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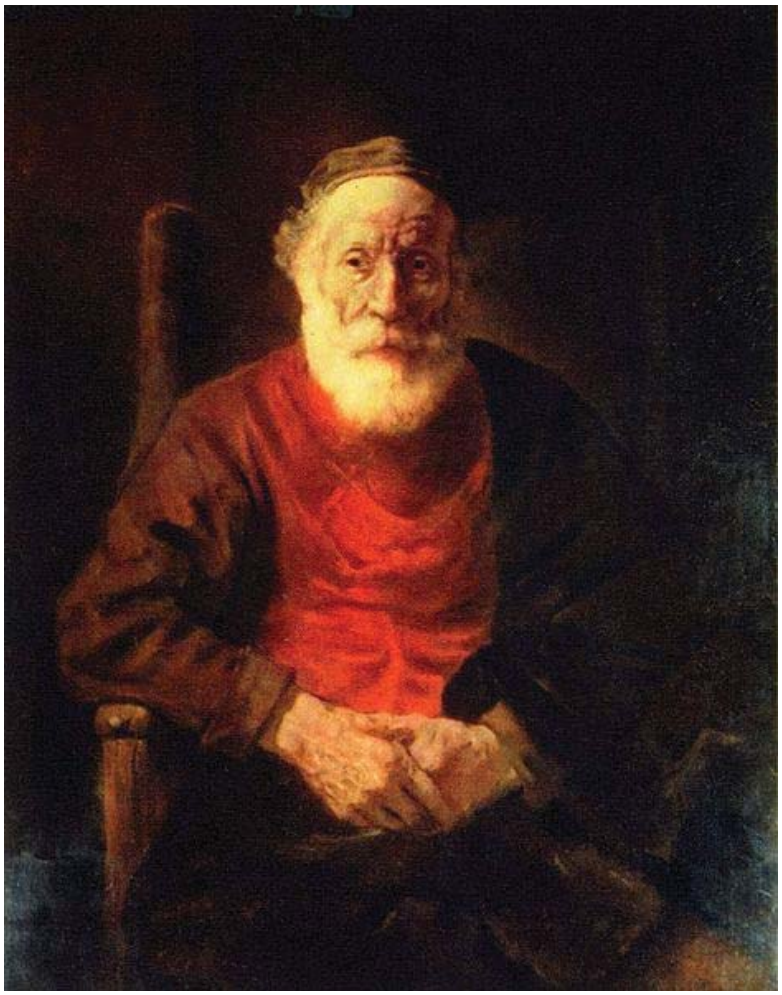

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Rembrandt van Rijn (July 15, 1606 – October 4,1669): Portrait of an old man in red (oil on canvas, 108 x 86 cm; Hermitage Museum, St. Petesburg, Russia).
In our fasting age world, older poeple will increasingly play an important role – through volunteer work, transmitting experience and knowledge, helping their families and increasing their participation in the paid labour force. Their contribution in such activities can only be ensured if older persons enjoy adequate levels of healthcare. The International Day of Older Persons that is marked at October 1 is an opportunity to remind us to do everything in ensuring older poeple an active and healthy ageing.

Rembrandt van Rijn (15. juli 1606 – 4. oktobar 1669): Portret starca u crvenoj boji (ulje na platnu, 108 x 86 cm; Muzej Ermitaž, Sankt Peterburg, Rusija).
U našem sve starijem svetu, stari ljudi igraće sve važniju ulogu – kroz volonterski rad, prenošenje iskustva i znanja, pomaganje svojoj porodici i povećano sudelovanje u plaćenim poslovima. Njihov doprinos u takvim aktivnostima jedino je moguć ako im se obezbedi adekvatan nivo zdravstvene zaštite. Međunarodni dan starijih osoba, koji se obeležava 1. oktobra, prilika je da se podsetimo da treba učiniti sve kako bi se starijim ljudima obezbedilo aktivno i zdravo starenje.

SHORT COMMUNICATION

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Fatal pulmonary thromboembolism after prolonged physical immobilization in hospitalized psychiatric patients

Fatalna plućna tromboembolija posle produžene fizičke imobilizacije kod hospitalizovanih psihijatrijskih bolesnika

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Abstract

Background/Aim. Pulmonary thromboembolism (PTE) may be one of the causes of sudden death in hospitalized psychiatric patients. The aim of our study was to investigate whether fatal PTE in these patients may be the result of their prolonged physical immobilization, particularly when there were associated risk factors, and to emphasize the importance of this problem. **Methods.** A retrospective analysis of medical records of psychiatric patients died suddenly at the Department of Intensive Care of the Clinic of Psychiatry "Dr Laza Lazarevic", Belgrade, in the period January 1, 2010 – December 31, 2011, was performed. Data of those for which the autopsy showed PTE as the immediate cause of death were extracted, and the presence of risk factors for the development of deep vein thrombosis analyzed. **Results.** In the observed period, out of 4,001 hospitalized psychiatric patients 53 died, and for 18 of them autopsy was required due to sudden death. In five patients, autopsy revealed PTE as a direct and sole cause of death. All the five patients were males, mean age 45.2 years, and during hospitalization all received strong antipsychotics and diazepam. Of the total duration of their hospital stay (mean 8.2 days), they were temporarily immobilized during an average 4.2 days. Four of them had acute infection, three were active smokers, and the two had a body mass index > 30 kg/m^2. **Conclusion.** Our results suggest a possible link between prolonged physical immobilization of psychiatric patients who also receive antipsychotic therapy, and total PTE.

Key words:
pulmonary embolism; psychiatry; patients; risk factors; immobilization.

Apstrakt

Uvod/Cilj. Plućna tromboembolija (PTE) može da bude jedan od uzroka iznenadne smrti kod hospitalizovanih psihijatrijskih bolesnika. Cilj našeg rada bio je da ispitamo da li fatalna PTE kod ovih bolesnika može da bude posledica njihove produžene nepokretnosti, posebno kada postoje i pridruženi faktori rizika, te da ukažemo na značaj ovog problema. **Metode.** Izvršena je retrospektivna analiza bolničke dokumentacije psihijatrijskih bolesnika koji su iznenada preminuli u Odeljenju za intenzivnu terapiju Klinike za psihijatriju "Dr Laza Lazarević" u Beogradu, u periodu 1. januar 2010 – 31. decembar 2011. i izdvojeni su podaci o onima za koje je autopsijom ustanovljeno da je neposredni uzrok smrti bila PTE. U njihovim istorijama bolesti analizirano je prisustvo faktora rizika od razvoja tromboze dubokih vena. **Rezultati.** U posmatranom periodu, od ukupno 4 001 hospitalizovanog psihijatrijskog bolesnika preminulo je 53, od kojih je za 18 tražena autopsija zbog iznedne smrti. Kod pet bolesnika autopsijski je utvrđeno da je neposredni i jedini uzrok smrti bila PTE. Svih pet bili su muškog pola, prosečne starosti 45,2 godine, i tokom hospitalizacije dobijali su snažne antipsihotike i diazepam. Od ukupnog trajanja njihove hospitalizacije (prosečno 8,2 dana), oni su bili privremeno imobilisani tokom prosečno 4,2 dana. Četvorica su imala akutnu infekciju, trojica su bili aktivni pušači, a dvojica su imali indeks telesne mase > 30 kg/m^2. **Zaključak.** Naši rezultati ukazuju na moguću povezanost produžene fizičke imobilizacije psihijatrijskih bolesnika, koji istovremenu primaju antipsihotičnu terapiju, i fatalne PTE.

Ključne reči:
pluća, embolija; psihijatrija; bolesnici; faktori rizika; imobilizacija.

Introduction

Deep vein thrombosis (DVT) is pointed out in the literature as one of the leading causes of morbidity and mortality in nonsurgical patients. Nowadays, this problem has not been enough considered in the population of hospitalized psychiatric patients [1]. According to the literary data, DVT frequency in the risky hospitalized patients without prophylactic therapy is 10–40%, where, 70–80% of such thrombosis are clinically silent -nor asymptomatic [2].

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Clinical manifestations of massive pulmonary thromboembolism (PTE) as the most serious DVT complication are regularly dramatic, but in some patients subtle or unspecific clinical symptoms can be seen. Then pulmonary embolism as the cause of sudden unexpected death appears as „unsuspected killer“ [2, 3].

In this study we described autopsy series of five patients with a period of prolonged physical immobilization that preceded PTE.

