekotina manjih od 30%, operativni tretman primjenjen je u 27 slučajeva (81.8%), dok je kod opekotina sa ukupnim procentom preko 30% operativni tretman bio indiciran u 6 slučajeva (18.2%). X-square nije potvrđena korelacija između modaliteta tretmana i površine opekotine. Komplikacije su evaluirane u 20 slučajeva od ukupnog broja (32.3%). Kod hirurškog tretmana u 11 slučajeva evidentirane su komplikacije (30.8%), što upućuje da postoji razlika u broju komplikacija u odnosu na vrstu tretmana, a što je potvrđeno X-square i ANOVA testom. Komplikacije se javljaju u većem procentu kod udruženih bolesti, 14 slučajeva (92.3%) i kod opekotina višeg stepena, IIb/III stepen, 11 slučajeva (91.7%). Putem briseva potvrđena je kolonizacija opekotinske rane u 41 slučaju (66.1%), sa Gram pozitivnim (Staphylococcus aureus; Staphylococcus epidermidis) i sa Gram negativnim mikroorganizmima (Pseudomonas aeruginosa, MRSA, Enterobacter cloacae) Zaključak: način tretmana opekotinske povrede je ovisan od stepena opekotine i tipa etiološkog faktora. Prilikom procjene opekotinske povrede mora se uzeti u obzir tip etiološkog faktora, dužina ekspozicije, komorbiditeti (postojanje udruženih bolesti), kao i dob pacijenta. Korektno indiciran operativni tretman u smislu ekscizija i kožnih transplantacije povoljno utječe na stepen morbiditeta i invaliditeta. Konzervativna terapija sa primjenom lokalnih hemoterapeutika povoljno utječe na reduciranja koloniziranja opekotinske rane virlulentnim patogenima, koji mogu rezultirati konverzijom površnih u duboke opekotine i generaloziranom sepsom. Kompleksnost opekotinske povrede zahtjeva multidisciplinaran pristup.

Ključne riječi: opekotinska trauma, modalitet tretmana, komplikacija, udružene bolesti

One of the major complications of burn wounds is infection dependent negative influence on wound healing, graft survival and

The predominant pathogens associated with burn wound Staphylococci are able to survive burn as they are located deep within first 48 hours after burn. Pseudomonas aeruginosa is introduced after pulmonary complication often occur with smoke inhalation, although response resuscitative measures in acute phase can also cause fibrinolysis activation induced by the burn can lead to pulmonary

Population-based research has identified long-term post burn increased incidence of cancers (9,10) after severe and minor burns.

One of the most important complication in patients with the chance of survival is noninflammatory acute kidney injury.

Currently, the challenge is to improve any post traumatic stress be slightly unaesthetic because of depigmentation or

MATERIALS AND METHODS

We evaluated the results of the operative and conservative Reconstructive and Plastic Surgery of the Clinical Center University yearperiod (1 January 2013 to 1 January 2016). The statistical analysis statistical and mathematical program MS Excel 2010 for evaluating was made through X-square test with Yates' correction for analysis of variance (ANOVA). X-square test met the criteria of

INTRODUCTION

The most common and devastating form of trauma are the burns. Patients require immediate care in order to minimize morbidity and mortality in terms of care for dehydration, inhalation injury, infection control and nutritional support. The most important key to minimize morbidity and mortality is to remove dead tissues by performing escharotomy, followed by skin grafting in which patients with burns remain immunosuppressed, katabolic and sensitive to infection. Managing the pain and tissue exudates, followed by preventing the wound trauma and reducing the patients comfort caused by dressing changing, in early stages of injuries are one of the most challenging assignments.

with two or more independent groups of the observed cases, with the definitive assessment of the differences in patterns of observed properties. The results of statistical tests with $p<0.05$ or on the level reliability 95% were considered statistically significant.

We evaluated the occurrence of the early and the late complication of burn disease. In our tested sample we estimated the occurrence of the early general complications such as burn shock, acute renal failure and pulmonary complications (acute lung injury and smoke inhalation injury) and also local complication such as Compartment syndrome caused by the development of local edema associated with circular deep burns (early local complications) and keloid and hypetrophic scars (late local complication). Burn wound sepsis, classified as early local complication of burn disease, which implies the colonization of pathogenic microorganisms above 107 per gram of tissue, which represents an invasive infection, in our tested groups could not be evaluated due to absence of standard analysis of this parameter in our clinical procedures. We only presented the results of the analysis of swabs from burn wound and the types of microorganisms without estimating the number of

which can progress in sepsis. Bacteria exert a direct bacterial level scarring (1,2).

infection are Staphylococcus aureus and Pseudomonas aeruginosa. hair follicles and sweat glands and colonize the burn wound in the an average of 5-7 days by translocation (3,4). In addition to smoke inhalation can directly induce lung damage, inflammatory pulmonary damage in absence of inhalation injury. Coagulation and edema, pneumonia and respiratory distress syndrome.

cardiovascular (5,6) and musculoskeletal morbidity (7,8), as well as

extensive burn injuries covering over 15-20% TBSA decreasing

disorder which burn patients may suffer from their scars that can hyperpigmentation or it can be hypertrophic.

treatment of 62 patients with burn injury treated at the Clinic of of Sarajevo, caused by different etiologic factors over the three was carried out by the classification variables and by importing to purpose. The testing of difference between the observed groups continuity (Yates' chi-squared test) using t-test and one-way comparative study

pathogens per gram of tissue, so that the occurrence of burn wound sepsis could not be accurately determined.

RESULTS

Figure 1 Etiologic factors of the burn disease.

According to the data presented in Figure 1, the flame was the most common etiologic factor in our tested sample occurring in 41 cases (66.2%). The boiling liquid as etiologic factor was evaluated in 11 cases (17.7%), and the contact with hot object in 10 cases (16.1 %).

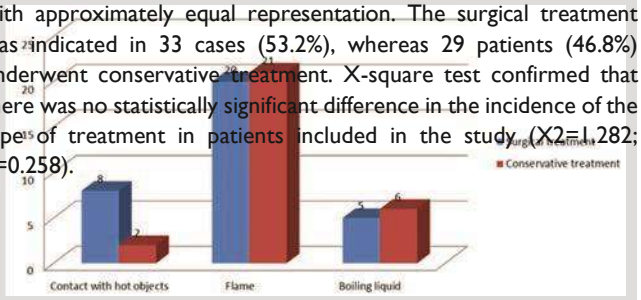

Figure 2 Percentage of the therapeutic modalities.

The two types of therapeutic modalities were applied (Figure 2) with approximately equal representation. The surgical treatment was indicated in 33 cases (53.2%), whereas 29 patients (46.8%) underwent conservative treatment. X-square test confirmed that there was no statistically significant difference in the incidence of the type of treatment in patients included in the study (X2=1.282; p=0.258).

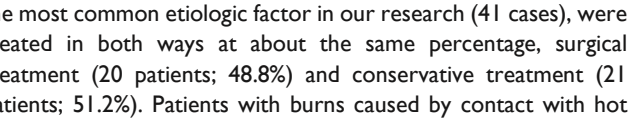

Figure 3 Correlation between the type of etiologic factor and treatment modalities.

Patients with burns caused by the flame (Figure 3), which was the most common etiologic factor in our research (41 cases), were treated in both ways at about the same percentage, surgical treatment (20 patients; 48.8%) and conservative treatment (21 patients; 51.2%). Patients with burns caused by contact with hot objects (10 cases) underwent surgical treatment in 8 cases (80%) and conservative treatment in 2 cases (20%). The burns caused by boiling liquids (11 cases) represented indication for surgical treatment in 5 cases (45.5%) and in for conservative treatment in 6 cases (54.5%). X-square test confirmed that there was no clear correlation between therapeutic modality and type of etiologic factor (X2=2.622; p=0.270).

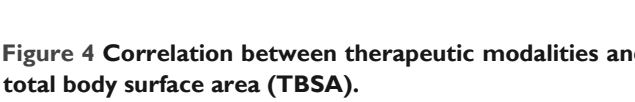

Figure 4 Correlation between therapeutic modalities and total body surface area (TBSA).

Out of the total of 62 patients included in our research (Figure 4), patients with burns covering less than 30% of the total body surface area (TBSA>30%-53 patients), underwent surgical treatment in 27 cases (81.8%) and conservative treatment in 26 cases (89.6%). Patients with burns covering over 30% of the total body surface area (TBSA<30% -9 patients), presented indication for surgical treatment in 6 cases (18.2%) and for the conservative treatment in 3 cases (10.4%). X-square test confirmed that there was no clear correlation between the modality treatment and the total body surface area (X2=1.906; p=0.172).

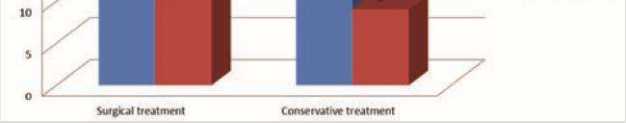

Figure 5 Correlation between the applied treatment modality and incidence of complications.

Considering the correlation between the incidence of complication and applied treatment modalities (Figure 5), it was evident that there were complications associated with burn disease in 20 cases (32.3%) in respect of 42 cases with no complication (67.7%). X-square test confirmed that there was statistically significant difference in the incidence of complications. Majority of the cases were associated with no complication (X2=4.754; p=0.038). Further analysis showed that there was no statistically significant difference in the number of patients with complications in relation to the type of treatment. In cases with indication for surgical treatment, we evaluated complications in 11 cases (30.8%), while the conservative treatment was associated with complications in 9 cases (34.7%). This was confirmed by X-square test (X2=0.108; p=0.811). ANOVA test (analysis of variance) proved that there was no statistically

significant difference in the occurrence of complications compared to length of hospitalization (F=1.008; p=0.422).

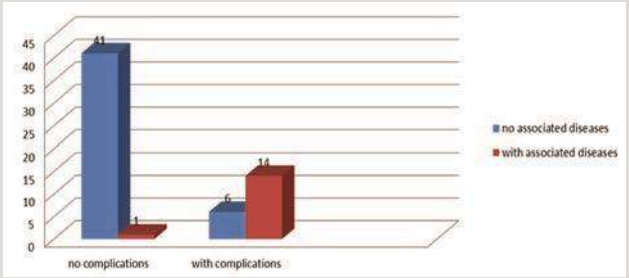

Figure 6 Incidence of the burn disease complications compared to associated diseases (comorbidity).

Observing the incidence of the burn disease complications compared to the comorbidity (Figure 6), it was evident that complications related to burn injury occurred in 20 cases. However, out of the overall number of complications, associated diseases were present in 14 cases (92.3%). Burns not associated with diseases but with complications were evaluated in 6 cases (12.8%). X-square test confirmed statistically significant difference in the incidence of complications in relation to the associated diseases. Patients with associated diseases had higher number of complications (X2=15.709; p=0.033)

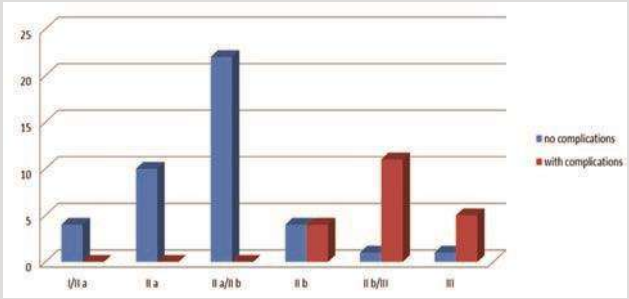

Figure 7 Frequency of the burn disease complications compared to the depth of burns.

There was obvious correlation between the frequencies of the burn disease complications compared to the depth of burns (Figure 7). Among 20 cases with complications associated with burns, majority was associated with grades IIb/III- deep partial thickness/full thickness burns (11 cases; 91.7%). There was statistically significant difference in the incidence of complications in relation to the degree of the burns (X2=46.707; p=0.009).

Figure 8 Microbiological evaluation of the bacterial contamination on the burn wound.

During the evaluation of the bacterial contamination and the assessment of the burn degree, due to detection of wound colonization and potential sepsis, which could lead to conversion superficial in deep burn, swabs were made in 43 cases. Burn wound sepsis, defined as the number of a minimum of 107 microorganisms per gram of tissue, could not be microbiologically confirmed or excluded in the absence of these procedures in the standard microbiological analysis at our clinic. In the total number of analyzed samples we got a sterile swab in 2 cases (3.2%), Staphylococcus aureus in 15 cases (24.2%), Staphylococcus epidermidis in 8 cases (12.9%), Pseudomonas aeruginosa in 6 cases (9.7%), Enterobacter cloacae in 9 cases (14.5%), MRSA in 3 cases (4.8%). The microbiological analysis was not performed in 19 cases.

DISCUSSION

The depth of burns and length of hospitalization depends on the etiologic factor (11). Depending on the severity and the degree of the burns, all patients were treated with two available options. The treatment modalities were not in correlation with the etiology and total body surface area (TBSA). In our tested group of patients, burns with surface area covering over 30% (TBSA <30%) as well as burns with surface area covering less than 30% (TBSA >30%) were treated surgically, which was in direct correlation with the depth of burns.

The flame was significantly the most common etiologic factor of the extensive burns in the majority of cases in our test group.

The associated burns were related to the percentage of complications. The resulting clinical findings were always in correlation with the preexisting or associated burns (diabetes mellitus, microangiopathy, malnutrition, anemia), whereby the lower degree burns were associated with the aggravation of the general condition. The severity of the burn injury increases with the appearance of the early and late complications, of which infections and metabolic imbalance are prevalent (12). The correlation between complication and associated diseases was also confirmed in our research. The considerable number of complication was associated with comorbidity.

The frequency of complications was different compared to the average age of the patients. It was significantly higher compared to patients without complications. There was no statistically significant difference in the incidence of complication in relation to the etiologic factor in our research. Each etiologic factor may cause deep burns depending of the length of exposure.

The occurrence of complications is directly correlated with the depth of the burns. The number of complication was significantly higher in deeper burns; the clinical findings depend on the degree and surface of the burns. The occurrence of the contractures with functional outages was correlated to the IIb and III degree burns in the majority of clinical findings as late complications.

The higher degree burn wound with potentially prolonged healing is indication for surgical treatment. Surgical treatment reduces the possibility of the burn wound sepsis, which represents the basis for the occurrence of sepsis as an early general complication of burn disease.

Japoni, et al. examining series of extensively burned patients, proved that Pseudomonas aeruginosa, which occurred on wet burn surfaces, was the most dangerous and the most pathogen microorganism, particularly in the cases of immune deficiency. In the early stages of the burns injuries, predominance of the Gram-positive microorganisms compared to Gram-negative has been evident, while the Gramnegative predomination has been evident 4-10 days after injury (13). Burned tissue is a major source of infection. This is one of the most important and potentially serious complications that may occur in the acute period following burn injury. Epidemiology has changed thanks to infection control measures, the adoption of strict policy on antibiotic administration, identification of newly emerging resistant strains of bacteria (extended spectrum beta lactamase [ESBL]) producing Gram-negative *Pseudomonas*, *Acinetobacter* and Biofilm formation from Gram-positive staphylococci, methicillin-resistant *Staphylococcus* aureus (MRSA), and methicillin-sensitive *Staphylococcus aureus*. Multidrug resistant organisms have likewise made their contribution to epidemiology.

Initially burn wounds are sterile but very quickly become colonized. Subsequently, non-invasive wound infection develops and may progress into invasive sepsis. Limited infection with purulent discharge underneath a burn eschar invades the surrounding normal tissues. Bacteraemia causes sepsis and ultimately damage to several organ systems (14). Results of swabs analysis in our tested sample confirmed the presence of Gram-positive staphylococci (Stapyhlococcus aureus; Staphylococcus epidermidis) and Gram-negative microorganisms (Pseudomonas aeruginosa; MRSA; Enterobacter cloacae) which confirms that the burn wound may be colonized by the various types of microorganisms presenting the front door to sepsis.

CONCLUSION

The selection of the treatment modality correlated with the total body surface area (TBSA) and the depth of the burn. Etiologic factor is of great importance in the evaluation of the burn injury. Some etiologic factors result in potentially deeper burns (contacts with source of electricity, gas explosions). In cases of gas explosions we had to consider the possibility of inhalation of the hot air with resulting lung damage. The goal of burn injury treatment is to correctly and timely set indication which potentially reduces morbidity and mortality, prevents complications and affects positively on functional recovery. The older age with higher possibility of existence of associated disease negatively affects the prognosis. Besides the early resuscitation phase which prevents the shock, the use of the topical antibiotics with systemic antibiotic therapy and surgical treatment, such as necrectomy and reconstruction with the free skin transplants, prevents the colonization of the burn wound and consequential burn wound sepsis representing the front door for sepsis. The primary tangential excision and free skin transplantation result in reducing morbidity and mortality, restoration of function, reduction of invalidity and aesthetically acceptable scars. Timely adequate therapy, with regular microbiological analysis and proper antibiotic administration is the key surviving factor. Appropriate reanimation therapy saves patients in the first days after burn injury as well as correctly indicated surgical therapy, which significantly improves the final prognosis.

Conflict of interest: none declared.

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Original article

Effect of antihypertensive therapy on the selected parameters of metabolic syndrome

Efekti antihipertenzivne terapije na odabrane parametre metaboličkog sindroma

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ABSTRACT

The aim of the study was to determine the values of selected parameters of the metabolic syndrome (MetS) and to compare the effect of combined antihypertensive therapy on the examined parameters. The study was designed as a prospective study of parallel groups. Patients were randomized to receive angiotensin-converting enzyme inhibitors (ACEIs) + calcium channel blockers (Ca2+ blockers) (n=80), ACEIs + thiazide diuretics (TDs) (n=80) and angiotensin II receptor blockers (ARBs) + TDs (n=80). The study was conducted over a period of 12 months. Outcome variables were: weight, waist circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse, HbA1c, fasting blood glucose (FBG), insulin resistance (IR), total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides. Measurements were taken at the beginning of the study and after 3, 6, 9 and 12 months respectively. Level of significance was set up to value $p<0.05$. According to the results at the end of the study, there was a statistically significant reduction of the following parameters in the group where ACEIs were combined with Ca2+ blockers: DBP (-24.57±0.03 mm Hg, $p<0.001$), IR (-23.54±0.03, $p<0.001$), HbA1c (-1.56±0.01%, $p<0.001$), total cholesterol (-0.51±0.01 mmol/L, $p<0.001$), LDL cholesterol (-1.10±0.03 mmol/L, $p<0.001$), triglycerides (-0.89±0.02 mmol/L, $p<0.001$), with a significant increase in HDL cholesterol (+0.26±0.01 mmol/L, $p<0.001$) compared to other two groups. The group prescribed with ACEIs + Ca2+ blockers had following effects on SBP and FBG when compared to group prescribed with a ACEIs + TDs and ARBs + TDs, respectively: SBP (-29.61±0.05 mm Hg, $p=0.010$) and FBG (-1.86±0.02 mmol/L, $p=0.026$). Combined antihypertensive drugs – ACEIs + Ca2+ blockers - showed the greatest effect in reducing diastolic blood pressure and insulin resistance, with a consequent positive effect on the lipid profile in patients with hypertension and MetS.

Key words: metabolic syndrome, hypertension, antihypertensive drugs

SAŽETAK

Cilj istraživanja bio je utvrditi vrijednosti odabranih parametara metaboličkog sindroma (MetS) te uporediti efekat kombinacije antihipertenzivne terapije na ispitivane parametre. Sprovedena je prospektivna studija tri paralelene studijske grupe, proporcionalne veličine, kojima je slučajnim odabirom dodjeljena jedna od tri kombinacije lijekova: inhibitori angiotenzin konvertirajućeg enzima (ACEI) + blokatori kalcijevih kanala (Ca2 + blokatori) (n = 80), ACEI + tiazidni diuretik (TD) (n=80) i blokatori angiotenzin II receptora (ARB) + TD (n = 80). Istraživanje je provedeno u periodu od 12 mjeseci. Praćene su sljedeće varijable: težina, obim struka, sistolički (SBP) i dijastolički (DBP) krvni tlak, puls, HbA1c, glikemija na tašte (FBG), inzulinska rezistencija (IR), ukupni holesterol, HDL holesterol, LDL holesterol i trigliceridi. Mjerenja su sprovedena na početku studije i nakon 3, 6, 9 i 12 mjeseci. Postavljen je nivo signifikantnosti $p< 0,05$. Prema rezultatima, došlo je do statistički značajnog smanjenja sljedećih parametara u grupi gdje je primjenjivana kombinacija ACEI sa blokatorima kalcijevih kanala: DBP (-24,57 ± 0,03 mm Hg, $p <0,001$), IR (-23.54 ± 0,03, $p <0.001$), HbA1c (-1.56 ± 0,01%, $p<0,001$), ukupni holesterol (-0.51 ± 0,01 mmol/L, $p <0.001$), LDL kolesterol (-1.10 ± 0,03 mmol / L, $p < 0.001$), trigliceridi (-0.89 ± 0,02 mmol / L, $p <0,001$), uz značajno povećanje HDL kolesterola (+ 0,26 ± 0,01 mmol/L, $p <0,001$) u odnosu na druge dvije grupe. U grupi u kojoj je primjenjivana kombinacija ACEI +blokatora kalcijevih kanala postignuti su sljedeći efekti na vrijednosti SBP i FBG u odnosu na druge dvije tretmanske grupe: SBP (-29.61 ± 0,05 mm Hg, $p = 0,010$) i FBG (-1.86 ± 0,02 mmol/L, $p=0,026$). Kombinacija antihipertenziva ACEI + blokatori kalcijevih kanala pokazala je najveći uticaj na sniženje dijastoličkog krvnog tlaka i inzulinske rezistencije sa posljedičnim pozitivnim efektom na lipidni profil u pacijenata sa hipertenzijom i MetS.

Ključne riječi: metabolički sindrom, hipertenzija, antihipertenzivni lijekovi

INTRODUCTION

Metabolic syndrome (MetS) is a collection of metabolic disorders (abdominal obesity, hyperglycemia, yslipidemia and hypertension) which increase the risk of developing diabetes mellitus type 2 (T2DM) and cardiovascular disease (CVD) (1). The prevalence of the metabolic syndrome increases significantly with increasing insulin resistance (IR). MetS is considered the first in a series of risk factors for atherothrombotic complications. The presence or absence of metabolic syndrome should be considered as an indicator of long-term risk for CVD. Central obesity is an essential element in the definition of the different values of waist circumference for different racial/ethnic groups. The cur-

rent research highlights the role of metabolic syndrome as the

leading cause of CVD, and it has been proven that the prevalence of metabolic syndrome increases depending on the degree of obesity and reaches a value of 50% in obese young people. Increasing incidence of metabolic syndrome in obese will be a significant problem in the future, indicating a need for further research on the association between insulin resistance, hyperlipidemia, hypertension, DM, obesity and atherosclerosis as risk factors for developing metabolic syndrome. Among the drugs of first choice are drugs acting on the renin-angiotensin-aldosterone system (ACE inhibitors or ARBs) and calcium channel blockers. This is because Mets is considered "pre-diabetic state", and these antihypertensive drugs can either improve insulin sensitivity or have no effect on it. Also, it has been shown that obese hypertensive patients exhibit significantly better reduction in weight and improvement of insulin resistance when treated with newer antihypertensive drugs compared with older antihypertensive agents (especially beta-blockers) (2,3). Of the newer antihypertensive drugs, angiotensin receptor blockers (ARBs) are associated with the lowest rate of discontinuation of therapy and with the lowest incidence of new cases of T2DM (4,5). ACE inhibitors and ARBs arei associated with reduced risk of CV incidents, in particular reduction of coronary events (6). The aim of the study was to determine the value of the selected parameters of the metabolic syndrome mentioned earlier and to compare the effect of combination antihypertensive therapy on these parameters.

MATERIALS AND METHODS

We conducted a prospective clinical study with three corresponding groups with proportional sample sizes at the Clinical Center University of Sarajevo.

The study included 240 patients with metabolic syndrome and hypertension. After signing the voluntary informed consent, respondents were divided into three groups consisting of 80 patients: Group A (n=80), patients treated with a combination of ACEIs + Ca2+ blocker; Group B (n=80), patients treated with a combination of ACEIs + diuretic; Group C (n=80), patients treated with a combination of ARB + diuretic.

The study was conducted over the period of 12 months, with a total of five control checkups, specifically at the beginning of the study, and after three, six and nine months, and finally at the end of the study. Each checkup involved measurements of body weight, waist circumference, systolic and diastolic blood pressure, pulse, followed by blood sampling to determine the values and level of HbA1c, fasting blood glucose, insulin resistance, total cholesterol, HDL and LDL cholesterol and triglycerides.

Testing normality of distribution of continuous numerical attach the inspection was carried out, the histogram, quantile diagrams and formal testing using the Kolmogorov-Smirnov test.

Analysis of categorical variables was performed using Pearson's X2-test or Fisher's exact test probability. Kruskal Wallis H test were analyzed statistically significant difference value between the ages of the three observed groups. Post-hoc analysis was performed using the Mann Whitney U test, and the threshold of statistical significance adjusted Bonferroni's formula to control inflation mistakes I type. The threshold of significance was set at the conventional level for the omnibus tests for the post-hoc analysis was performed Bonferroni 's-correction, in order to control the inflation of type I error due to multiple tests.

RESULTS

Out of the total number of patients treated with the combination of ACEIs + Ca2+ blocker (n=80), 48 (76.0%) were male and 32 (40.0%) were female. Out of the total number of patients treated with the combination of ACEIs + diuretic (n=80), 51 (63.8%) were male and 29 (36.3%) patients were female. Out of the total number of patients treated with the ARBs + diuretic combination (n=80), 45 (56.3%) were male and 35 (43.8%) patients were female. There was no statistically significant difference in the frequency of male and female patients among the groups [X2=0.938, p<0.05]. Table 1 shows the absolute and relative frequencies of respondents by gender and type of treatment.

Table 1 Gender structure of respondents according to the type of treatment.

			male	female	total
Number of patients	ACEI + Ca^{2+} blocker	N	48	32	80
		%	60.0%	40.0%	100.0%
	ACEI + diuretic	N	51	29	80
		%	63.8%	36.3%	100.0%
	ARB + diuretic	N	45	35	80
		%	56.3%	43.8%	100.0%
Total		N	144	96	240
		%	60.0%	40.0%	100.0%

Systolic and diastolic blood pressure

After 12 months, the target value of systolic blood pressure (<130 mmHg) was achieved in the following groups: ACEIs + Ca2+ blockers (79/80 or 98.7%) , ACEIs + diuretic (79/80 or 98.7%) and ARBs + diuretic (80/80 or 100.0%). There was no statistically significant difference in the achieved target systolic blood pressure (< 130 mm Hg) between groups (p>0.05). Also, the target values of diastolic blood pressure (< 80 mm Hg) were achieved in the following groups: ACEIs + Ca2+ blocker (65/80 or 81.3%), ACEIs + diuretic (44/80 or 55%) and ARBs + diuretic (51/80 or 63.8%). There was a statistically significant difference in the frequency of achieving the target value diastolic blood pressure between the groups after 12 months of observation [X2=12.863, p=0.002]. For all other control measurements, no significant differences were found in the frequency of achieving the target value of diastolic blood pressure between the groups (p>0.05) .

Insulin resistance

After 12 months, the target value of insulin resistance (<2) was achieved in the following groups: ACEIs + Ca2+ blocker (68/80 or 85%), ACEIs + diuretic (58/80 or 55%) and ARB + diuretic (47/80 or 58.8 %) (Figure 1).

Figure 1 Chart of achieved target insulin resistance values (< 2) by groups.