Methods

A retrospective analysis of medical records of psychiatric patients died suddenly at the Department for Intensive Care of the Clinic for Psychiatric Disorders “Dr Laza Lazarevic”, Belgrade, in the period January 1, 2010 – December 31, 2011, was performed, data of those for which the autopsy showed that PTE was the immediate cause of death were extracted, and the presence of risk factors for the development of deep vein thrombosis analyzed.

Results

We analysed retrospectively medical documentation of the Clinic for Psychiatric Disorders “Dr Laza Lazarevic”, Belgrade, as well as autopsy findings of the Institute for Pathology, Faculty of Medicine, Belgrade, during a period from January 1, 2010 – December 31 2011. The agitated psychotic patients, admitted to the Clinic were treated at the Department for Intensive Care. Out of 4,001 patients treated in this Department in the period observed, the number of dead persons was 53. Due to sudden, unexpected death, clinical autopsies were requested for 18 patients. Analyses of these autopsy reports revealed PTE as the leading and the only cause of death in five patients. Their clinical and demographic characteristics, as well as the potential risk factors for DVT (obesity, smoking and the acute infections) were noticed (Table 1).

On admission to the Clinic there were no data for existing malignant or previous surgical diseases, or diagnosed DVT in the patients. The average age of the examined pa-

Table 1

Autopsy series of 5 male patients with total pulmonary thromboembolism (PTE)

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Average value
Age (years)	59	43	50	25	50	45.40 ± 12.74
BMI > 30 kg/m^2	no	no	yes	yes	no	
Number of hospitalizations	first	multiple	multiple	first	multiple	
Psychiatric diagnosis	F10/F06.2*	F29	F20	F23	F 20.5	
Other somatic diseases	yes I 10	no	yes I 10	no	no	
Length of hospit.stays (days)	9	5	9	13	5	8.20 ± 3.45
Length of temp.restraint (days)	5	4	5	4	3	4.20 ± 0.84
Antibiotic therapy	Ceftriaxone 2 g i.v. 4 days		Ceftriaxone 2 g/day i.v. 4 days	Ceftriaxonum 2 g i.v. 2 days	no	
Convetional antipsychotic	Haloperidol 10 mg i.m. first 3 days	Haloperidol 15 mg i.m. First 3 days	Haloperidol 10 mg i.m. 1 day	Haloperidol 20 mg i.m. 8 days,4 mg per os 4 days	Haloperidol 15 mg/day i.m.,Chlorpromazine 100 mg/per os, 5 days	
Atipical antipsychotic	no	no	Rispolept 2 mg per os p.d. 8 days	no	no	
Anxiolytic	Diazepam 30 mg i.m. first 3 days	Diazepam 30 mg i.m. 4 days	Diazepam 30 mg i.m. 7 days	Diazepam 20 mg i.m. 4 days	Diazepam 30 mg i.m. 5 days	
Psychostabilizer	no	no	no	Carbamazepine 600 mg.per os p.d. 8 days,300 mg per os p.d.1 day,200 mg per os 4 days	no	
Acute infection/febrile state	yes	yes	yes	yes	no	
Antihypertensive th.	Hemopres© 2x1 tbl.	no	Captopril 25 mg per os Lisinopril 10 mg per os p.d.	no	no	
Smoking	yes	no	yes	no	yes	

F10 (Mental disorders and behavioural disorders caused by use of alcohol); *F06.2 (Organic delusional disorder similar to schizophrenia; F29 (Non-organic psychosis, non-specific; F20 (Schizophrenia; F23 (Acute and transient mental diseases); F20.5 (Residual schizophrenia); I 10 (Hypertensio arterialis); Hemopres® (hydrochlorothiazide, amiloride); BMI – body mass index

tients was 45.40 ± 12.74 years. By objective examination, none of the patients showed either signs of fresh traumatism or anamnestic data to inherited hematological diseasea. There was alcohol abuse in the anamnesis of only one patient. Two patients had hypertension controlled with antihypertensive drugs (Table 1). Routine laboratory examinations in all the patients were within limits of the referent values after admission to the Clinic, except signs of liver damage of etilic genesis in the patient No 1 (Table 2).

a clear indication for temporary two hours physical immobilization with intermittent periods of thirty minutes deliberation. Patients were under the intensive control of medical staff including follow-up of vital parameters, displaying of possible injuries, right belts setting [4–6]. According to data from the literature prolonged physical immobilization of three or more days with simultaneous appliciation of antipsychotics is a major risk factor for DVT appearance being in correlation with the data given in our study [7–9].

Table 2

Routine blood and serum laboratory analysis on the first day after patients admission to the Clinic

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Reference values
WBC ($x10^9$/L)	5.7	8.6	9.7	10.0	4.0	3.5–10
RBC ($x10^{12}$/L)	4.78	5.14	5.42	4.96	5.18	3.80–5.80
HGB (g/L)	114	146	149	141	154	110–165
HCT (g/L)	0.365	0.453	0.454	0.43	0.472	0.350–0.500
PLT ($x10^9$/L)	231	170	237	375	218	150–390
LYM (%)	26.4	20.2	9.9	24.7	37.5	17.0–78.0
MON (%)	4.8	5.8	3.1	3.1	6.7	4.3–10.0
GRA (%)	68.8	74	76	72.2	55.8	43.0–76.0
Acid uric (umol/L)	396	380	368	351		208–430
Glucose (mmol/L)	4.1	4	6.7	4.7	5.1	3.9–5.8
Urea (mmol/L)	7.4	2.8	6.8	2.9	3.8	2.5–8.3
Creatinine (umol/L)	83	102	92	104	102	53–106
Cholesterol (mmol/L)	3.3	4.7	5.2	3.4	–	3.6–5.7
Triglycerides (mmol/L)	0.69	2	1.22	2.24	–	0.4–2.26
HDL- C	–	–	–	1.19	–	0.78–1.94
LDL- C	–	–	-79	1.9	–	2–5.7
Total bilirubin (umol/L)	69.5	8.7	14.8	5.5	7.7	5.1–20.5
Total protein (g/L)	67	71	79	65	66	64–83
Iron (mmol/L)	5.4	15.6	14.1	19	18.4	11.3–31.3
AST (U/L)	88	25	32	39	33	3.0–37.0
ALT (U/L)	113	39	27	79	40	3.0-41.0
Gamma GT DRY (U/L)	135	36	28	62	45	9.0–55
CK (U/L)	24	101	272	130	140	38.0–171
CRP (ng/L)	–		3.5	2.6	4.3	0–5
Potassium (mmol/L)	3.9	3.53	3.52	4.61	3.73	3.5–5.3
Sodium (mmol/L)	130.6	139.8	145.9	142.7	135.9	135–148
Sedimentation (mm/h)	12	2	10	10	3	2.0–12
Fibrinogen (g/L)	–	2	2	2	2	2.0–4

WBC – leukocytes; RBC – erythrocytes; HGB – hemoglobin; HCT – hematocrit; PLT – platelets; LYM – lymphocytes; MON –monocytes; GRA – granulocytes; HDL-C. – high density cholesterol; LDL-C. – low density cholesterol; AST – aspartate aminotransferase; ALT – alanine aminotransferase; Gamma GT – gamma-glutamyl transpeptidase; CK – creatine kinase; CRP – C-reactive protein.

Neurological examinations excluded neurological diseases. Except the reduction of psychotic anxiety and the introduction of behavioral control no important progress of psychotic phase was noticed in all 5 patients.

Average hospital stay of the presented patients lasted 8.2 ± 3.45 days, and their temporarily physical immobilisation was 4.2 ± 0.84 days (Table 1).

Discussion

A true pathophysiological mechanism of DVT occurrence still remains insufficiently clear, so its multifactorial origin is probably in question [1]. There are a great number of risk factors for DVT occurrence classified in major (reduced mobility, surgical interventions, malignancy etc.) and minor ones (obesity, cardiovascular disorders, estrogen hormone therapy, etc. [4].

In all five presented patients signs of psychomotoric agitation and behavioral discontrol were present, so they were dangers *per se* and for the others. Due to this, there was

Temporary immobilization of the presented patients lasted averagely 4.20 ± 0.84 days. Hemodynamic changes in blood circulation as a result of prolonged physical immobolization increase risk of vein thromboembolism leading to vein stasis that, with a possible existence of vascular endotelial damages and dehydration-hipovolemy, is an increasing risk for thrombembolism (Virhovljev`s triad) [10].