There was a statistically significant difference in the frequency of achieving the target value of insulin resistance between the groups after 12 months of observation [2 =13.707, p=0.001]. For all other control measurements, no significant differences were found in the frequency of achieving the target value of insulin resistance between the groups (p >0.05).

HbA1c

After 9 months, the target HbA1c value (< 6.2%) was achieved in the following groups: ACEIs + Ca2+ blocker (70/80 or 87.5%), ACEIs + diuretic (57/80 or 71.3%) and ARBs + diuretic (68/80 or 85 %).

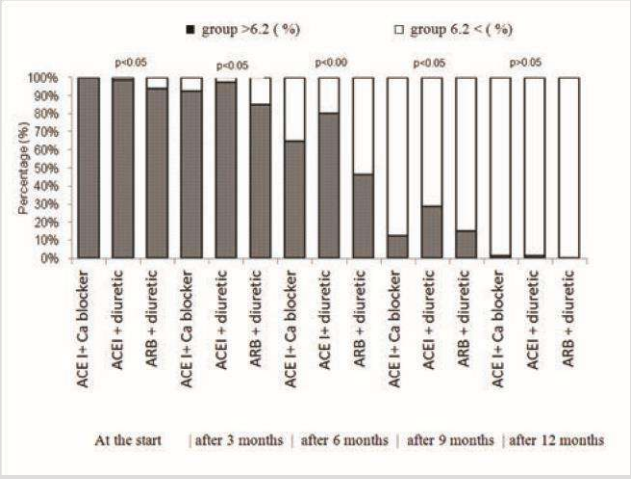

Figure 2 Chart of achieved target HbA1c values (< 6.2 %) by groups.

There was a statistically significant difference in the frequency of achieving target HbA1c values between the groups after 9 months of observation [X2 =8.041 , p=0.018]. However, there was no significant difference after 12 months (Figure 2).

Total cholesterol

After 12 months, the target value of total cholesterol (< 5.2 mmol / L) was achieved in the following groups: ACEIs + Ca2+ blocker (35/80 or 43.8%), ACEIs + diuretic (5/80 or 6.3%) and ARBs + diuretic (30/80 or 37.5%).

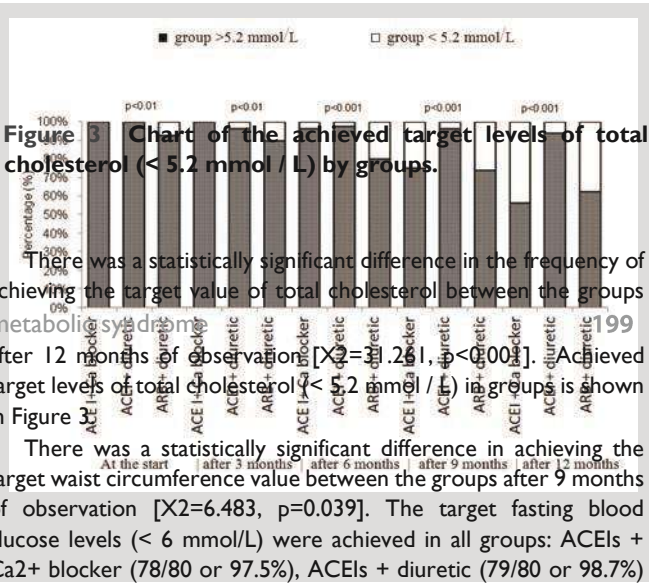

Figure 3 Chart of the achieved target levels of total cholesterol (< 5.2 mmol / L) by groups.

There was a statistically significant difference in the frequency of achieving the target value of total cholesterol between the groups after 12 months of observation [X2=31.261, p<0.001]. Achieved target levels of total cholesterol (< 5.2 mmol / L) in groups is shown in Figure 3.

There was a statistically significant difference in achieving the target waist circumference value between the groups after 9 months of observation [X2=6.483, p=0.039]. The target fasting blood glucose levels (< 6 mmol/L) were achieved in all groups: ACEIs + Ca2+ blocker (78/80 or 97.5%), ACEIs + diuretic (79/80 or 98.7%) and ARBs + diuretic (79/80 or 98.7%). However, there was no statistically significant difference in achieving target FBG values between the groups (p>0.05).

DISCUSSION

The results of our study showed that the combination antihypertensive therapy - ACEIs + Ca2+ blockers - showed the greatest effect in reducing diastolic blood pressure and insulin resistance, with a consequent positive effect on the lipid profile in patients with hypertension and MetS. At the end of our study, the group on ACEIs + Ca2+ blockers demonstrated a statistically significant reduction in diastolic blood pressure values compared with other two groups, and when compared to the ACEIs + TDs group, there was a statistically significant reduction in systolic blood pressure. There was a statistically significant difference in the calculated target values of diastolic blood pressure among the three groups.

ACEIs + Ca2+ blockers have a synergistic effect in lowering blood pressure with good tolerability and low frequency of side effects, which makes this combination therapy the antihypertensive therapy of choice for patients wiht MetS (2).

Vitale, et al. (7) monitored metabolic effects of losartan and telmisartan, two ARBs used in treatment of hypertensive patients with metabolic syndrome. In a double-blind randomized study, patients with metabolic syndrome received a daily dose of telmisartan (80 mg, n=20) or losartan (50 mg, n=20) during the monitoring period of 3 months. Compared with losartan, 3-months daily dosage of telmisartan significantly reduced values of SBP (-13.5 ± 0.8 mmHg) and DBP (8.9 ± 0.6mmHg). A multicentre prospective study by Racine et al. (8) showed that losartan as monotherapy or in combination with hydrochlorothiazide (HCTZ) is effective in reducing SBP and DBP without increasing the risk of diabetes in hypertensive patients with metabolic syndrome. Spinar J, et al. (9), compared the effects of ACEIs and ARBs in hypertensive patients with metabolic syndrome. The study included 439 patients randomized into two groups: 1st - ramipril or perindopril (ACEIs) and 2nd - losartan (ARB); HCTZ (diuretic) and amlodipine (Ca2+ blocker) were added to both groups. Blood pressure was reduced in both the ACEIs group and losartan group ($p>0.05$). At the end of our study, the group on ACEIs + Ca2+ blocker demonstrated a statistically significant reduction in the following parameters: insulin resistance, HbA1c, total cholesterol, LDL cholesterol, triglycerides, when compared with the other two groups; fasting blood glucose was significantly lowered in this group compared to the ARB + diuretic group; there was also a significant increase in HDL cholesterol levels compared to two other groups. At the end of the study there were significant differences in achieved target values between groups on ACEIs + Ca2+ blocker, ACEIs + diuretic and ARBs + diuretic for the following parameters: insulin resistance; total cholesterol; HDL cholesterol and triglycerides. Compared with losartan, telmisartan reduced the values of fasting blood glucose, fasting insulin, insulin resistance and HbA1c after 3 months (7). Metabolic effect of telmisartan and losartan in hypertensive patients with metabolic syndrome and patientes with diabetes showed: antihypertensive combination of ACE + Ca blocker has the best effect in the reduction of mortality (73.9%), followed by the combination of ACEI + diuretic (12.5%) and monotherapy with ACE inhibitor(2.0%), a blocker of Ca (1.2%) and the ARB (0.4%) (10,11).

Our research demonstrated a statistically significant positive linear correlation between the reduction of insulin resistance and lowering of triglycerides in the group precribed ACEIs + Ca2+ blocker and the group prescribed ACEIs + diuretic; reductions in LDL cholesterol in the group prescribed with ACEIs + Ca2+ blocker and the ARBs + diuretic group; we also found that in the group prescribed with ARBs + diuretic and ACEIs + diuretic there was a reduction in total cholesterol, but there was a statistically significant negative linear correlation between the reduction of insulin resistance and increase in HDL cholesterol in the group prescribed with ACEIs + diuretic. Insulin promotes antilipolysis and stimulates lipoprotein lipase (LPL) in adipose tissue. Therefore, when insulin resistance develops, there is an increase in lipolysis with a production of more fatty acids - these fatty acids further impair insulin-mediated glucose uptake, which manifests as high blood sugar. Some of the free fatty acids are taken up by the liver and converted to very-low density lipoproteins (VLDLs), which are precursors to low-density lipoproteins. Acting in this way, insulin resistance leads to increase in LDL and decrease in HDL cholesterol. Lack of LPL stimulation leads to hypertrigliceridemia.

There are some limitations to this study. Firstly, the number of patients included in the study was smaller than in the similar studies. Secondly, it would have been interesting to measure inflammatory biomarkers and relate changes in mechanics to changes in biomarkers. However, for technical reasons, those measurements were not available. However, only a small number of patients were concerned.

CONCLUSION

The combined antihypertensive therapy - ACEIs + Ca2+ blockers - showed the greatest effect in reducing diastolic blood pressure and insulin resistance with a consequent positive effect on the lipid profile in patients with hypertension and MetS. Thus, combined antihypertensive therapy proved effective in patients with MetS and resulted in protection from target organ damage, consequently reducing morbidity and mortality in these patients.

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Review article

Screening for dyslipidemia in children - prevention of premature cardiovascular disease

Skrining dislipidemije u djece - prevencija prijevremenog kardiovaskularnog rizika

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ABSTRACT

Dyslipidemia is a major cardiovascular disease risk factor for accelerated atherosclerosis and early clinical manifestations of cardiovascular disease. In childhood, primary dyslipidemia is more common than secondary dyslipidemia, and it is hereditary metabolic disorder of lipoproteins. Given that primary dyslipidemia runs from the child's birth and that there is no symptomatic clinical manifestation, it is important to determine, as early as possible, disorder of the lipid profile in children and relatives, and prevent or reduce the accelerated atherosclerosis and early cardiovascular clinical expression. Using universal screening for dyslipidemia, which should cover as many prepubertal children with proper state of health, we can identify the disorder of lipid profile in children, and slow down or reduce the early clinical manifestations of atherosclerotic cardiovascular disease. The basic therapeutic approach to prevent and control children with dyslipidemia includes practicing healthy eating habits, regular physical activities, limiting sedentary lifestyle and avoiding inhalation of smoke, and use of lipid-altering drugs in indicated cases.

Key words: atherosclerosis, cardiovascular disease, children, screening for dyslipidemia, prevention and treatment

SAŽETAK

Dislipidemija je najznačajniji kardiovaskularni riziko-faktor koji uvjetuje ubrzanu aterosklerozu i prijevremeno kliničko ispoljavanje kardiovaskularne bolesti. U dječjoj dobi učestalija je primarna dislipidemija naspram sekundarnoj dislipidemiji, a predstavlja nasljedni metabolički poremećaj lipoproteina. S obzirom da primarna dislipidemija traje od rođenja djeteta i da nema manifestnu kliničku ispoljenost, veoma je bitno što ranije utvrditi poremećaj lipidnog profila u djece i srodnika, kako bi prevenirali ili reducirali ubrzanu aterosklerozu i prijevremenu kardiovaskularnu kliničku ekspresiju. Univerzalnim skriningom displipidemije, kojom treba obuhvatiti što veći broj prepubertetske djece urednog zdravstvenog stanja, možemo utvrditi poremećaj lipidnog profila u djece, te usporiti ili reducirati prijevremeno kliničko ispoljavanje aterosklerotske kardiovaskularne bolesti. Temeljni terapijski pristup preveniranja i nadzora djece s dislipidemijom uključuje prakticiranje zdravih prehrambenih navika, redovito prakticiranje tjelesne aktivnosti, ograničavanje sjedilačkih navika i izbjegavanje udisanja duhanskog dima, a u indiciranim slučajevima treba primjeniti hipolipemike.

Ključne riječi: ateroskleroza, bolesti srca i krvnih žila, dijete, skrining dislipidemije, prevencija i liječenje

INTRODUCTION

Autopsy, epidemiological and clinical studies indicate that dyslipidemia and other cardiovascular risk factors (obesity, hypertension, diabetes and smoking) presented in children are predictors of clinical manifestations of atherosclerosis in young adults identified with calcification of the coronary blood vessels using computerized tomography, with thickening of the intima-media complex on the carotid artery and reduction of the flow in brachial arteries mediated with dilation and determined by ultrasound (1,2,3).

Dyslipidemia is the most important cardiovascular risk factor that can condition the accelerated atherosclerosis and early clinical manifestation of cardiovascular disease. It is believed that one third of men before age of 50 and one third of woman before the age of 60 respectively has dyslipidemia, wherein 50% of them are hereditary disorders (4). It is very important to reveal hereditary disorder of lipid in early childhood, given that hereditary lipid disorders significantly accelerate the atherosclerotic process and condition the early clinical manifestations of cardiovascular disease.

Despite progress in protecting cardiovascular health, cardiovascular diseases are still the leading causes of death worldwide. It is believed that the fundamental reason is insufficient attention to the primary prevention of atherosclerotic cardiovascular disease, which should begin in early childhood.

Primary prevention of atherosclerotic cardiovascular disease in children includes: practicing healthy lifestyles (diet, adequate physical activity, reducing sedentary lifestyle and avoiding smoking and exposure to tobacco smoke) and screening for cardiovascular risk factors in children (obesity, hypertension, dyslipidemia and dysglycemia).

The etiology of dyslipidemia

Dyslipidemia (traditional cardiovascular risk factor); and nontraditional (emerging cardiovascular risk factors i.e., different sizes of lowdensity lipoprotein (LDL) particles, lipoprotein (a), apolipoprotein B, and apolipoprotein A) are responsible for the occurrence of atherosclerosis and its common complications (coronary heart disease, stroke and peripheral arterial occlusive disease) caused by stimulation of interaction between the blood and the vessel wall.

In atherogenesis, size and density of LDL particles are more significant than the total amount of LDL particles, i.e., predominance of small, dense LDL particles, compared to the large LDL particles increase cardiovascular risk for three to seven times (5).

Many epidemiological and clinical studies conducted in the last two decades indicate that lipoprotein (a) [Lp (a)] is genetically determined cardiovascular risk factor which plasma concentration in every person is different independent of diet, physical activity and drugs (2,6). In every day practice concentration of the Lp (a) is not measured in the assessment of cardiovascular risk, but should be considered to determine if the presence of cardiovascular disease is in the family, and not determined by traditional cardiovascular risk factors (6,7).