During and after the period of prolonged immobilization performed by physical examination, none of the patients presented clinical symptoms and DVT signs. Formation of microembolus is often asymptomatic and means the first step in PTE pathonegesis. Sudden unexpected death may happen in physical mobilization, i.e. by activating these "silent thrombs" [11].

In the period of 4.0 ± 3.08 days following measures of temporary physical immobilization, the presented patients experienced sudden unexpected death, so clinical autopsy was requested. Although physical immobilization still con-

tinues to be the subject of converse discussions including ethic aspects, taking into consideration that it is realized against the patients` will, sometimes it is necessary because a recommended medical therapy for treatment of aggressive patients is not sufficient to attain a so-called "chemical immobilization" of these patients [4, 5].

Therefore, many authors think about the application of mechanical prophylaxis, special exercises for the lower limbs, as well as introduction of low molecular heparin during physical immobilization.

All the five presented patients were treated by psychopharmacotherapy including an incisive antipsychotic, haloperidol, as well as anxiolytic diazepam, in two patients adding atypical (case 3) and sedative antipsychotic (case 5). Only one patient received psychostabilizer (case 4).

World multilateral studies connect the increased risk for DVT with application of antipsychotic therapy (32% higher risk in relation to patients without antipsychotics in therapy) [9, 12]. Especially, it is very important to point out the role of low potent antipsychotics of the first generation (chlorpromazine, thioridazine) but also clozapine and antipsychotics of the second generation (risperidone, olanzapine) [13, 14]. Certainly, there is some risk, but it is considerably lower when incisive antipsychotics (haloperidol) are in question and in relation to atypical antipsychotics it is 28% and 73%, respectively. Also, two patients receiving simultaneously two or more antipsychotics had the increased risk in relation to those being on monotherapy. Namely, it has been shown that this risk is significantly higher already in the first three months after drug introduction [9].

Biological mechanisms` link of antipsychotic therapy and DVT remains unknown although many hypotheses point out that increased risk might be the result of sedative effects of drugs, as well as obesity, decreased fibrinolytic activity as a part of metabolic syndrome, hyperleptinemy, circulating antiphospholipid antibodies, hyperhomocisteinemy, increased platelet aggregation and so on [1, 10]. There are no relevant studies connecting the use of anxiolytics and psychostabilizer and DVT [11].

Increased platelets aggregation as well as increased secretion of adrenaline in acute psychotic excitation patients lead to increased blood coagulation making us to conclude that psychosis can also be „procoagulating phase". The mentioned study [15] confirms the presence of higher markers of thrombogenesis in plasma of acute psychotic patients compared to healthy persons (D-dimer, factor VIII as well as soluble P-selectin).

Three of five our patients were smokers while two of them were obese (BMI > 30 kg/m^2). According to data from the literature, either smoking or obesity are very important factors of risk for DVT appearance. They are brought to the link with increased fibrinogen, factor VIII and factor IX in the plasma as well as fibrinolysis decrease. Also, it is mentioned that the level of interleukin (IL) 6, as the main procoagulating cytokin in humans, as well as the level of C-reactive protein are increased in smokers` [16].

In four of five presented patients, following measures of prolonged immobilization, high febrility, sedimentation rebounds and leukocytosis were developed, so parenteral antibiotic therapy was included because of confirmed respiratory infection in these patients.

Recent studies bring respiratory infection (but also urinary system and skin infection) to the link with up to two times increased risk for DVT, especially in the first two weeks after the beginning of infection, setting the same aside as a factor of risk for DVT [17].

Many psychotic patients are not able to show symptoms adequately which could point out to DVT, as pain in legs, swelling, red coloring and so on, owing to psychic functions disorders in relation to qualitative consciosness changes and damaged cognition. Sometimes such symptoms can be wrongly interpreted by clinicians as oedema owing to cardial decompensation, cellulitis, rheumatic swellings.

Also, symptoms as feeling pressure in chest heart palpitation, heavy breathing are attributed to psychotic anxiousness, they experience horrible perceptive illusions and so on, but in reality they can be symptoms of unrecognized submassive pulmonary embolism.

Limits of our study are related to the *post mortem* diagnose of PTE, so it does not include patients with DVT and PTE diagnosed and adequately treated during hospitalization. It is possible that in some cases of fatal PTE sudden unexpected heart death is pronounced on the basis of clinical parameters.

Conclusion

Following previous learnings from the literature, the results of our study suggest that it would be useful to give special attention to immobilized psychotic patients taking into consideration potential risk factors for DVT and PTE. Failure of standardized protocols for DVT prevention with possible fatal outcome in hospitalized psychiatric patients underlines the need for further prospective research in this direction.

REFERENCES

1. *Malý R, Masopust J, Hosák L, Konupcíková K.* Assessment of risk of venous thromboembolism and its possible prevention in psychiatric patients. Psychiatry Clin Neurosci 2008; 62(1): 3−8.
2. *Lucena J, Rico A, Vázquez R, Marín R, Martínez C, Salguero M,* et al. Pulmonary embolism and sudden–unexpected death: Prospective study on 2477 forensic autopsies performed at the Institute of Legal Medicine in Seville. J Forensic Leg Med 2009; 16(4): 196–201.
3. *Laack TA, Goyal DG.* Pulmonary embolism: an unsuspected killer. Emerg Med Clin North Am 2004; 22(4): 961−83.
4. *Mitic-Milikic M, Vukcevic M.* Modern attitudes in the diagnosis of pulmonary embolism. Vojnosanit Pregl 2004; 61(2): 187−91. (Serbien)
5. *Currier GW, Allen MH.* Emergency psychiatry: physical and chemical restraint in the psychiatric emergency service. Psychiatr Serv 2000;51(6): 717−9.

6. *Rocca P, Villari V, Bogetto F.* Managing the aggressive and violent patient in the psychiatric emergency. Prog Neuropsychopharmacol Biol Psychiatry 2006; 30(4): 586−98.
7. *De Hert M, Einfinger G, Scherpenberg E, Wampers M, Peuskens J.* The prevention of deep venos thrombosis in physically restrained patients with schizophrenia. Int J Clin Pract 2010; 64(8): 1109−115.
8. *Hewer W, Kauder E, Vierling P.* Fatal pulmonary embolism following antipsychotic treatment and psysical restraint. Pharmacopsychiatry 2009; 42(5): 206−8.
9. *Liperoti L, Gambassi G.* Antipsychotics and the risk of venous thromboembolism. BMJ 2010; 341: c4216.
10. *Rosendal FR.* Risk factors for venous thrombotic disease. Thromb Haemost 1999; 82(2): 610−9.
11. *Van Neste EG, Verbruggen W, Leysen M.* Deep venous thrombosis and pulmonary embolism in psychiatric setting. Eur J Pyschiat 2009; 23(Suppl 1): 19–28.
12. National Institute for Health and Clinical Excellence [Internet]. Venous thromboembolism: reducing the risk: Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital; 2010. London: National Institute for Health and Clinical Excellence; 2012. [cited 2012 May 25]; [about ten screens]. Available from: http://publications.nice.org.uk/venous-thromboembolism-reducing-the-risk-cg92
13. *Zornberg GL, Jick H.* Antipsychotic drug use and risk of first-time idiopathic venous thromboembolism: a case-control study. Lancet 2000; 356(9237): 1219–23.
14. *Borras L, Eytan A, de Timary P, Constant EL, Huguelet P, Hermans C.* Pulmonary thromboembolism associated with olanzapine and risperidone. J Emerg Med 2008: 35(2): 159−61.
15. *Masopust J, Maly R, Andrys C, Valis M, Bazant M, Hosak L.* Markers of thrombogenessis are activated in unmedicated patients with acute psychosis: a matched case control study. BMC Psychiatry. 2011; 11: 2.
16. Tapson VF. The role of smoking in coagulation and thromboembolism in chronic obstructive pulmonary disease. Proc Am Thorac Soc 2005; 2(1): 71−7.
17. *Thomsen RW, Smeeth L, Sorensen HT.* Acute infections and venous thromboembolism. J Intern Med 2012; 271(6): 608−18.

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Impaired endothelial function in lone atrial fibrillation

Oslabljena endotelna funkcija u izolovanoj atrijalnoj fibrilaciji

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Abstract

Background/Aim. Impaired endothelial function has been previously documented in patients with atrial fibrillation (AF) and underlying comorbidities or older patients with idiopathic AF. The aim of this study was to evaluate systemic endothelial function in younger AF patients (less than < 60 years old) with lone AF (that is, without associated cardiopulmonary comorbidities, including arterial hypertension), by comparing brachial artery flow-mediated dilation (FMD) in lone AF patients with FMD of healthy subjects in sinus rhythm. **Methods.** Two groups of participants were prospectively enrolled. The first group comprised of 38 AF patients (the mean age 45 ± 11 years, 68% male) with persistent (> 7 days) lone AF. The second group comprised of 28 healthy controls in sinus rhythm (the mean age 43 ± 13, 53% male), matched by age, gender and atherosclerotic risk factors. All the participants underwent physical examination, laboratory analysis [including determination of C-reactive protein (CRP)], standard echocardiography and exercise-stress testing. Brachial artery FMD and endothelium independent dilation (NMD) were assessed with a high-resolution ultrasound probe and arterial diameters taken from 5 consecutive cardiac cycles were averaged for each measurement to accommodate to beat-to-beat flow variations in AF. **Results.** There were no differences between the 2 groups regarding age, gender and most clinical, laboratory and echocardiographic characteristics (all $p > 0.05$), apart from the increased heart rate ($p = 0.018$), body mass index ($p = 0.027$), CRP levels ($p = 0.007$) and left atrial anteroposterior dimension ($p < 0.001$) in AF patients. FMD of AF patients [median value 5.0%, interquartile range (IQR) 2.87%–7.50%] was significantly lower ($p < 0.001$) than FMD of healthy controls (median value 8.85%, IQR 5.80%–12.50%), whereas there were no differences in median NMD values ($p > 0.05$). In the multivariate analysis, the independent FMD determinants in our study population were the presence of AF, smoking and total cholesterol levels (all $p < 0.001$). In patients with AF, the strongest independent FMD determinant was arrhythmia duration ($p < 0.001$), followed by smoking ($p = 0.013$) and total cholesterol levels ($p = 0.045$). **Conclusions.** Our findings confirm that sustained AF is associated with systemic endothelial dysfunction even in relatively young patients with no cardiovascular disorders or risk factors. AF is an independent contributor to lower FMD and a prolonged arrhythmia duration may confer the risk for more profound endothelial damage.

Key words:
atrial fibrillation; endothelium, vascular; brachial artery; echocardiography; risk assessment; heart rate; body mas index; c-reactive protein.

Apstrakt

Uvod/Cilj. Dosadašnja istraživanja pokazala su prisustvo sistemske endotelne disfunkcije kod bolesnika sa atrijalnom fibrilacijom (AF) i pridruženim komorbiditetima ili kod starijih bolesnika sa idiopatskom AF. Cilj ovog istraživanja bio je poređenje endotelne funkcije, procenjene metodom vazodilatacije izazvane protokom (FMD) brahijalne arterije, kod bolesnika sa AF mlađih od 60 godina, bez pridružnog kardiovaskularnog ili drugog oboljenja, uključujući i arterijsku hipertenziju (*lone* AF), sa endotelnom funkcijom zdravih osoba u sinusnom ritmu. **Metode.** U prospektivnu studiju bile su uključene 2 grupe ispitanika. Prvu grupu je činilo 38 bolesnika sa perzistentnom (> 7 dana) *lone* AF, srednje starosti 45 ± 11 godina, od kojih je 68% bilo muškog pola. Drugu grupu činilo je 28 zdravih osoba u sinusnom ritmu, srednje starosti 43 ± 13 godina (53% muškarci), koji se nisu razlikovali od obolelih od AF po starosti, polu ili aterosklerotiskim faktorima rizika. Kod svih ispitanika obavljeni su kardiološki pregled, laboratorijske analize [uključujući i određivanje C-reaktivnog proteina (CRP-a)], ehokardiografski pregled i test opterećenjem. Endotel-zavisna (FMD) i endotel-nezavisna (NMD) vazodilatacija brahijalne arterije procenjeni su pomoću ultrazvuka visoke rezolucije, a arterijski prečnici određeni su kao srednja vrednost merenja tokom 5 uzastopnih srčanih ciklusa kako bi se umanjila promena protoka krvi karakteristična za nepravilni srčani ritam u AF. **Rezultati.** Nisu postojale razlike između obolelih od AF i kontrolne grupe u pogledu većine kliničkih, laboratorijskih i ehokardiografskih pokazatelja ($p > 0,05$), osim povišenih vrednosti srčane frekvencije

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($p = 0,018$), indeksa telesne mase ($p = 0,027$), nivoa CRP-a ($p = 0,007$) i anteroposteriornog prečnika leve pretkomore ($p < 0,001$) kod bolesnika sa AF. Endotel-zavisna vazodilatacija kod obolelih od AF [medijana FMD 5,00%, interkvartilni opseg (IQR) 2,87%–7,50%] bila je značajno niža ($p < 0.001$) nego FMD kod zdravih osoba (medijana FMD 8,85%, IQR 5,8%–12,50%), dok u pogledu vrednosti NMD-a nije bilo razlike ($p > 0,05$). U multivarijantnoj analizi, nezavisni pokazatelji vrednosti FMD kod učesnika istraživanja bili su: prisustvo AF, pušenje i koncentracija ukupnog holesterola ($p < 0,001$ za sve). Kod obolelih od AF najvažniji nezavisni pokazatelj snižene vrednosti FMD-a bilo je trajanje AF ($p < 0,001$), a pored toga nezavisni prediktori nižeg FMD-a bili su pušenje ($p = 0,013$), kao i koncentracija serumskog holesterola ($p = 0,045$). **Zaključak.** Rezultati ovog istraživanja pokazuju da je sistemska endotelna disfunkcija prisutna čak i kod mlađih bolesnika sa AF koji nemaju pridružena kardiovaskularna ili druga oboljenja. Prisustvo AF je nezavisni pokazatelj snižene verdnosti FMD-a, a trajanje aritmije povezano je sa povišenim rizikom od većeg stepena endotelnog oštećenja.

Ključne reči:
fibrilacija pretkomora; endotel krvnih sudova; a. brachialis; ehokardiografija; rizik, procena; srce, frekvencija; telesna masa, indeks; c-reaktivni protein.

Introduction

Atrial fibrillation (AF) is the most prevalent sustained cardiac arrhythmia in adult population [1]. It is usually associated with underlying comorbidities (e.g. arterial hypertension, coronary artery disease, valvular heart disease, diabetes mellitus, thyroid and pulmonary disorders) and a variety of risk factors (e.g. obesity, metabolic syndrome, sleep apnea, excessive alcohol consumption and competitive sports) [2–5]. Lone AF is defined as the occurrence of AF in subjects younger than < 60 years without associated comorbidities (including hypertension) or recognized risk factors [6, 7]. AF is considered a benign condition with favorable long-term prognosis [8, 9]. However, even in patients with lone AF, an evidence of damage/dysfunction of atrial endocardium, platelet activation and increased inflammatory and oxidative stress has been found [10, 11].

Over the past decade, systemic arterial endothelial dysfunction has been demonstrated both experimentally and clinically in various subsets of AF patients [12–14]. In clinical research, brachial artery flow-mediated dilation (FMD) is the most often used method to investigate systemic endothelial function [15–17]. This technique relies on brachial artery dilation produced by endothelial release of endogenous vasodilatators [principally nitric-oxide (NO)] in response to increased blood flow and shear stress. Although there has been some concern about FMD application in the settings of oscillatory blood flow in AF, recent studies have demonstrated good reproducibility and correlation with other determinants of endothelial damage in AF [16, 18].

It has been recognized that circulating indices of endothelial damage are related to increased risk of stroke in AF and endothelial dysfunction in peripheral vessels has been associated with adverse vascular events in patients in sinus rhythm [19, 20]. However, the prognostic implications of systemic endothelial dysfunction, determined by FMD in AF patients are still unknown. Nevertheless, impaired endothelial function is considered to be an important facilitator of thrombus formation [19].

To determine the association of AF and endothelial dysfunction, it would be the most appropriate to investigate apparently healthy individuals with AF, such as patients with lone AF. However, most previous research on endothelial function in lone AF included patients with hypertension or subjects older than > 60 years, clearly breaching the definition of lone AF.