Apolipoprotein B (apoB) is more sensitive indicator of cardiovascular risk than LDL cholesterol, given that apoB can estimate small, dense LDL particles, which are hard to assess in the cases of borderline or mildly elevated LDL-cholesterol.

Determination of apoB might be useful in the diagnosis of hereditary dyslipidemia, such as Abetalipoproteinemia or familial hypobetalipoproteinemia, in which apoB is completely absent from the plasma or has a concentration of 20-30% lower than the desired value (6). Apolipoprotein A-I (apoA-I) is the same or slightly better indicator of cardiovascular risk in relationship to HDL-cholesterol (HDL-C) (6).

Dyslipidemia is typically classified into primary and secondary. Secondary causes of dyslipidemia in children and young adults are heterogeneous, i.e. it is subject to certain conditions, diseases or medication (Table 1) (8,9,10,11).

Table 1 Etiology of dyslipidemia in childhood.

Lifestyle	
Inadequate nutrition	
Physical inactivity	Drugs
Smoking	Corticosteroids
Obesity	Beta-blockers
Endocrine and metabolic disease	Anabolic steroids
Type I and type II diabetes mellitus	13-cis-Retinoic acid
Hypopituitarism	Immunosuppressive drugs
Hypothyroidism	Others
Gaucher's disease	Anorexia nervosa
Niemann-Pick disease	Systemic lupus erythematosus
Renal disease	Dysglobulinemia
Glomerulonephritis	Idiopathic hypercalcemia
Nephrotic syndrome	Klinefelter's syndrome
Hemolytic-uremic syndrome	Kawasaki disease
Chronic renal failure	Rheumatoid arthritis
Hepatic disease	Cancer survivor
Congenital biliary atresia	Kidney transplantation
Benign recurrent intrahepatic cholestasis	Heart transplantation
Cirrhosis	
Liver failure	

Modified from Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (8), Neal WA (9), Alwaili K, Alrasadi K, Awan Z, Genest J. (10), Zappalla FR, Gidding SS (11).

In childhood primary dyslipidemia is more frequent than secondary dyslipidemias, and it includes metabolic hereditary disorders of the lipoproteins caused by mutation of one or more genes. Junk food, obesity and lack of exercise have modifying effect on the expression of primary dyslipidemia.

Primary dyslipidemia can be divided into hypercholesterolemia, hypertriglyceridemia, and mixed dyslipidemia, and other genetically conditioned dyslipidemia (12).

From hereditary diseases disorders of lipoprotein metabolism (Table 2) the development of atherosclerosis is particularly affected by family hypercholesterolemia, family functional deficiency of the apoB, polygenic hypercholesterolemia, familial dysbetalipoproteinemia and family mixed hyperlipidemia (12,13).

Table 2 Classification of the most common primary dyslipidemia in children

Disease	Elevated level of lipoproteins	Clinical finding	Type of inheritance	Incidence
Familial Hypercholesterolemia	LDL-C	Tendon xanthomas, premature corneal arcus, coronary artery disease	Autosomal dominant	1-500
Familial Ligand Defective apoB-100	LDL-C	Tendom xanthomas, coronary artery disease	Autosomal dominant	1-1000
Sitosterolemia	LDL-C	Tendom xanthomas, coronary artery disease	Autosomal recessive	<1/ 1 000 000
Polygenic Hypercholesterolemia	LDL-C	Coronary artery disease	Polygenic	1/30
Familial Combined Hyperlipidemia	LDL-C, TG	Coronary artery disease	Autosomal dominant	1/200
Familial Dysbetalipoproteinemia	LDL, TG	Tuberoeruptive xanthomas, peripheral vascular disease	Autosomal dominant	1/10 000
Familial Hyperchylomicronemia	TG ↑↑	Tuberoeruptive xanthomas, hepa-tosplenomegalia, pancreatitis	Autosomal recessive	1/ 1000 000
Familial Hypertriglyceridemia (Fredrickson Type IV)	TG ↑	± Coronary artery disease	Autosomal dominant	1/500
Familial Hypertriglyceridemia (Fredrickson Type V)	TG ↑↑	Xanthomas, ± Coronary artery disease	Autosomal dominant	

LDL-C, low-density lipoprotein cholesterol; TG, triglycerides. Modified from Neal WA (9).

The largest number of children with primary dyslipidemia does not usually present clinical symptoms, although in terms of pathophysiology the disease is present at birth. In order to prevent accelerated atherosclerosis and early cardiovascular disease it is

necessary to determine the biochemical disorders of the lipid profile in these children and their relatives.

Family hypercholesterolemia is an autosomal-dominant hereditary disorder of cell receptors for LDL characterized by an increase in total and LDL-cholesterol (LDL-C), and increased risk of premature cardiovascular disease. Despite the high frequency of the available effective treatment, familial hypercholesterolemia is insufficiently diagnosed and treated, particularly among children - it is considered that about 20% of diagnosed patients are with familial

hypercholesterolemia, of which very few receives appropriate therapy (14,15). Untreated familial hypercholesterolemia increases early cardiovascular risk by 20 times (14).

Heterozygous form of familial hypercholesterolemia is one of the most common monogenic hereditary diseases, the frequency of 1/300 to 1/500 live births (9,14). Approximately 50% of untreated men and 25% of untreated women with heterozygous familial hypercholesterolemia will develop cardiovascular disease by the age of 50 (2). Mostly children with a heterozygous familial hypercholesterolemia do not have clinical symptoms, but markers of atherosclerosis are presented in the carotid and brachial ultrasound of the blood vessels (2,16).

Homozygous familial hypercholesterolemia form occurs at 1/1 000 000 live births. Planar xanthomas and gluteal folds finger area will occur in almost all children by the age of 5, while in 10, 20, or 30 years they will develop cardiovascular disease, which may be fatal (2).

Family apoB deficiency is an autosomal-dominant inherited disease characterized by elevated LDL-C, and increased risk for early atherosclerotic cardiovascular disease. Molecular genetic analysis is differentiated from heterozygous familial hypercholesterolemia (12,13).

Polygenic hypercholesterolemia is an inherited dyslipidemia, characterized by increased concentrations of total and LDL-C due to the interaction of several genes and diet with an abundance of cholesterol and saturated fatty acids. Premature atherosclerosis occurs earlier in people with polygenic hypercholesterolemia compared to people with normal lipid profile (12).

Family dysbetalipoproteinemia is characterized by the increase in triglycerides and cholesterol caused by inherited disorders associated with hypercaloric diet - rich in saturated fats, obesity, diabetes, hypothyroidism, liver or renal disease (9,13). Hereditary disorder lasts from birth but cardiovascular disease occurs in forties or fifties.

Family mixed dyslipidemia is a complex polygenic disease with increased concentrations of cholesterol and/or triglycerides; elevated small, dense LDL particles, apoB, and reduced HDL-C in at least two members of the family. It is associated with premature cardiovascular disease, and about 20% of patients with early myocardial infarction have a family mixed hyperlipidemia (15).

Classification of the lipid profile

According to the NCEP Expert Panel on cholesterol levels in children and adolescents (17) and the Bogalusa Heart Study (18) values of the lipid profile (total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides and non-HDL-cholesterol) are classified as desirable, borderline and high/lower (Table 3).

Table 3 Reference lipid values for children and adolescents.

Lipoproteins	Acceptable	Borderline	High/low*
TC	<4.4 mmol/L	4.4-5.1 mmol/L	≥5.2 mmol/L
LDL-C	<2.8 mmol/L	2.8−3.3 mmol/L	≥3.4 mmol/L
Non-HDL-C	<3.2 mmol/L	3.2−3.7 mmol/L	≥3.8 mmol/L
HDL-C	>1.1 mmol/L	0.9−1.1 mmol/L	*<0.9 mmol/L
TG			
0-9 years	<0.8 mmol/L	0.8−1.1 mmol/L	≥1.2 mmol/L
10-19 years	<1.0 mmol/L	1.0−1.4 mmol/L	≥1.5 mmol/L

TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.
Modified from American Academy of Pediatrics. National Cholesterol Education Program (17), Srinivasan SR, Myers L, Berenson GS (18).

In order to correctly detect dyslipidemia it is recommended to take a sample of venous blood in fasting (at least 10 hours of fasting) in a halfsitting position of the patient, wherein the tourniquet should be in place kept for the venipuncture for one minute (7).

It is recommended to determinate complete lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides) in the reference laboratory.

To reduce the possibility of analytical errors it is recommended to take two lipid profile (fasting blood) at intervals of not less than two weeks and more than three months, and calculate the average value of lipid parameters (8).

If the patient is not fasting we can determine: total cholesterol, HDL cholesterol and non-HDL cholesterol. Non-HDL-cholesterol [nonHDL-C = (total cholesterol) - (LDL-cholesterol)] includes atherogenic apoB-containing lipoproteins [lipoproteine very low density - VLDL, intermediate-density lipoproteins - IDL, low-density lipoprotein LDL and Lp (a)] and it has a similar predictive value for adult dyslipidemia and LDL cholesterol (8).

In the assessment of dyslipidemia in children it is important to determine the apoA-I and apoB with a goal to detect hereditary disorders of HDL-cholesterol (reduced apoA-I) and the familial mixed hyperlipidemia (elevated apoB).

Determination of Lp (a) may be important as a predictor of ischemic or hemorrhagic stroke in hereditary predisposed children, as in majority of these cases the cholesterol is in the range of desired values (18).

One of the important questions is at what age a child should do the lipid profile, which is associated with variations in lipid values that are low after birth and gradually growing a few weeks after giving birth, in order to stabilize after the age of two and held constant to the tenth year of life, in values of lipids in adulthood (2,19).

During the adolescent period values of the total and LDL cholesterol decrease 10-20% or more of their average value, and would not be able to detect familial hypercholesterolemia if screening for familial hypercholesterolemia was made in adolescent period (2,19).

Screening for dyslipidemia

Considering that atherosclerosis begins in early childhood, and dyslipidemia is one of the most important cardiovascular risk factors, screening for dyslipidemia imposed as a priority in the prevention, diagnosis and treatment of cardiovascular disease in children.

Screening for dyslipidemia in children, as a strategy of primary prevention of development of early clinical manifestations of atherosclerosis, will allow us to slow or prevent the early development of atherosclerotic cardiovascular disease. We find it necessary to talk about the need for dyslipidemia screening and not just screening for hypercholesterolemia, because with the screening we could also discover other types of dyslipidemia (hypertriglyceridemia and decreased HDL-C).

Universal (general) and targeted (selective) screenings are two main approaches to detect dyslipidemia in childhood. Targeted screening for dyslipidemia should be implemented in the case of early familial cardiovascular disease, in the case of dyslipidemia in parents, the presence of risk factors in the child (obesity, hypertension, diabetes 1 and 2, smoking exposure, low HDL-C and inactivity) or certain pathological state of the child (AIDS, Kawasaki's disease, systemic lupus erythematosus, juvenile rheumatoid arthritis, nephrotic syndrome, chronic renal failure and condition after transplantation of heart and kidney), and in case of unknown or unclear family history of cardiovascular disease, and unknown lipid profile of close relatives (8,11,20,21,22).

Universal screening of dyslipidemia refers to the detection of dyslipidemia in all or as many children regardless of the family history of early cardiovascular disease or value of the lipid profile of the parents or close relatives. Insufficient sensitivity of family history of premature cardiovascular disease, ignorance of the value of the lipid profile of the parents or close relatives and good health condition of parents promote the importance of universal screening for dyslipidemia in children (15,23,24,25).

Universal screening of dyslipidemia can detect children with undiagnosed hereditary dyslipidemia, and lipid profile assessment of parents and relatives can discover their cardiovascular risk (26,27). It is recommended that screening for dyslipidemia should be conducted between the age of two and ten, i.e. based on guidelines of the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents universal screening for dyslipidemia is recommended between 9 and 11 and between 18 and 21 years (2,18,19,28).

The therapeutic approach to dyslipidemia

In order to prevent or reduce the occurrence of dyslipidemia, obesity, hypertension and insulin resistance the following is recommended: practicing and eating food with a lower content of total fat, saturated fat, trans fat, cholesterol, refined carbohydrates and salt. Children must consume more fruits, vegetables, legumes, whole grains, nuts, low-fat or fatfree milk and milks products, poultry and fish instead of red meat, avoid or reduce the junk food, sweets and refreshments (8,21,29,30). These suggestions apply equally to both children and adolescents (population access of the control of cardiovascular risk).

In addition to practicing healthy eating habits, prevention and treatment of dyslipidemia and all the other cardiovascular risk factors involve daily physical activities for a period of one or more hours per day, limiting sedentary lifestyle to two hours a day and avoiding active and passive smoking (8,31,32).

Pharmacological treatment is recommended for children over eight years of age, when even after six-month of practice and healthy lifestyle the LDL-C is still high, and the goal of treatment is to reduce LDL-C and to maintain it on the value of minimum <3.4 mmol / L, and 2.8 mmol/L, the ideal value.

The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) recommends the use of pravastatin for children with familial hypercholesterolemia over 8 years of age, and for children over the age of 10 the FDA recommended the use of simvastatin, lovastatin and atorvastatin (31) .

EMEA and FDA recommends the use of ezetimibe for children over 10 years of age with familial hypercholesterolemia (combination therapy with statin), polygenic hypercholesterolemia and family mixed hyperlipidemia (2,31,34). Omega-3 fatty acids contained in fish oil have a beneficial effect in children with hypertriglyceridemia (35).

CONCLUSION

Universal screening of the complete lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides and non-HDL cholesterol) in the reference laboratory should include as many prepubescent

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children as possible, as well as diagnosing hereditary disorder of lipids in early childhood, which significantly accelerates atherosclerosis and causes the early clinical manifestations of cardiovascular disease. Practicing healthy eating habits, regular physical activities, limiting sedentary lifestyle and avoiding inhalation of smoke have a fundamental role in the prevention and control of dyslipidemia in children

Conflict of interest: none declared

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Review article

Vitamin D in physiatry practice

Vitamin D u fizijatrijskoj praksi

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ABSTRACT

Introduction: vitamin D plays a crucial role in musculoskeletal health. Recent evidence suggests that deficiency of vitamin D is associated with many non-skeletal disorders. Physiatrist should be continuously educated on the role and impact of vitamin D on the individual systems in the body, in order to timely prevent and treat diseases in patients who undergo rehabilitation. Materials and methods: this paper used data from 4 review studies, 2 meta-analyzes, 2 clinical guides and 24 other studies. Results: the status of vitamin D in the body is measured and monitored by the concentration of the metabolite 25-hydroxyvitamin D (25- (OH) vitamin D), which is expressed in ng/ml or nmol /l. Depending on its concentration, vitamin D deficiency is defined as a "deficit" or "insufficiency". "Deficit" leads to rickets and osteomalacia, "insufficiency" is associated with osteoporosis, and has great influence on bone fractures and falls. Recent evidence "insufficiency" associates with diseases such as cancer, diabetes mellitus, multiple sclerosis, cognitive dysfunction, autism, Parkinson's disease, heart disease. The main sources of vitamin D are ultraviolet B radiation, food and supplements. In the treatment of vitamin D deficiency, it is important to achieve "optimal" concentration of vitamin D, and according to majority of authors that is the value of ≥ 75 nmol/l. In order to prevent D vitamin "deficit" and "insufficiency", or for their treatment, there are recommendations for necessary daily intake. Recommendations vary on a regional and national levels, and are continuously revised. Conslusion: physiatry, as an integrative branch of medicine, not only includes the underlying disease for which the patient is treated, but also includes the treatment of comorbidity, or prevention of various complications and new disease, which requires careful observation and timely action. Therefore, the knowledge of the physiology of vitamin D and its impact on the function of the musculoskeletal and other systems in the body, is of great importance for the daily practice of physiatry. Institutions for physiotherapy and rehabilitation are very appropriate for diagnosing, treating and studying vitamin D deficiency.

Key words: vitamin D, physiatry

SAŽETAK

Uvod: vitamin D ima izuzetno važnu ulogu u muskuloskeletnom zdravlju, a noviji dokazi upućuju da je njegov nedostatak povezan i sa brojnim vankoštanim poremećajima. Fizijatar treba biti kontinuirano educiran o ulozi i uticaju D vitamina na pojedine sisteme u organizmu, kako bi pravovremeno prevenirao i tretirao bolesti kod pacijenata koji se rehabilitiraju. Materijal i metode: za rad su korišteni podaci iz 4 pregledne studije, 2 meta-analize, 2 vodiča i 24 studije. Rezultati: status D vitamina u organizmu mjeri se i prati preko koncentracije metabolita 25-hidroksivitamina D (25-(OH) vitamin D), koji se izražava u ng/ml ili nmol/l. Ovisno o njegovoj koncentraciji, nedostatak vitamina D definiše se kao "deficit" ili "insuficijencija". "Deficit" vodi u rahitis i osteomalaciju, "insuficijencija" je udružena sa osteoporozom, i ima veliki uticaj na koštane prelome i padove. Noviji dokazi "insuficijenciju" povezuju i sa bolestima drugih sistema, kao što su kancer, dijabetes melitus, multipla skleroza, kognitivne disfunkcije, autizam, Parkinsonova bolest, srčana oboljenja. Osnovni izvori D vitamina su ultravioletno B zračenje, hrana i suplementi. U tretmanu nedostatka D vitamina važno je postići "optimalnu" koncentraciju D vitamin, koja po većini autora podrazumijeva vrijednost ≥ 75 nmol/l. U cilju sprečavanja nastanka „deficita" i „insuficijencije" D vitamina , ili za njihov tretman, izradjuju se preporuke za potrebni dnevni unos. Preporuke se razlikuju na regionalnim i nacionalnim nivoima, a kontinuirano se i revidiraju. Zaključak: fizijatrija, kao integrativna grana medicine, ne uključuje samo osnovnu bolest zbog koje se pacijent tretira, nego podrazumijeva i liječenje komorbiditeta, odnosno prevenciju nastanka različitih komplikacija i novih bolesti, što zahtijeva pomnu observaciju i pravovremeno djelovanje. Stoga je i poznavanje fiziologije D vitamina i njegovog uticaja na funkciju muskuloskeletnog, kao i drugih sistema u tijelu, od izuzetne važnosti za svakodnevnu fizijatrijsku praksu. Institucije za fizijatriju i rehabilitaciju su odgovarajuća mjesta za dijagnosticiranje, tretiranje i studiranje nedostatka D vitamina.

Ključne riječi: D vitamin, fizijatrija

INTRODUCTION

Vitamin D plays a crucial role in musculoskeletal health. More recent evidence suggests that low serum levels of 25-hydroxyvitamin D are associated with numerous non-skeletal disorders. Physical and rehabilitation medicine, as complex and intergrative branch of medicine, beside patients with musculoskeletal diseases, increasingly treats patients with internal and oncological diseases. Therefore, knowledge of the role and impact of vitamin D on the individual systems in the body has a special importance for physiatry practice, not only in the treatment of osteoporosis, osteomalacia and rickets, but also in the treatment of other diseases whose etiology is related to vitamin D deficiency.

Vitamin D has been named an anti rickets vitamin, but it is often called the sunshine vitamin. For historical reasons, is among the vitamins, but majority of its characteristics are hormonal (steroid structure). In the last decade it is in a particular focus of interest, what is contributed by return of rickets in Europe. In 1975 there were about 250 peer-reviewed papers published with the term "vitamin D", 30 years later, in 2007, that number had risen to about 1,600 papers, and in 2013 to 3774 work (1).

In the body this vitamin can be synthesized in the skin from provitamin under the influence of ultraviolet rays, or can be entered by food. It is the most represented in fish oil and meat, milk and dairy products, egg, seeds and mushrooms. Therefore, daily requirements for vitamin D are achieved by exposure to the sun or by food intake.

In addition to having a very important role in the musculoskeletal health, recent evidence suggests that low serum

concentrations of 25-hydroxyvitamin D are linked to numerous non-skeletal disorders, such as cancer, heart disease, high blood pressure, diabetes, cognitive dysfunction associated with aging, Parkinson's disease, multiple sclerosis and autism. However, does the low value of 25-hydroxyvitamin D is a cause or consequence of the disease, still is not clear (2).

The primary role of vitamin D is to maintain calcium and phosphate homeostasis in the plasma. It stimulates their absorption from the gastrointestinal tract, and for maintaining the concentration of calcium ions in plasma have the assistance of parathyroid hormone (PTH).

Vitamin D deficiency is clinically manifested by hypocalcemia, hypophosphatemia or by general demineralization of the bones, by pain in bones and muscles, by spontaneous fractures and muscle weakness. This is caused by insufficient absorption of calcium and phosphate. Children can come to the emergence of rickets and adults to osteomalacia.

The application of high doses of vitamin D leads to disturbances in the metabolism of calcium, and the first symptoms of hypervitaminosis are related to hypercalcemia. These are fatigue, indigestion, weight loss, anemia and even depression. There is an additional deposition of calcium in the kidneys and pancreas. However, it is very difficult to overdose on vitamin D.

METABOLISM OF VITAMIN D

A group of vitamin D includes 7 vitamins, which differ in the structure of the side chain in position 17. But when it comes to vitamin D in the narrow sense, it is referring to the mixture of vitamin D2 (ergocalciferol) and D3 (cholecalciferol). Ergosterol (provitamin of ergocalciferol) is of vegetable origin, and vitamin D3 is of animal origin, or is synthesized from 7-dehydrocholesterol, a cholesterol derivative, under the action of ultraviolet rays. Vitamin D is practically insoluble in water, but soluble in alcohol, chloroform and ether, and in vegetable oils. It is not stable in the crystalline state, so it is often found in oily solutions, which are stable.

After it is synthesized in the skin or after food intake, vitamin D from the blood is deposited in various tissues, including liver, adipose tissue and muscle (Figure 1). The biological half-life of vitamin D is approximately 60 days, to be finally brought into the 25- hydroxyvitamin D (25 (OH) vitamin D) in hepatocytes.

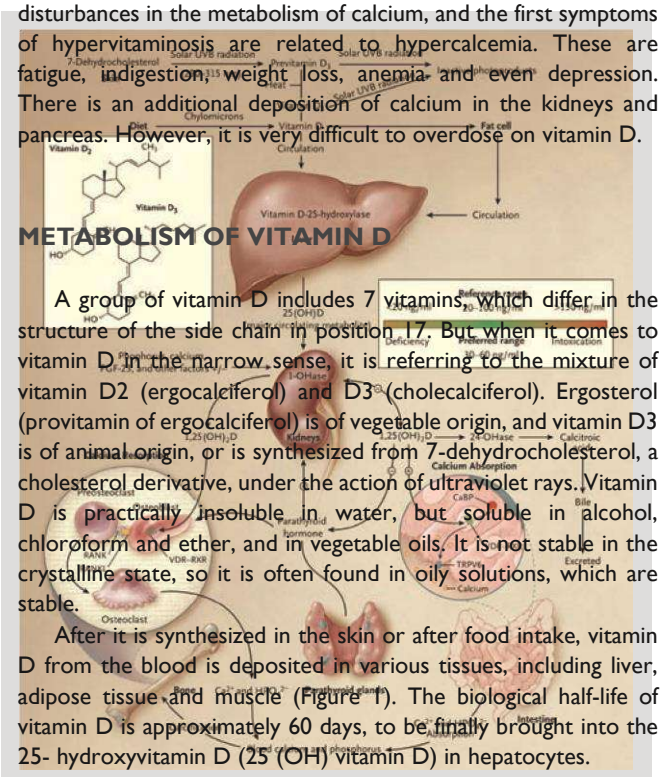

Figure 1 Metabolism of vitamin D.

(Michael F. Holick. Vitamin D Deficiency. N Engl J Med 2007; 357:266-281)

These forms of metabolized vitamins D2 and D3 are, in fact, steroid hormones. Vitamin D3 in this form is called calcidiol. Then, the 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3 require α 1 hydroxylation, to switch to the biologically active form, the hormone 1,25-dihydroxyvitamin D (1,25 (OH)2 vitamin D). This form of metabolized vitamin D3 is called calcitriol. This process is mostly happening in the kidneys and is under the influence of the parathyroid hormone. 1,25 (OH)2 vitamin D has a primary role in maintaining the calcium homeostasis. It improves the intestinal absorption of calcium, and in coordination with PTH, deposites calcium in bones, or less frequently, mobilizes calcium from the bones. It also promotes renal reabsorption of calcium and phosphorus. The result is a positive balance of calcium, increase of the serum calcium and phosphorus levels, and decrease of the PTH concentration. Biological activity of calcidiol represents less than 1% of the biological activity of calcitriol. It is considered that vitamin D2 is not as effective as Vitamin D3 (3).

MEASUREMENT AND ANALYSIS OF VITAMIN D

The serum concentration of 25-hydroxyvitamin D is the best indicator of nutritional and functional status of vitamin D. The blood sample taken at any time of the day is suitable for measurement of 25-hydroxyvitamin D. The circulating calcitriol (1,25-dihydroxyvitamin D3 or 1,25-dihydroxycholecalciferol) is a hormone which regulates the intestinal absorption of calcium and phosphate, and is not appropriate indicator of the clinical status of vitamin D. The exception is in patients with impaired synthesis of calcitriol (renal insufficiency, lymphoma, sarcoidosis), or in patients with the rare disorder of phosphate and vitamin D metabolism.

There are several laboratory techniques for measuring 25-hydroxyvitamin D. Different laboratories have different referential values. They all relatively well identify the level of vitamin D in serum; however, they can make an error in terms of the lower value of 20%. This variability in the measurement of serum 25-hydroxyvitamin D sets imperative that clinical laboratories have to have continuous control as an integral part of accreditation for quality control of laboratories that measure 25-hydroxyvitamin D.

Monitoring of 25-hydroxyvitamin D in serum

There was a significant increase in testing of 25-hydroxyvitamin D in clinical practice. However, it should be measured only if deficiency is suspected, or if the lack of it will influence the response in some patients (eg. the impaired intestinal absorption such as celiac disease, or in osteoporosis which requires a pharmacological treatment). In the treatment of vitamin D deficiency, 25-hydroxyvitamin D in serum should demonstrate the effectiveness of therapy. The half-life of 25-hydroxyvitamin D in the body is 15-20 days. With standard dosing, serum 25-hydroxyvitamin D reaches its plateau levels after three to four months, and should not be checked before three months of treatment starting. For administration of high doses of oral and parenteral supplementation of vitamin D (for example, 500 000 IU), the peak concentration of 25-hydroxyvitamin D can be achieved for one month. According to the recommendations of the Canadian Society for osteoporosis, in patients taking higher daily doses of vitamin D than standard (2000 IU) serum 25-hydroxyvitamin D should be monitored (1). For healthy people, or those who use supplements in routine doses, monitoring is not indicated.

STATUS OF VITAMIN D

The concentration of vitamin D in serum is measured in nanograms per milliliter (ng/ml), or in nanomoles per liter (nmol/l). To convert result in ng/ml into nmol/l a result should be multiplied by 2.5. For example, 20 ng/ml is equal to 50 nmol/l.

Many experts as a physiological values of the vitamin D recommend level range between 20 and 40 ng/ml, while others recommend a range of 30 and 50 ng/ml. Globally, there is a consensus that the level of 25-hydroxyvitamin D below 25 nmol/l (or 10 ng/ml) is qualified as "deficient", but there is currently no standard definition or consensus for the "optimal" level of 25-hydroxyvitamin D. Lack of definition and consensus have led to the emergence of several terms, depending on the country or region, such as "deficient", "insufficient", "adequate" or "optimal" level of 25-hydroxyvitamin D in the blood. Of course, this makes difficulties for comparisons and obtaining exact data on the prevalence of vitamin D deficiency (4).