Therefore, the aim of this study was to evaluate the association of AF with endothelial dysfunction by comparing brachial artery FMD of younger patients with persistent lone AF with FMD of healthy control subjects in sinus rhythm.

Methods

This single-center, cross-sectional study was conducted between November 2009 and April 2011. Patients with lone AF and healthy volunteers in sinus rhythm, matched by age, gender and atherosclerotic risk factors, were prospectively enrolled.

Before recruitment, all the participants underwent physical examination, routine biochemistry analyses, thyroid function assessment, determination of C-reactive protein (CRP) levels (by a commercially available immunoassay for high-sensitivity detection – detection limit 0.1 mg/L), 12-lead electrocardiogram (ECG), exercise stress testing and standard transthoracic echocardiographic examination.

The patients were eligible if persistent, lone AF was confirmed by 12-lead ECG. Persistent AF was defined as a sustained arrhythmia lasting for more than 7 days with repeated ECG demonstration of AF without intervening periods of sinus rhythm. AF duration was determined as accurately as possible according to patient-reported symptom onset and available medical documentation. AF was considered lone in patients younger than 60 years of age if there were no known associated cardiovascular disorders, or precipitating factors for AF. Therefore, none of the AF patients had a history of hypertension or other cardiovascular disorders prior to AF onset and all the patients were normotensive on the initial clinical evaluation before the initiation of medical therapy. All the patients had normal baseline laboratory tests, thyroid function, ECG and echocardiographic findings (mild left atrial dilatation < 4.5 cm was allowed). Ischemic heart disease or positive exercise stress test, valvular dysfunction (including mitral valve prolapse), cardiomyopathies, heart failure, preexcitation syndrome, diabetes mellitus, chronic pulmonary diseases, acute or chronic inflammatory disorders, malignancy, recent body trauma or surgery were exclu-

sion criteria. AF patients received a beta-blocker or verapamil for heart rate control and digoxin was added when rate control (< 80 beatas/min at rest) was not achieved with the highest tolerated dose of either agent alone. Warfarin was administered to all AF patients, targeting international normalized ratio (INR) of 2.0 to 3.0. No other medications were allowed.

The control subjects were considered eligible if they had no history of cardiovascular or other disorders and their physical examination, biochemistry, ECG, exercise stress test and echocardiogram were normal. Control subjects received no medications.

Written informed consent was obtained from all the participants.

Endothelial function was assessed using a high resolution (7.5 MHz, Agilent Image Point HX) vascular ultrasound probe. Vascular studies were performed by the 2 experienced investigators in a temperature-controlled room between 11 am and 1 pm. All the subjects were instructed not to eat, drink caffeinated beverages or take vitamin C supplements at least 12 hours before the study, and to refrain from alcohol consumption, smoking or physical exercise at least 1 day in advance of the study. After resting in supine position for 15 minutes, their heart rate and blood pressure were measured and baseline arterial image was acquired from the right arm 2–5 cm above the antecubital fossa. When a suitable 2-dimensional longitudinal axis image of the vessel was obtained and digitally recorded, the position of the ultrasound probe was fixed and remained unchanged throughout the examination. Arterial diameter measurements were performed off-line as a distance between the near and far wall lumen-intima boundaries at end-diastole (onset of the R wave on the ECG). To accommodate for beat-to-beat flow velocity variations in AF, arterial diameters taken from 5 consecutive cardiac cycles were averaged for each measurement. The same method was applied in the healthy controls.

After determination of baseline arterial diameter (D_{base}), a sphymgomanometric cuff was placed on the forearm and inflated to ≥ 200 mmHg for 5 minutes. Hyperemic stimulus was produced by rapid cuff deflation. Digital recording of the brachial artery was resumed 30 s before and continued for 90 s after cuff deflation. Approximately 60 s after cuff deflation brachial artery was measured again to determine the diameter of the maximal endothelium-dependent dilation (D_{max}). FMD was calculated using a formula: FMD = [(D_{max} – D_{base}) / D_{base}] × 100 (%).

Endothelium-independent dilation (NMD), a measure of vascular smooth muscle vasoreactivity, was assessed 15 to 20 min after FMD to allow for the restoration of baseline conditions. Five min after sublingual administration of 0.4 mg of nitroglycerine, brachial artery diameter was measured to determine nitroglycerine-induced dilation (D_{NTG}). NMD was calculated using a formula: NMD = [(D_{NTG}-D_{base}) / D_{base}] × 100 (%).

Vascular studies were successful in all the participants. Inter- and intraobserver variations for baseline brachial artery measurements in our laboratory are 0.04 ± 0.03 mm and 0.02 ± 0.02 mm, respectively.

Statistical analzsis

Sample size was determined from a pilot study that included 15 patients with persistent lone AF and 15 healthy controls. Respective mean values and standard deviations (SD) of FMD were determined to be 5.5% ± 2.8% and 8.8% ± 3.3%. It was determined that a minimum of 21 cases should be included in each group to detect the difference in FMD means with a 90% power and type I error probability of 0.05.

Following a test of statistical normality (Kolmogorov-Smirnov test), continuous variables are presented as mean ± SD or median and interquartile range (IQR), depending on a distribution. Categorical variables are reported as counts (n) with percentages (%). To analyze statistical differences between the 2 study groups the Student's *t* test, Mann-Whitney's test or Pearson's χ^2 test were used, as appropriate. The association of clinically significant variables with FMD was tested using a univariate linear regression analysis, and variables related to FMD ($p < 0.1$) were entered into a stepwise multivariate linear regression model. All the analyses were performed using SPSS statistical software, version 17.0. The statistical significance was set at a p value < 0.05 and 95% confidence intervals (CI) were used (2-sided).

Results

The present study included 38 patients with persistent, lone AF (24 to 60 years old, 68.4% male), and 28 healthy control subjects (27 to 60 years old, 53.6% male). Clinical characteristics of the participants are presented in Table 1. There were no differences between AF patients and the controls with respect to age, gender and most clinical and echocardiographic characteristics ($p > 0.05$ for all). However, the AF patients had a higher resting heart rate ($p = 0.018$), body mass index ($p = 0.027$) and serum CRP levels ($p = 0.007$). Left atrial anteroposterior diameter was also greater in the AF patients compared with the controls ($p < 0.001$).

In the AF group, arrhythmia persisted from 2 to 44 weeks before the enrollment (median AF duration was 16 weeks). All the AF patients received heart rate controlling medications (27 patients received beta-blocker monotherapy, 7 patients received verapamil only and 4 patients received a combination of either a beta-blocker or verapamil with digoxin) (Table 1).

A vascular study revealed similar median baseline brachial artery diameters in both AF patients and the controls (Table 2). An absolute increase in arterial diameter after cuff deflation was observed in all healthy subjects, but in 4 of the 38 AF patients (10.5%) no endothelium-dependent dilation occurred (Table 2). Maximal endothelium-dependent diameter change (D_{max}-D_{base}) was considerably greater in healthy subjects than in AF patients ($p = 0.001$) (Table 2).

On the other hand, arterial dilation was observed in all the subjects after nitroglycerine application, and there was no difference in the absolute diameter change (D_{NTG}-D_{base}) or median NMD value ($p > 0.05$ for both) as presented in Table 2.