The US Institute of Medicine (IOM) made the evidence based recommendation for vitamin D status in 2011 (5):

- serum level of 25-hydroxyvitamin D <30 nmol/l (or 12 ng/ml) is deficient ("deficit")
- serum level of 25-hydroxyvitamin D in the range of 30-50 nmol/l (12-20 ng/ml) is not sufficient ("insufficiency")
- serum level of 25-hydroxyvitamin D> 50 nmol / l (20 ng/ml) is enough for almost the entire population (97.5%).

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The National Association for Osteoporosis of United Kingdom (UKNOS) in 2013 suggested that this recommendation should be accepted by UK doctors (6).

The lower limit for the "optimal" range is controversial, but available evidence from some studies supports setting this limit to 75-80 nmol/l. For this level of 75 nmol/l there is a meta-analysis, which resulted in achieving prevention of fracture (7). Also, after a long period of taking higher doses of vitamin D, and with setting the lower limit at 75-80 nmol/l, normalizes serum PTH, muscle function of the lower extremities and intestinal absorption of calcium. However, some countries, such as Austria, Germany and Switzerland, have adopted the view that the levels of serum 25-hydroxyvitamin D> 50 nmol/l is already an indicator for optimal vitamin D status.

The term "deficit" is used for advanced clinical condition of chronically low levels of vitamin D in serum (as the malabsorption of calcium and phosphate resulting in hypocalcemia, hypophosphatemia and secondary hyperparathyroidism). In this condition occurs proximal myopathy and develop rickets in children or osteomalacia in adults. The term "insufficiency" of vitamin D is used for milder deficiency, due to the reduced calcium absorption and subsequent mild secondary hyperparathyroidism, which leads to an increased loss of bone mass. Insufficiency of vitamin D usually occurs in patients with osteoporosis, and is manifested by low bone density, or an increased tendency to fractures and falls.

Epidemiology of vitamin D status

Achieving the optimal level of 25-hydroxyvitamin D is a global problem. Severe deficiency, i.e. "deficit" is most pronounced in the Middle East and South Asia, with high prevalence of rickets. Hypovitaminosis D is particularly pronounced in immigrant populations in areas with less UV radiation. Several areas in Africa and Asia cannot be processed due to the unavailability of epidemiological data. In the area of Scandinavia can be observed reduced incidence of vitamin D deficiency, which is attributed to the diet rich in vitamin D. Enrichment of foods with vitamin D in North America successfully increased levels of 25- (OH) vitamin D levels in the general population (8).

Factors associated with vitamin D deficiency

Many factors are associated with vitamin D deficiency, some

are causative (eg. a contraindication for ultraviolet/sun exposure, malapsorption), and the second sheet is where the deficit or insufficiency of vitamin D are frequent (e.g. chronic renal failure) (9,10). Lack of vitamin D should be considered in patients with osteoporosis, especially if there is no response to treatment (11). Elderly patients living in institutions are at high risk for vitamin D deficiency due to lack of sun exposure (12). Completely avoiding sunlight increases the risk of "deficit" of vitamin D. It is believed that more people over the age of 50 are at higher risk for deficiency of vitamin D because the skin has a decreased ability to synthesis, and renal function declines. People with dark skin pigment are more likely to lack vitamin D, because they need 10 times the sun exposure of members of the white race. Also, dermatological sunscreens may reduce the synthesis of vitamin D, but are not associated with the "deficit" of vitamin D, and should not therefore be avoided (13). People with obesity are also at risk, because they need more vitamin D than people of normal weight. Gastrointestinal diseases such as Crohn's disease, celiac disease or inflammatory bowel disease, cause a reduced fat absorption, and so the absorption of liposoluble vitamin D. The risk group includes infants fed only breast milk.

SOURCES OF VITAMIN D

The vitamin D in the body comes from three sources: a) synthesized in the skin upon exposure to sunlight, specifically under the influence of ultraviolet light B (UVB); b) from food c) from supplements.

a) Ultraviolet B radiation stimulates the synthesis of cholecalciferol in the skin, which is than stored in the adipose tissue, or hydroxylated in the liver, and is converted to 25 hydroxyvitamin D, which is then further hydroxylated in the kidneys to a biologically active form of 1.25-dihydroxyvitamin D. Ultraviolet B radiation (wavelengths 290-315 nm) stimulates the synthesis of vitamin D from 7-dehydrocholesterol in the skin, which is the main source of vitamin D in the body. The amount of exposure required to achieve adequate vitamin D status depends on latitude, altitude, time of the year or the day, the weather, the environmental aspects, age, type of skin pigment, on clothing, activities, and finally the surface of the irradiated skin. To afford 25 mg (1000 IU) of vitamin D3 from moderate irradiation with ultraviolet B radiation, young adult white race should expose 25% of its skin surface (mostly arms and legs) to one quarter of the minimal erythemal dose (4 minutes), while the elderly or people with darker skin need exposure of 18 minutes (14). Unfortunately, many of the damaging effects of UVB radiation are cumulative, and they should be taken into account. This is the reason why dermatologists recommend taking supplements of vitamin D, instead of a large, or in general, exposure to the sun. Effects of latitude on the synthesis of vitamin D may be associated with bone fractures: with every 10 ° away from the equator, the probability of hip fracture increased by 0.6%. In winter, above 35 ° north latitude, sunlight does not contain the proper amount of ultraviolet B radiation, enough to produce vitamin D3 (15).
b) Sources of vitamin D in food are limited. The richest natural sources are fatty fish and eggs, milk and dairy products, but in small quantities it is represented in the flesh, seeds and mushrooms. A good source is the food that is artificially fortified with vitamin D (most often it is milk and dairy products, margarine and other spreads, cereals). In the food are added both vitamin D, and cholecalciferol (D 3) and ergocalciferol (D2) (16). Different regions and countries have different regulations for the fortification of food with vitamin D. Some authors believe that the impact of food on the level of vitamin D is minimal (3.7-5.9 μg or 148 to 236 IU per day), in fact the majority of circulating vitamin D is generated from sun exposure (17). However, the WHO states that statistics do not support this view, and that the amounts of vitamin D, which in some countries is found in food, are far from negligible, especially in winter (18). However, it is not enough to achieve the desired level, and many others recommend the addition of supplements.
c) Vitamin D3 is taken as a basic human vitamin D supplement, while vitamin D2 is used for supplementation with large doses. When supplements of vitamin D are used in the treatment of "insufficiency", the dose should be sufficient to increase the 25-hydroxyvitamin D to desirable levels. Daily dose of vitamin D3 of 20-25 μg (800-1000 IU), and it raises serum 25-hydroxyvitamin D for about 15-30 nmol /

l. Recently the upper limit of the daily dosage is raised to 50 μg (2000 IU.). It is believed that this dosage is safe for long-term applications without the need for regular control (19).

EFFECTS OF VITAMIN D

Effect of vitamin D on musculoskeletal system

Vitamin D ensures mineralization of the organic matrix of the bones. Also, mediates release of calcium and phosphate from the bones, in order to achieve mineral homeostasis. The active form, 1.25-dihydroxyvitamin D (calcitriol), together with vitamin D receptors forms a complex, which is essential for absorption of active calcium from the intestine, for longitudinal bone growth, and for osteoblast and osteoclast activity. In addition to its role in the formation of bone, calcitriol promotes bone resorption by increase of number and activity of osteoclasts. In osteoblasts it acts by activation of RANKL and RANK system, leading to differentiation of osteoclasts. Vitamin D receptors (VDR) are transcription factor that regulates the expression of genes for biological activation of vitamin D. Without vitamin D, only 10 to 15% of calcium and 60% of phosphorus, entered by food intake, is absorbed. Interaction between 1.25 dihydroxyvitamin D receptors and vitamin D increases the efficiency of calcium absorption up to 30-40%, and of phosphorus up to 80% (20). According to a study of Bischoff-Ferrari et al, serum levels of 25-hydroxyvitamin D are directly related to bone mineral density, and the maximum density is achieved when the level of 25-hydroxyvitamin D reached 40 ng/ml or more. When the level was 30 ng/ml or less, there was a significant decrease in calcium absorption in the intestine, which causes an increase in PTH. Parathyroid hormone enhances tubular reabsorption of calcium and stimulates the kidneys in the production of 1.25-dihydroxyvitamin D.

Parathormon also activates osteoblasts, which stimulate the transformation of preosteoclasts into mature osteoclasts. Osteoclasts dissolve mineralized matrix of collagen in bones, causing

osteopenia and osteoporosis and increased risk of fracture (21). Lack of calcium and vitamin D in utero, in childhood or in adulthood, may prevent the maximum deposition of calcium in the skeleton. How vitamin D deficiency progresses, there is a stimulation of the parathyroid gland and secondary hyperparathyroidism. Parathyroid hormone leads to hypomagnesemia and phosphaturia, resulting in reduced mineralization of the matrix and leads to rickets in children or osteomalacia in adults.

Osteomalacia is a defect of skeletal mineralization, which is presented as diffuse bone pain, polyarthralgia, or muscle weakness that most affects the spine, chest, shoulders and hips (22). And without presence of osteomalacia, vitamin D deficiency can be manifested by musculoskeletal pain and muscle weakness, what is documented with numerous studies. Bone pain even occurs with minimal deficiency of vitamin D. It is believed that the cause of pain is hydration of demineralized gelatinous matrix under the periosteum. While osteomalacia is associated with isolated or generalized bone pain, osteoporosis is not characterized by pain. Osteomalacia can often be diagnosed by moderate thumb pressure on the sternum or the front of the tibia, causing bone pain. In the diagnosis of osteomalacia can be found: decreased vitamin D in the blood, decreased calcium in the blood and in 24-hour urine, reduced phosphorus in the blood, elevated alkaline phosphatase in the blood, elevated PTH levels, Looser transformation zones/fissures and thinner cortex on the X-ray,

and micro-CT bone biopsies would show greater representation of matrix in relation to mineral content.

Lack of vitamin D, in addition to causing pain in the muscles, causes loss of muscle strength and muscle mass, increasing moderate atrophy of fibers type I and type II, particularly in the older age group, what is defined as sarcopenia. In fact, the lack of action of vitamin D on muscle is best observed in osteomalacia. One study found that 93% of people aged 10-65 years, who were admitted to the hospital because of pain in the muscles and bones, under a wide variety of diagnoses, including fibromyalgia, chronic fatigue syndrome or depression, actually had a lack of vitamin D (23).

Institutions for physiatry and rehabilitation are appropriate places for diagnosing, treating and studying of vitamin D deficiency. According to authors Heath and Elovic, lack of vitamin D should be introduced in the differential diagnosis when evaluating musculoskeletal pain. In the target group should be patients with MRI diagnosed spinal stenosis and degeneration of intervertebral discs (24). During stationary rehabilitation effect of vitamin D can be estimated, not only to pain and muscle strength, but also to the patient's functionality.

Effect of vitamin D on fractures

Many studies have demonstrated that low concentrations of 25-hydroxyvitamin D are associated with bone fractures, while higher levels showed a significant reduction of fracture (25,26). Bischoff-Ferrari and colleagues combined data from five trials (n = 9829), in which were used doses of vitamin D3 from 17.5 or 20 mg (700 or 800 IU), and reduction of non-vertebral fractures was 23% (27). The most important is that the dose raises serum 25-hydroxyvitamin D above 75 nmol / l, which means that, if necessary, could be increased. Given that the current definition of posological tolerability of vitamin D is raising the upper limit, it is reasonable to recommend 20-50 μg (800-2000 IU) of vitamin D3 in the prevention of fractures in patients with osteoporosis.

Effect of vitamin D on falls

Vitamin D can affect the reduction of falls by improving muscle strength and function of the lower extremities. Meta-analysis of five studies, which appropriately defined and determined fall, showed that vitamin D significantly reduces the risk of the fall (22%) (28). It has been shown that vitamin D3 at a daily dose of 20 micrograms (800 IU) reduces the risk of falls, particularly in studies which appropriately defined and determined the fall.

Effect of vitamin D on other systems

Calcitriol receptor (VDR), and the enzymes involved in its synthesis, such as 1-α hydroxylase, and cytochrome P450 27B1 isozyme, are found in many tissues, including the skin, colon, prostate, breast, pancreas, heart, immune system (monocytes, macrophages and lymphocytes), and brain. However, calcitriol produced in these tissues is not released normally in circulation, and is not regulated by the serum calcium, phosphate and parathyroid hormone. Calcitriol can lower blood pressure by reducing the production of rennin, can stimulate the production and secretion of insulin through the pancreatic α cells, and can modulate the immune system by acting on lymphocytes and macrophages. Laboratory tests

have shown his antiproliferative and prodifferentiation potential. There are quite a few human studies that have shown a reduced risk of developing all types of cancer (except skin), cardiovascular disease, type 1 diabetes, multiple sclerosis or better resistance to infection in a sufficient daily intake of vitamin D (29). Although these studies concluded that the adequate daily intake dose, which must achieve serum concentration of calcitirol higher than 75 nmol/l, and although therapy with vitamin D for those diseases and conditions in daily practice is already applied, additional investigations are needed for precise posology.