Table 1

Clinical characteristics of the study participants

Clinical characteristics	AF group (n = 38)	Control group (n=28)	*p*
Age (years), $\bar{x} \pm SD$	45.3 ± 11.4	43.1 ± 13.2	0.970
Gender (male), n (%)	26 (68.4)	15 (53.6)	0.219
Resting heart rate (bpm), $\bar{x} \pm SD$	74.0 ± 8.5	69.8 ± 5.8	0.018
Body mass index (kg/m^2), $\bar{x} \pm SD$	23.2 ± 1.6	22.2 ± 2.1	0.027
Systolic blood pressure (mmHg), $\bar{x} \pm SD$	122.5 ± 11.6	126.3 ± 9.1	0.704
Diastolic blood pressure (mmHg), $\bar{x} \pm SD$	76.2 ± 4.7	78.8 ± 4.9	0.639
Total cholesterol (mmol/L), $\bar{x} \pm SD$	4.6 ± 0.8	4.5 ± 0.5	0.340
Triglycerides (mmol/L), $\bar{x} \pm SD$	1.2 ± 0.4	1.1 ± 0.2	0.710
Fasting blood glucose (mmol/L), $\bar{x} \pm SD$	4.3 ± 0.5	4.2 ± 0.8	0.908
C-reactive protein (mg/L), $\bar{x}$ (min – max)	1.9 (1.4–3.5)	1.3 (1.1–1.9)	0.007
Current smokers, n (%)	6 (15.8)	4 (14.3)	0.866
LAD (cm), $\bar{x} \pm SD$	4.0 ± 0.4	3.4 ± 0.3	< 0.001
LV EDD (cm), $\bar{x} \pm SD$	5.0 ± 0.5	4.9 ± 0.5	0.217
LV ESD (cm), $\bar{x} \pm SD$	3.4 ± 0.5	3.2 ± 0.4	0.345
LVEF (%), $\bar{x} \pm SD$	59.5 ± 8.1	61.5 ± 4.5	0.262
Medications, n (%)			
digoxin	4 (10.5)	/	/
verapamil	8 (21.1)	/	/
beta-blocker	30 (78.9)	/	/

AF – atrial fibrillation; LAD – left atrial anteroposterior dimension; LV EDD – left ventricular end-diastolic dimension; LV ESD – left ventricular end-systolic dimension; LVEF – left ventricular ejection fraction; BMP – beat per minute.

Table 2

Results of endothelium-dependent and endothelium-independent dilatation of the brachial artery

Parameters	AF group (n = 38)	Control group (n = 28)	*p*
Endothelium-dependent dilation			
baseline arterial diameter – D_{base} (mm), $\bar{x}$ (min – max)	4.10 (3.95–4.30	3.83 (3.51–4.02)	0.150
maximal endothelium dependent diameter change – D_{max}-D_{base} (mm), $\bar{x}$ (min – max)	+0.20 (0.11–0.30)	+0.29 (0.22–0.35)	0.001
subjects without endothelium-dependent dilatation, n (%)	4 (10.5)	0 (0.0)	0.077
Endothelium-independent dilation			
diameter change after nitroglycerine – D_{NTG}-D_{base} (mm), $\bar{x}$ (min – max)	+0.52 (0.46–0.58)	+0.53 (0.47–0.55)	0.165
NMD, $\bar{x}$ (min – max)	13.35 (12.27–14.60)	13.65 (12.85–14.90)	0.222

Values are presented as median (interquartile range) and n (%); D_{base} – baseline arterial diameter; D_{max} – maximal endothelium-dependent dilation; D_{NTE} – nitroglycerine-induced dilation; AF – atrial fibrillation; NMD – endothelium-independent dilation.

Figure 1 shows the median FMD values for AF patients and healthy subjects. As presented in Figure 1 endothelium-dependent dilation was significantly better in healthy subjects (median value 8.85%, IQR 5.80%–12.50%) in comparison with AF patients (median value 5.00%, IQR 2.87%–7.50%) – $p < 0.001$.

The results of the regression analysis of clinical and echocardiographic FMD determinants of all study participants and AF patients are presented in Table 3.

In the univariate analysis of all the study participants, AF presence, resting heart rate, smoking, left atrial diameter, CRP and total cholesterol levels were predictive of FMD. In the multivariate analysis, the only independent FMD determinants were AF presence, smoking and total cholesterol levels (all $p < 0.001$).

The results of the univariate analysis for the AF patients revealed that AF duration, left atrial dimension, diastolic blood pressure, smoking, CRP and total cholesterol levels were predictive of FMD (all $p < 0.05$). In the multivariate analysis, the strongest FMD predictor in AF patients was arrhythmia duration ($p < 0.001$), followed by smoking ($p = 0.013$) and total cholesterol levels ($p = 0.045$).

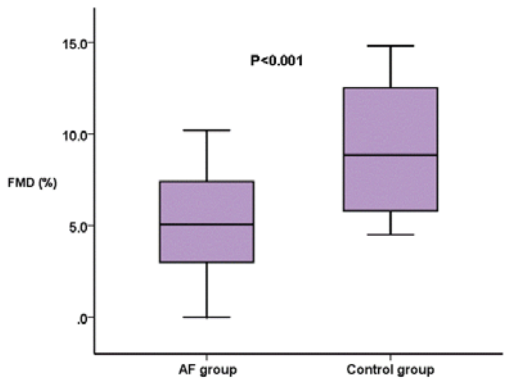

Fig. 1 – Median flow-mediated dilation (FMD) values in the atrial fibrilation (AF) patients (the AF group) and the healthy individuals (the control group).

Table 3

Flow-mediated dilation (FMD) predictors in the study participants

Variable	Univariate regression analysis			Multivariate regression analysis		
	B	95% CI	*p*	B	95% CI	*p*
All participants						
AF presence	-4.1	-5.7 to -2.6	< 0.001	-3.8	-5.0 do -2.6	< 0.001
C-reactive protein	-2.2	-3.0 to -1.4	0.001	/	/	/
heart rate	-0.2	-0.3 to 0.1	0.002	/	/	/
smoking	-5.2	-7.4 to -3.0	< 0.001	-3.9	-5.7 to -2.1	< 0.001
left atrial dimension	-4.4	-6.6 to -3-2	< 0.001	/	/	/
total cholesterol level	-2.6	-3.7 to -1.4	< 0.001	-1.3	-2.2 to -0.4	< 0.001
AF patients						
C-reactive protein	-1.9	-2.6 to -1.1	< 0.001	/	/	/
AF duration	-0.2	-0.3 to -0.2	< 0.001	-0.2	-0.4 to -0.1	< 0.001
left atrial dimension	-3.1	-5.2 to -0.9	0.006	/	/	/
smoking	-5.3	-7.3 to -3.3	< 0.001	-2.4	-4.3 to -0.5	0.013
diastolic blood pressure	-0.2	-0.4 to -0.0	0.048	/	/	/
total cholesterol	-2.2	-3.2 to -1.3	< 0.001	-0.8	-1.7 to -0.0	0.045

AF – atrial fibrillation.

Discussion

In the present study we demonstrated that systemic endothelial function, assessed by brachial artery FMD, was significantly impaired in the patients with sustained lone AF in comparison with the healthy individuals, whilst endothelium-independent dilation was preserved. In the present study population, AF is an independent predictor of lower FMD. In addition, arrhythmia duration is the strongest determinant of reduced FMD in patients with AF.

These findings are in agreement with the results of previous studies. The first to report on the presence of systemic endothelial dysfunction in AF were Takahashi et al. [13] who demonstrated impaired endothelium-dependent dilation, assessed by venous occlusion pletismography in a group of AF patients. This study prompted interest into noninvasive evaluation of systemic endothelial function in AF, resulting in the publication of several trials, showing that the FMD technique could be reliably utilized for endothelial function assessment in AF [18, 21–25]. These trials invariably demonstrated impaired FMD in the AF patients in comparison with the healthy subjects [18, 24, 25], as well as an improvement in endothelial function with the restoration of sinus rhythm [21–25]. The implication of these findings was that AF presence could be regarded as a risk factor for systemic endothelial dysfunction. However, most of these trials have been conducted in patients with underlying comorbidities, most often hypertension, coronary artery disease and diabetes, which are recognized risk factors for endothelial damage. There have been a few studies that enrolled a relatively small subset of predominantly older patients with idiopathic AF that also confirmed impaired FMD [18, 21, 22].

In contrast, our study is the first to demonstrate impaired FMD in relatively young patients (mean age 45 years) with lone AF and low cardiovascular risk profile, which is of great importance considering that aging and the presence of various atherosclerotic risk factors could adversely affect endothelial function [26, 27]. Nevertheless, two well recognized risk factors for endothelial damage, i.e. smoking [28, 29] and serum cholesterol levels [30], were independent predictors of lower FMD in the present study. Besides the influence of these established risk factors, we documented that AF is an independent predictor of reduced FMD. This observation is in line with a previously published trial that found AF presence to predict lower FMD even after adjustments for various comorbidities [18]. Another noteworthy finding is an independent inverse relationship of AF duration and FMD which may indicate that the development of endothelial dysfunction in AF is time-dependent and that longer arrhythmia duration may be associated with a more profound endothelial damage. Interestingly, our findings also revealed an inverse association in the univariate analysis of the left atrial dilation and FMD in the AF patient group. It could be inferred that there are similar underlying pathophysiologic processes linking left atrial remodeling with systemic endothelial dysfunction.

The precise pathophysiologic mechanisms behind systemic endothelial dysfunction in AF have not been fully elucidated. Under physiologic conditions, endothelial NO production is regulated by laminar shear stress [31]. In AF, irregular heart beats produce turbulent blood flow and oscillating shear stress in systemic vessels with a negative influence on NO production and endothelial NO synthase expression [12], which is further supported by findings of reduced plasma nitrite/nitrate levels in AF [32]. In our study, heart rate was inversely related to FMD in the univariate analysis, possibly reflecting an unfavorable effect of changed hemodynamics in AF. An interesting hypothesis proposes that AF-induced damage to the endocardium of the left atrium may contribute to systemic endothelial dysfunction by reducing circulating nitroso-compounds that serve as endogenous NO donors to systemic vessels [12, 33], further supporting the concept that endothelial dysfunction is a systemic phenomenon in AF patients [18]. Other factors such as activation of renin-angiotensin system [34], neurohumoral activation [35] and heightened inflammatory [36] and oxidative stress [37] could be also implicated in the development of endothelial dysfunction in AF, particularly with longer arrhythmia duration. In keeping with the association of AF and inflammation, CRP levels in AF patients in the present study were significantly higher than in healthy individuals and CRP was inversely related

with FMD in the univariate analysis. However, an independent association of CRP and FMD was not confirmed in the multivariate analysis. Thus, we concluded that elevated CRP levels were contributory, but not crucial for FMD impairment in our patients.

Study limitations

There is a concern about the influence of a relatively small sample size of the present study on the interpretation of the results. However, both patient and control groups were sufficiently homogenous and the differences in main findings between the groups were substantial enough to allow the conclusion that sample size did not impose significant limitations. The other concern is about the possible shortcomings of the FMD technique to accurately evaluate endothelial function in AF. To minimize the effect of beat-to-beat flow variations on endothelial function assessment, we adopted a modified FMD technique that has been shown to correlate with other markers of endothelial damage in AF [18]. Furthermore, physical activity was not evaluated and it was recognized that regular exercise improves endothelial function [38]. On the other hand, AF-related symptoms may impose limitations on physical activity, thus exerting a negative influence on the endothelium in AF patients. Additionally, the results of the present study would have been strengthened should we have correlated FMD with other established indices of endothelial damage and the left atrial volume instead of the left atrial anteroposterior diameter. Finally, it must be recognized that the influence of medications given to AF patients (beta-blockers, verapamil, digoxin and warfarin) were not controlled in our investigation. Nevertheless, there were no reports on the negative effects of these medications on endothelial function.

Conclusion

Our findings confirm that sustained AF is associated with systemic endothelial impairment even in relatively young patients with no cardiovascular disorders or risk factors. AF is an independent contributor to lower flow-mediated dilation and prolonged arrhythmia duration may confer the risk for more profound endothelial damage. These findings merit further research to clarify clinical relevance and potential therapeutic implications, particularly in thromboembolic risk stratification and prevention of the AF-related thromboembolism.

REFERENCES

1. *Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH,* et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J 2006; 27(8): 949−53.
2. *Kannel WB, Abbott RD, Savage DD, McNamara PM.* Coronary heart disease and atrial fibrillation: The Framingham Study. Am Heart J 1983; 106(8): 389−96.
3. *Kannel WB, Wolf PA, Benjamin EJ, Levy D.* Prevalence, incidence, prognosis and predisposing conditions of atrial fibrillation: population-based estimates. Am J Cardiol 1998; 82(8A): 2N−9N.
4. *Onundarson PT, Thorgeirsson G, Jonmundsson E, Sigfusson N, Hardarson T.* Chronic atrial fibrillation – epidemiologic features and 14-year follow-up: a case control study. Eur Heart J 1987; 8(5): 521−7.
5. *Schoonderwoerd BA, Smit MD, Pen L, Van Gelder IC.* New risk factors for atrial fibrillation: causes of "not-so-lone atrial fibrillation". Europace; 2008: 10(6): 668−73.
6. *Camm JA, Kirchhof P, Lip GYH, Schotten U, Savelieva I, Ernst S*, et al. Guidelines for the management of atrial fibrillation. The Task Force for the Management of Atrial Fibrillation of the European Society of cardiology (ESC). Eur Heart J 2010; 31(19): 2369−429.
7. *Potpara TS, Lyp GYH.* Lone atrial fibrillation: what is known and what is to come. Int J Clin Pract 2011; 65(4): 446−57.
8. *Jahingir A, Lee V, Friedman PA, Trusty JM, Hodge DO, Kopecky SL,* et al. Long-term prognosis and outcomes with aging in patients with lone atrial fibrillation. A 30-yeare follow-up study. Circulation 2007; 115(24): 3050−6.
9. *Potpara T, Grujic M, Marinkovic J, Vujisic-Tesic B, Ostojic M, Polovina M.* Mortality of patients with lone and idiopathic atrial fibrillation is similar to mortality in general population of Serbia. Vojnosanit Pregl 2010; 67(1): 132−5.
10. *Mondillo S, Sabatini L, Agricola E, Ammaturo T, Guerrini F, Barbati R*, et al. Correlation between left atrial size, prothrombotic state and markers of endothelial dysfunction in patients with lone chronic nonrheumatic atrial fibrillation. Int J Cardiol 2000; 75(2−3): 227−32.
11. *Goette A, Weber M, Lendeckel U, Welte T, Lutze G Klein H.* Effect of physical exercise on platelet activity and the von-Willebrand-factor in patients with persistent lone atrial fibrillation. J Interv Card Electrophysiol. 2004; 10(2): 139−46.
12. *Cai H, Li Z, Goette A, Mera F, Honeycutt C, Feterik K, Wilcox JN,* et al. Downregulation of endocardial nitric oxide synthase expression and nitric oxide production in atrial fibrillation. Circulation 2002; 106(22): 2854−8.
13. *Takahashi N, Ishibashi Y, Shimada T, Sakane T, Ohata S, Sugamori T*, et al. Atrial fibrillation impairs endothelial function in forearm vessels in humans. J Cardiac Fail 2001; 7(1): 45−54.
14. *Freestone B, Chong AY, Nuttall S, Blann AD, Lip GY.* Soluble E-selectin, von Willebrand factor, soluble thrombomodulin, and total body nitrate/nitrite product as indices of endothelial damage/dysfunction in paroxysmal, persistent, and permanent atrial fibrillation. Chest 2007; 132(4): 1253−8.
15. *Celermajer DS, Sorensen KE, Gooch VM, Spiegelhalter DJ, Miller OI, Sullivan ID,* et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet 1992; 340(8828): 1111−5.
16. *Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA,* et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol 2002; 39(2): 257−65.
17. *Butt M, Dwivedi G, Blann A, Khair O Lip GY.* Endothelial dysfunction: methods of assessment & implications for cardiovascular disease. Curr Pharm Des 2010; 1(31): 3442−54.
18. *Freestone B, Chong A, Nuttall S, Lip GY.* Impaired flow mediated dilation as evidence of endothelial dysfunction in chronic atrial fibrillation: relationship to plasma von Willebrand factor and soluble E-selectin levels. Thromb Res 2008; 122(1): 85−90.
19. *Lip GY, Lane D, Van Walraven C, Hart RG.* Additive role of plasma von Willebrand factor levels to clinical factors for risk