PREVENTION AND TREATMENT OF VITAMIN D

For the prevention and treatment of "deficit" and "insufficiency" of vitamin D, there are recommendations for required daily intake. Recommendations vary on a regional and national level, and constantly are revised. Council for vitamin D in Central Europe gave the following recommendations (30):

General recommendations
Infants 0-6 months: 400 IU daily
Infants 6-12 months: 400-600 IU daily
Children/Adolescents: 600-1000 IU daily
Adults: 800-2000 IU daily
Pregnant women: 1500-2000 IU daily

Recommendations for risk groups
Premature infants: 400-800 IU daily
Obese children: 1200-2000 IU daily
Obese adults: 1600-4000 IU daily
Night work: 1000-2000 IU daily

The World Health Organization has developed guidelines for intake of vitamin D in children and pregnant women. For the treatment of "insufficiency" of vitamin D, primarily osteoporosis, and other diseases such as cancer, heart disease, diabetes, cognitive dysfunction associated with aging, Parkinson's disease, multiple sclerosis and arthritis, the recommended initial daily dose of vitamin D is from 5000 IU to 10 000 IU, and is taken until reaching the desired level of 25- (OH) vitamin D to 75 nmol/l or 30 ng/ml. The most commonly prescribed supplements are of vitamin D3. This period usually lasts up to three months, after which laboratory control is needed, and according to findings the dose should be reduced to long-term maintenance dose, which is determined by the individual clinical assessment (800-1000-2000 IU). This estimate takes into account several elements, such as latitude, time of year, sun exposure, skin color, body mass index, diet, intestinal absorption. For clinical practice it is very useful estimation that 1μg (40 IU) of vitamin D3 increases serum 25- (OH) vitamin D for 0.7-2.0 nmol/kg daily (31). Assuming that person by food intake and moderate exposure to the sun during summer day, reaches serum levels of 25 (OH) vitamin D to 50 nmol/l, there is still need for additional 25 μg (1,000 IU) of vitamin D3 to exceed 75 nmol/l

(optimum level). Some individuals, particularly those who live without the sun or the elderly, must have even greater intake. Fortified foods should be accounted. Long-term daily dose of vitamin D3 up to 2000 IU is considered to be safe (32).

Treatment of vitamin D “deficit”, which means rickets and

osteomalacia, implies a much higher doses, such as 1250 μg (50,000 IU) daily for two to four weeks, then the dose is administered weekly, or every 2 weeks, with monitoring of serum 25- (OH) vitamin D for month and for three months. For treating rickets may be applied single daily dose of 15 000 μg (600,000 IU), or can be gradually administered 125-250 μg daily (5000-10000 U) during 2-3 months (33). Milder deficiency can be treated with lower doses (29).

It is very important to ensure sufficient daily intake of calcium with vitamin D, from 1000-1200 mg.

Toxicity due to intake of vitamin D is not observed in a daily dose less than 10,000 IU in several studies.

CONCLUSION

Physiatry, as an integrative branch of medicine, not only includes the underlying disease for which the patient is treated, but also the treatment of comorbidity, or prevention of various complications and new disease, which requires careful observation and timely action. Therefore, kknowledge of physiology of vitamin D and its impact on the function of the musculoskeletal and other systems in the body, is of great importance for the daily practice of physiatry. Institutions for physiatry and rehabilitation are very appropriate for diagnosing, treating and studying of vitamin D deficiency.

Conflict of interest: none declared.

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Nephrotic syndrome as a cardinal feature of thrombotic thrombocytopenic purpura

ABSTRACT

Thrombotic thrombocytopenic purpura (TTP), also known as Moschcowitz syndrome is a rare thrombotic microangiopathy syndrome to be treated as medical emergency. TTP was originally characterized by pentad of thrombocytopenia, hemolytic anemia, renal impairment, fever, and neurological changes, often with insidious onset. Although the kidney is one of a target organ in TTP, proteinuria in these setting remains poorly described. In particular, severe proteinuria is uncommon feature of TTP. The majority of these patients had already been diagnosed with systemic lupus erythematosus. We report a case of a female patient with refractory TTP accompanied by nephrotic-range proteinuria developed simultaneously. Performed renal biopsy demonstrated no renal histopathology other than small vessel thrombosis. She did not improve after 38 plasmapheresis sessions. A 4-week course of weekly intravenous doses of Rituximab achieved complete disappearing of clinically symptoms with normalization of platelet count and lactate dehydrogenase and improving renal function. Although most cases series have demonstrated semiquantative proteinuria in TTP patients, nephrotic syndrome might not be expected to occur with thrombotic microangiopathic histology. It could be a reason why proteinuria quantification has performed occasionally in TTP cases.

Key words: thrombotic thrombocytopenic purpura (TTP), proteinuria, nephrotic syndrome

SAŽETAK

Trombotička trombocitopenična purpura (TTP), također poznata kao Moschcowitz sindrom je rijedak trombotički mikorangiopatski sindrom koji se tretira kao medicinska urgencija. TTP karakterizira trombocitopenija, hemolitička anemija, renalna slabost, groznica i neurološke promjene, koje često imaju podmukli početak. Mada je bubreg jedan od često pogođenih organa u TTP, proteinurija u ovom okruženju je slabo opisana. Posebno treba naglasiti, težak stepen proteinurije je neuobičajena karakteristika TTP-a. Veliki broj ovih pacijenata ima već postavljenu dijagnozu sistemskog lupus eritematozusa. Prikazali smo slučaj pacijenta ženskog spola sa refraktarnom TTP udruženom sa nefrotskom proteinurijom koja se razvila istovremeno. Urađena biopsija bubrega pokazala je samo trombozu malih krvnih sudova. Nakon provedenih 38 ciklusa plazmafereze, nije bilo odgovora. Četiri ciklusa sedmično ordiniranog Rituximaba dovele su do kompletnog povlačenja kliničkih simptoma sa normalizacijom broja trombocita i laktat dehidrogenaze, te oporavljanja renalne funkcije. Mada serija slučajeva ukazuje na semikvantitativnu proteinuriju kod TTP pacijenata nefrotski sindrom se ne očekuje sa trombotičkom mikorangiopatskom histologijom. To može biti razlog zbog čega se redovno ne radi kvantifikacija proteinurije u slučajevima sa TTP.

Klučne riječi: trombotička trombocitopenična purpura (TTP), proteinurija, nefrotski sindrom

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP), also known as Moschcowitz syndrome is a rare blood disorder characterized by clotting in small blood vessels of the body, resulting in a low platelet count (1). In the larger series female predominance of approximately 2:1 has been noted. The average age of onset is 40 years old (2).

manifestations. Presenting symptoms and signs of TTP include thrombocytopenia, hemolytic anemia (MAHA), fever, neurological changes and renal impairment.

Renal impairment in TTP originally presents by proteinuria and microhaematuria, acute kidney injury requiring haemodialysis is rare. It is important to determine the causes of acute kidney injury during TTP. Distinct causes and pathophysiologic mechanisms which are not mutually exclusive can be involved, namely: acute tubular necrosis secondary to hemodynamic instability, hemolysis - induced tubular damage, drug

TTP can affect any organ system, but involvement of the peripheral blood, the central nervous system, and the kidneys causes the clinical

Nefrotski sindrom kao glavna karakteristika trombotičke trombocitopenične purpure

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induced nepfrotoxicity and glomerulopathy as manifestation of an

underlying autoimmune disease in an acquired TTP. Patients with larger amounts of proteinuria have more severe acute kidney injury and more likely they will receive a renal biopsy. Patients with TTP, particularly of the hereditary type, may develop chronic kidney failure. This complication may be a consequence of repeated insults by overt or subclinical microvascular thrombosis to the kidney, or it may have a separate cause (3).

Differential diagnosis of TTP includes first of all hemolytic-uremic syndromes (HUS), than immune thrombocytopenic purpura (ITP) and disseminated intravascular coagulation (DIC). Untreated, TTP has a mortality rate of as high as 90%. Acute morbidities include ischemic events such as stroke, transient ischemic attacks, myocardial infarction and arrhythmia, bleeding, and azotemia. Therapy should be initiated if the diagnosis of thrombotic thrombocytopenic purpura (TTP) is seriously considered (4). Plasma exchange with fresh frozen plasma is the therapy of choice for TTP. Adequate initial response is fulfilled if neurologic signs and symptoms disappear, the platelet count climbs to greater than 50,000/μL, and the LDH level declines (5). The total number of exchanges necessary for sustained response is not established.

CASE REPORT

A 38-year-old woman was admitted at the Clinical Center University of Sarajevo in October 2014 suspected of hemolytic-uremic syndrome (HUS). On presentation she was afebrile, oliguric, with no signs of bleeding, and physical examination of the nervous system was normal. Three days earlier she was admitted to a local hospital with fever, renal failure, transitory episode of dysarthria, anemia and thrombocytopenia.

Blood tests showed: red blood cells (RBC): 3 x109/L, Hemoglobin (HGB): 101 g/L, Platelet (PLT): 65x109/L, White blood cells (WBC): 20x109/L, with schistocytes in the film, immeasurable low level of haptoglobin, raised reticulocyte counts, LDH: 606 U/L, Bilirubin: 18.9 umol/l, increased level of serum urea /31.4mmol/l and creatinine 325 umol/L/. Her creatinine clearance was 0.3 ml/sec with proteinuria 19.6 g/d. The direct COOMBS test was negative. The clotting screen, CT scan of the head, serological tests for HIV, hepatitis B and C virus, stool culture for pathogenetic Escherichia coli, auto-antibody screen were normal. She was clinically diagnosed with TTP, and gingival biopsy confirmed diagnosis in the absence of ability to perform ADAMTS 13 assays. We started with plasma exchange (PEX), 2000-2500 ml plasma volume (PV). After the few PEX, LDH decreased, level of serum urea and creatinine normalized, but the patient developed clinical feature of nephrotic syndrome (anasarca, hypertension, hypothireosis), with proteinuria higher than on admission (40 g/d) and no improvement of platelet count (PLT: 60-80x109/L). Performed renal biopsy demonstrated no renal histopathology other than small vessel thrombosis. We continued PEX daily with steroids, diuretics and antihypertensives which resulted in clinical improvement of the patient's condition, but even after 28 PEX proteinuria and thrombocytopenia were still present. More intensive exchange, twice daily PEX did not prove to be effective. The patient underwent 34 PEX in total. In view of refractory TTP we started treatment with Rituximab once a week for 4 weeks (6). After the first cycle of Rituximab platelet count raised, and after the second and following cycles platelet count stayed within normal range. Renal function and proteinuria were observed by the nephrologist. During the therapy with Rituximab serum level of urea and creatinine remained normal, after four cycle of Rituximab proteinuria decreased from 40g/d to 3.81 g/d in December 2014. Follow up of the patient showed complete remission, with normal blood test, normal renal function and without proteinuria.

DISCUSSION

TTP was originally characterized by pentad of thrombocytopenia, hemolytic anemia, renal impairment, fever, and neurological changes, often with insidious onset. Although the kidney is one of the target organ in TTP, proteinuria in this setting remains poorly described. Nephroticrange proteinuria has been occasionally reported but might not be expected to occur with TTP. Indeed, the majority of such patients have already been diagnosed with systemic lupus erythematosus and present overlapping symptoms of these two diseases (7). On the other hand, the study performed at the Medical University of South Carolina in the period from January 2000 to October 2009 showed that urine analysis was not performed in all cases of TTP, in fact not in 11 % of 59 cases (8). Similarly, dipstick proteinuria has been frequently reported in TTP, but even in this setting, proteinuria quantification has been much less performed.

CONCLUSION

Proteinuria quantification should be performed in all TTP patients, especially if detected on dipstick screening. Also, cooperation between hematologist and nephrologist in TTP cases is very important.

Conflict of interest: none declared.

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Case report

Surgical treatment of a rare huge aneurysm of axillaris artery

Hirurški tretman veoma rijetke periferne aksilarne aneurizme

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ABSTRACT

Introduction: history of surgical treatment attempts of arterial aneurysms begin from 3rd century. Repair of axillary artery aneurysm was first reported in 1836, in a way that the third portion of the subclavian artery was ligated. In this article we present open vascular surgical procedure to resolve very rare peripheral axillar aneurysm. In a 42 years old woman the disease started from childhood in the form of little marbles in the right armpit, which was constantly increasing through life with exacerbation of the disease a month prior to her admission at our clinic. Classical open vascular procedure was performed with aneurysmectomy and interposition of vein conduit between axillar and brachial artery. Conclusion: open surgical intervention is still the best choice in the treatment of axillar aneurysm.

Key words: axillar aneurysm, open vascular surgery

SAŽETAK

Historija hirurškog tretmana aneurizmi arterije seže još od 3. stoljeća nove ere. Godine 1836. objavljena je prva rekonstrukcija aksilarne aneurizme u vidu ligiranja treće porcije subklavijalne arterije. U ovom članku se prezentira otvorena hirurška procedura veoma rijetke periferne aksilarne aneurizme. Ženski pacijent, 42 godina stara, bolest počela u djetinjstvu u obliku male kuglice u desnom pazuhu, koje je bila u stalnom porastu tokom života s pogoršanjem bolesti mjesec dana prije dolaska u našu kliniku. Klasični otvoreni vaskularni postupak je proveden uz aneurizmektomiju i interpoziciju auto safeno venskog grafta između aksilarne i brahijalne arterije. Zaključak: otvoreni hirurški zahvat je još uvijek najbolji izbor u liječenju aneurizme aksilarne arterije.

Ključne riječi: aksilarna aneurizma, otvoreni hirurški zahvat

INTRODUCTION

The most common vascular cause of death or disability is arterial aneurysm. History of surgical treatment attempts of arterial aneurysms begin from 3rd century, until in 1951 Dubost performed revascularization abdominal aortic aneurysm (AAA) using thoracic aortic homograft from deceased patient. Blakemore and Voorhees first used synthetic material for revascularization of arterial aneurysms which started modern age of vascular aneurysm repair.

Ad Hoc Committee on Reporting Standards of the Society for Vascular Surgery defined an aneurysm as "a permanent localized (i.e., focal) dilation of an artery having at least a 50% increase in diameter compared to the expected normal diameter of the artery in question."

Axillar artery aneurysms are rare and appear sporadically in patients involved in athletic activities, such as baseball pitchers with forceful extension, after trauma (blunt or penetrating) or with congenital predisposition. Signs and symptoms which lead us to confirm the diagnosis are digital pain and ischaemia (1-5).

Open surgery should be performed extra-carefully because of the surrounding brachial plexus and deep veins which are intimately fused with axillar aneurysm. In patients with high surgical risks endovascular repair should be considered as alternative method. There are several reports which confirmed this recommendation (6).

CASE REPORT

A 42 years old woman was hospitalized at the Clinic of Vascular Surgery of the Clinical center University of Sarajevo (CCUS) for 15 days. The disease began in childhood in the form of marbles in the right armpit, which was constantly increasing through life. Exacerbation of the disease started a month ago, with the occasional pain, numbness of the hands and forearms. Other diseases included: nonfunctional left kidney from 2012, allergy to penicillin, smoker. The family history: mother died from stomach carcinoma, father survived stroke.

Local findings: pulsatile mass was present in the right armpit synchronized with cardiac work, the size of an orange. Skin above pulsatile mass had no significant changes. Right hand had no apparent acute exacerbation of vascular status and no pathological neurological findings.

Ultrasound of the heart: 34mm aorta, left atrium 33mm, ejection fraction of 60%. Mitral leaflets thin and preserved mobility. Left atrium and chamber of neat dimensions, without failure in kinetics. Aortic root of normal width, aortic valve trefoil, thin leaflets, neat separation. Right heart chamber neat dimensions. Pericardium with physiological findings.

Pulmonary findings: pulmonary hilum post inflammatory changed, calcification shadows. Mutual basal emphasized drawing. Aperture arc, phreno costal sinuses are free. At the moment of examination in the

lung parenchyma no convincing active pathological changes. ABS: pH 7.433, pCO2: 4.91kPa, cHCO3: 24.2mmol / l, ctCO2 25.3mmol / l, pO28: 15kPa ↓, SO2: 94.3% ↓

initial part axillary artery at length from 113mm up to the middle part of the brachial artery, maximum antero-posterior diameter of 66mm and latero-lateral 45.8mm. The flow through the artery of the forearm is preserved (Figure 1, 2).

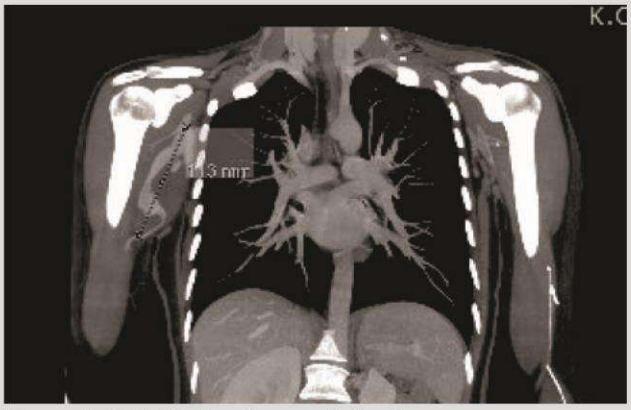

Figure 1 CTA finding (coronal view).

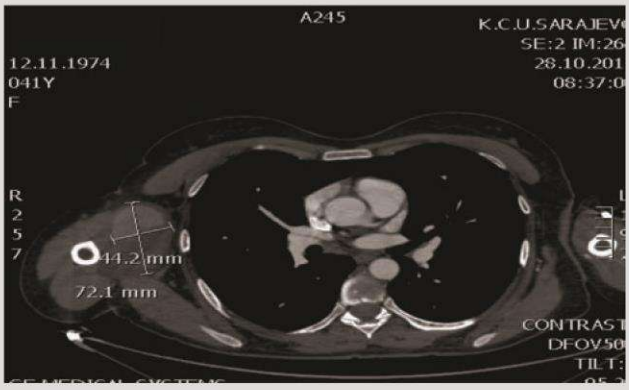

Figure 2 CTA (axial view).

Table 1 Laboratory findings.

Laboratory findings	26.10.	31.10.	01.11.	02.11.	ICU 03.11.	04.11.	05.11.
Na	140			140	139	137	
K	4.5			4.2	5	3.8	
Ca	2.49			2.32	1.92	1.94	
Cl	102			102	106	106	
Fe			19.8				
Gluc	4.8			6.5	11.6	5.1	
Urea	2.9			2.5	2.2	2.0	
Kreatinin	77			65	62	54	
AST	12						
ALT	11						
CK	45						
LD	158						
CRP	51.8	15.9	9.9				
Leukociti	7.59		7.65			11.2	8.77
Eritrociti	3.91		3.93		3.32	2.8	3.64
Hemoglobin	120		115		104	85	105
Trombociti	319		304		244	189	197
INR		0.99					
APTT		30.7					

Anesthesia report (pre-, intra-, postoperative):

Preoperative general status of the patient was in a satisfactory framework of vital parameters. The placement of arterial lines was implemented in the left radial artery and the patient was connected to the continuous monitoring (invasive/invasive). Permanent urinary catheter was placed. Midazolam 3 mg i.v. with opioid analgesic sufentanil 3ml iv. (15micrograms), dihidrobenzperidol 2.5 mg i.v was administered in premedication. For an introduction to a general balanced endotracheal anesthesia propofol was administered at a dose of 150 mg i.v. and the provision of atracurium muscle relaxation was administered at the initial dosage of 40 mg i.v. Intra-operative vital signs were stabile. Doses of packed red blood cells 340ml and SSP 180 ml and 4000 ml i.v. crystalloids were given. During the operation procedure patient had overall diuresis of 1000 ml. Postoperatively, the patient had stable vital signs, respiratory sufficient, set up in the intensive care unit with continues monitoring of vital signs and laboratory findings. Analgesic therapy was continuous administered.

Operative findings

The cut in the projection of the medial edge of the brachial muscle propagation towards the armpit with the preservation of the large pectoral muscle. It was put under control lower portions of the right axillary artery and the middle third of the brachial artery and nerve structures including the median and ulnar nerve. System applications 2000 i.u. not fractionated heparin (UFH).

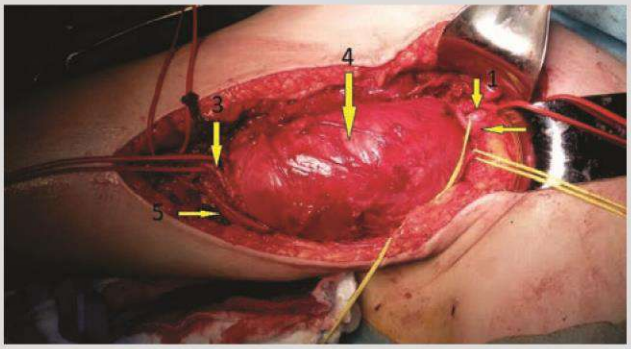

Figure 3 Intraoperative view (1. axillar artery, 2. nerve medianus, 3. brachial artery, 4. aneurismatic sack, 5. ulnar nerve).

After clamping and longitudinal aneurysmectomy, interposition the great saphenous vein, harvested from the left thigh, between axillary artery and the middle third of the brachial artery.

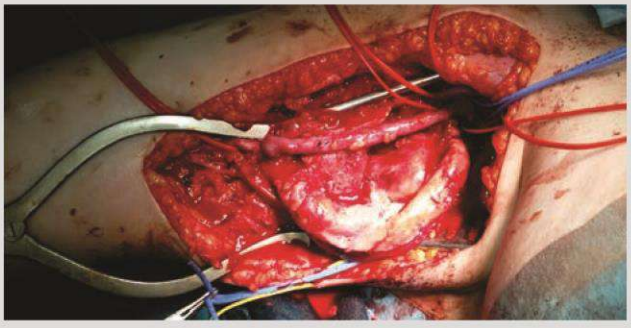

Figure 4 Peroperative statu after reconstructions with ASV graft.

Computed tomographic angiography: aneurysm extends from the

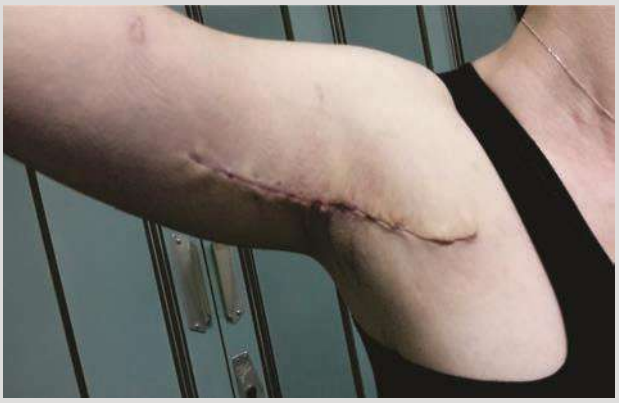

Figure 5 Local findings 20 days after the surgery.

DISCUSSION

We can freely say that axillar aneurysm is something that hapenes once in a lifetime of a vascular surgeon. Repair of axillary aneurysm was first reported in 1836 there, in a way that the third portion of the subclavian artery was ligated (7).

Axillar aneurysm can appear as a result of pentreting or blunt trauma (baseball pitchers), iatrogenically, after injuries that demands long time using crutches (8), in thoracic outlet syndrome. Szuchmacher et al. (9) reported 2 cases, Michalakis, et al. reported 1 case, atherosclerosis as a cause (10).

Our patient had no reported trauma, no medical proof of thoracic outlet syndrome. In histopathological evaluation atherosclerotic degenerative changes were found. Intra and postoperatively there was no thromboembolic incidents. During postoperative rehabilitation there were no neurological repercussions on functions of hand and fist. A day after the surgery edema appeared on her hand, which was successfully treated with elevation and cold compresses for 2 days continuously.

However, significant complications including higher risk of wound infection greater blood loss and injury to brachial plexuses is present in classical open vascular reconstruction. Endovascular repair of peripheral vascular aneurysms is a reliable treatment option and should be reserved for poor surgical candidates (11).

Fewer incidences of lesions to structures next to the aneurysm compared to surgery, have been described with endovascular procedure (11-13).

CONCLUSION

Axillar aneurysm is very rare and isolated disease. Vascular solution depends on vascular surgeon preferable choice. In our case we confirmed that open vascular surgery is the best choice especially where aneurysm neck is elongated and angulated as in this case.

Conflict of interest: none declared.

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Lijek se izdaje na ljekarski recept.
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ODOBRENE INDIKACIJE: Indiciran za liječenje osteoporoze kod žena u postmenopauzi. Smanjuje rizik od nastanka prijeloma kičmenih prsljenova i kuka. **KONTRAINDIKACIJE:** Preosjetljivost na aktivnu supstancu ili neku od pomoćnih supstanci lijeka, abnormalnosti jednjaka i drugi faktori koji usporavaju njegovo pražnjenje kao što su strikture ili ahalazija, nemogućnost stajanja ili uspravnog sjedenja u trajanju od najmanje 30 minuta i hipokalcijemija. **NAJČEŠĆI NEŽELJENI EFEKTI:** Glavobolja, omaglica, poremećaj okusa, upala oka, vrtoglavica, bol u trbuhu, dispepsija, opstipacija, dijareja, nadutost, ulkus jednjaka, otežano gutanje, abdominalna distenzija, regurgitacija želučane kiseline, alopecija, pruritus, osip, crvenilo, bol u mišićno-koštanom sistemu koja je ponekad jaka, oticanje zglobova, astenija, periferni edem. **MJERE OPREZA:** Alendronska kiselina se mora s oprezom primjenjivati u pacijentica s aktivnim oboljenjima u gornjem dijelu gastrointestinalnog sistema kao što su disfagija, bolesti jednjaka, gastritis, duodenitis, ulkusi ili nedavna anamneza (u posljednjih godinu dana) ozbiljnih gastrointestinalnih bolesti kao što su peptički ulkus ili aktivno gastrointestinalno krvarenje ili hirurški zahvat u gornjem dijelu gastrointestinalnog sistema, osim piloroplastike. U pacijentica s osteoporozom, koje su primjenjivale peroralne bisfosfonate zabilježena je osteonekroza vilice, te je prije početka liječenja u pacijentica sa lošim dentalnim statusom potrebno sprovesti stomatološki pregled uz primjenu odgovarajućih preventivnih stomatoloških mjera, a tokom liječenja ove pacijentice moraju izbjegavati invazivne stomatološke zahvate ako je to moguće. U pacijentica koje uzimaju bisfosfonate zabilježeni su i simptomi kao što su bolovi u kostima, zglobovima i/ili mišićima, koji su se povukli nakon prekida liječenja. U pacijentica koje su liječene bisfosfonatima, posebno kod onih koje su primale dugotrajnu terapiju zabilježene su i atipične frakture subtrohantera i dijafizealni prijelomi bedrene kosti, te treba sugerisati pacijenticama da prijave bilo kakvu bol u području bedra, kuka ili prepona. Prije početka liječenja potrebno je korigovati hipokalcemiju i druge poremećaje koji utiču na metabolizam minerala (nedostatak vitamina D i hipoparatireoidizam). Alendronat se ne preporučuje pacijentima s oštećenjem funkcije bubrega u kojih je klirens kreatinina manji od 35 ml/min. Ne primjenjuje se kod trudnica i dojilja. Bolesnici sa rijetkim nasljednim poremećajem nepodnošenja galaktoze, nedostatkom „Lapp laktaze" ili glukoza-galaktoza malapsorpcijom ne bi trebali uzimati ovaj lijek. **DOZIRANJE I NAČIN UPOTREBE, UPOZORENJA:** Preporučena doza je jedna tableta od 70 mg jednom sedmično. Lijek se mora uzimati ujutro, nakon ustajanja, najmanje 30 minuta prije uzimanja prvog dnevnog obroka, napitka ili drugih lijekova s punom čašom obične vode (najmanje 200 ml). Tableta se mora progutati cijela. Ne smije se drobiti ni žvakati, niti dopustiti da se tableta rastopi u ustima zbog mogućnosti razvoja orofaringealnih ulkusa. Nakon uzimanja lijeka pacijentice ne smiju leći najmanje 30 minuta. Ako je unos hranom nedovoljan, pacijentice uz lijek moraju uzimati suplemente kalcija i vitamina D (pričekati najmanje 30 minuta nakon uzimanja alendronata). Nije potrebno prilagođavati dozu u starijih osoba. Ne preporučuje se primjena alendronata u djece mlađe od 18 godina.

Molimo Vas da prije propisivanja lijeka proučite odobreni sažetak glavnih karakteristika lijeka i uputstvo o lijeku.