stratification of patients with atrial fibrillation. Stroke 2006; 37(9): 2294−300.
20. *Lind L, Berglund L, Larssun A, Sundström J*. Endothelial function in resistance and conduit arteries and 5-year risk of cardiovascular disease. Circulation 2011; 123(14): 1545−51.
21. *Guazzi M, Belletti S, Tumminello G, Fiorentini C, Guazzi MD*. Exercise hyperventilation, dyspnea sensation and ergoreflex activation in lone atrial fibrillation. Am J Physiol Heart Circ Physiol 2004; 287(6): H2899−905.
22. *Guazzi M, Belletti S, Bianco E, Lenatti L, Guazzi MD*. Endothelial dysfunction and exercise performance in lone atrial fibrillation or associated with hypertension or diabetes: different results with cardioversion. Am J Physiol Heart Circ Physiol 2006; 291(2): H921−8.
23. *Guazzi M, Belletti S, Lenatti L, Bianco E, Guazzi MD*. Effects of cardioversion of atrial fibrillation on endothelial function in hypertension and diabetes. Eur J Clin Invest 2007; 37(1): 26−34.
24. *Skalidis EI, Zacharis EA, Tsetis DK, Pagonidis K, Chlouverakis G, Yarmenitis S* et al. Endothelial cell function during atrial fibrillation and after restoration of sinus rhythm. Am J Cardiol 2007; 99(9): 1258−62.
25. *Shin SY, Na JO, Lim HE, Choi CU, Choi JI, Kim SH,* et al. Improved endothelial function in patients with atrial fibrillation through maintenance of sinus rhythm by successful catheter ablation. J Cardiovasc Electrophysiol 2011; 22(4): 376−82.
26. *Yavuz BB, Yavuz B, Sener DD, Cankurtaran M, Halil M, Ulger Z*, et al. Advanced age is associated with endothelial dysfunction in healthy elderly subjects. Gerontology 2008; 54(3): 153−6.
27. Black MA, Cable NT, Thijssen DH, Green DJ. Impact of age, sex, and exercise on brachial artery flow-mediated dilatation. Am J Physiol Heart Circ Physiol 2009; 297(3): H1109−16.
28. *Celermajer DS, Sorensen KE, Georgakopoulos D, Bull C, Thomas O, Robinson J,* et al. Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults. Circulation 1993; 88(5 Pt 1): 2149−55.
29. *Josephson HM, Gossett LK, Piper ME, Aeschlimann SE, Korcarz CE, Baker TB*, et al. Effects of smoking and smoking cessation on endothelial function: 1-year outcomes from a randomized clinical trial. J Am Coll Cardiol 2010; 55(18): 1988−95.
30. *Masoura C, Pitsaros C, Aznaouridis K, Skoumas I, Vlachopoulos C, Stefanidis C*. Arterial endothelial function and wall thickness in familial hypercholesterolemia and familial combined hyperlipidemia and the effect of statins. A systematic review and meta-analysis. Atherosclerosis 2011; 214(1): 129−38.
31. *Pan S*. Molecular mechanisms responsible for the atheroprotective effects of laminar shear stress. Antioxid Redox Signal. 2009; 11(7): 1669−82.
32. *Minamino T, Kitazake M, Sato H, Asanuma H, Funaya H, Koretsune Y*, et al. Plasma levels of nitrite/nitrate and platelet cGMP levels are decreased in patients with atrial fibrillation. Artherioscler Thromb Vasc Biol 1997; 17(11): 3191−5.
33. *Guazzi M, Arena R*. Endothelial dysfunction and pahophysiologica correlates in atrial fibrillation. Heart 2009; 95(2): 102−6.
34. *Wachtell K, Lehto M, Gerdts E, Olsen MH, Hornestam B, Dahlöf B*, et al. Angiotensin II Receptor Blockade Reduces New-Onset Atrial Fibrillation and Subsequent Stroke Compared to Atenolol The Losartan Intervention for End Point Reduction in Hypertension (LIFE) Study. J Am Coll Cardiol 2005; 45(5): 712−9.
35. *Parthenakis FI, Patrianakos AP, Skalidis EI, Diakakis GF, Zacharis EA, Chlouverakis G,* et al. Atrial fibrillation is associated with increased neurohumoral activation and reduced exercise tolerance in patients with non-ischemic dilated cardiomyopathy. Int J Cardiol 2007; 118(2): 206−14.
36. *Korantzopoulos P, Kolettis TM, Galarix D, Goudevenos JA*. The role of oxidative stress in the pathogenesis and perpetuation of atrial fibrillation. Int J Cardiol 2007; 115(2): 135−43.
37. *Boos CJ, Anderson RA, Lip GY*. Is atrial fibrillation an inflammatory disorder? Eur Heart J 2006; 27(2): 136−49.
38. *Hambrecht R, Adams V, Erbs S, Linke A, Kränkel N, Shu Y*, et al. Regular physical activity improves endothelial function in patients with coronary artery disease by increasing phosphorilation of endothelial metric oxide synthase. Circulation 2003; 107(25): 3152−8.

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Long-term outcome of a modified balloon dilatation in the treatment of patients with achalasia

Dugoročni ishod modifikovane balon dilatacije u lečenju bolesnika sa ahalazijom

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Abstract

Background/Aim. Balloon dilatation is a standard approach to the initial achalasia treatment. Modified dilatation is also applied to rise efficacy and to lower complications. **Methods.** A total of 57 patients were analysed within a median follow-up of 8.2 years. No premedication was used, dilatation was performed up to the pain treshold, while introduction and positioning of a dilatator was done in combination of endoscopic and radiological control. Dilatation effect was estimated by both Kim Symptom Scoring and objective parameters: body weight rise and radiological scintigraphic findings. **Results.** Excellent and good results were obtained in 50 (88%) of the patients, while in 7 (12%) of the patients surgery was performed. There was no difference in dilatation efficacy regarding sex of the patients, but the results were better in the patients above 40 years. Duration of symptoms, body weight loss, esophageal lumen width do not indicate the definitive dilatation outcome. Esophageal scintigraphy and body weight increase were in a direct correlation with the effect of dilatation measured with the Kim Symptom Scoring. After the one to two repeated dilatations the efficacy increased from 74% to 88% justifying the repetition of dilatation. In 2 (3.57%) of the patients, that is in 2.65% of the totally dilated patients, perforation was recorded. There was no lethal outcome of dilatation, and the other complications were not clinically significant. **Conclusion.** Modified balloon dilatation can be recommended for initial method in achalasia treatment due to high efficacy, easy performance in daily hospital while complications are in standard range.

Key words:
esophageal achalasia; radionuclide imaging; balloon dilatation; prognosis.

Apstrakt

Uvod/Cilj. Balon dilatacija je standardni pristup u početnom lečenju ahalazije. Primenjena je „modifikovana" tehnika dilatacije u lečenju ahalazije u cilju povećanja efikasnosti i smanjenja komplikacija. **Metode.** Analizirano je 57 bolesnika sa medijanom praćenja od 8,2 godine. Nije korišćena premedikacija, dilatacija je vršena do praga bola, a uvođenje i pozicioniranje dilatatora vršeno je kombinacijom endoskopske i radiološke kontrole. Efekat dilatacije određen je kombinacijom Kimovog sistema za ocenjivanje simptoma i objektivnih paramatara: porasta telesne mase i radioloških scintigrafskih nalaza. **Rezultati.** Odlični i dobri rezultati postignuti su kod 50 (88%) bolesnika, a kod 7 (12) nisu postignuti željeni rezultati i kod njih je primenjena klasična hirurška intervencija. Nije bilo razlika u efkasnosti dilatacije u odnosu na pol bolesnika, ali bolesnici stariji od 40 godina imali su bolje rezultate. Trajanje simptoma, gubitak telesne mase i širina lumena jednjaka pre dilatacije nisu ukazivali na definitivni ishod dilatacije. Scintigrafija jednjaka i porast telesne mase bili su u direktnoj korelaciji sa efektom dilatacije određenim Kimovim sistemom za ocenjivanje simptoma. Posle ponovljene jedne do dve dilatacije, efikasnost je porasla sa 74% na 88%, što ukazuje na opravdanost ponavljanja dilatacije. Kod 2 (3,57%) bolesnika, odnosno kod 2,65% svih dilatiranih, zabeležena je perforacija jednjaka. Smrtnih ishoda dilatacije nije bilo, a ostale komplikacije nisu bile od kliničkog značaja. **Zaključak.** Modifikovana balon dilatacija može se preporučiti kao početna metoda u lečenju ahalazije zbog visoke efikasnosti, jednostavog izvođenja u dnevnoj bolnici, uz komplikacije koje se kreću u standardnim okvirima.

Ključne reči:
jednjak, ahalazija; scintigrafija; dilatacija balonom; prognoza.

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Introduction

Achalasia is a serious neuromuscular disorder of the esophagus with no peristaltic activity of its body and especially the failure of the lower esophageal sphincter (LES) to relax with swallowing [1]. This functional disorder leads to food and liquid retention in the esophagus thus causing dysphagia, regurgitation, pain in the chest, loss in body weight and, sometimes, bronchopulmonary infections due to aspiration of esophageal contents. Etiology of achalasia has not completely been understood [2]. The occurrence of antibodies in the region towards the myenteric plexus is very likely to suggest a basically autoimmune disorder, but it remains unknown whether it is the primary or secondary defect [3, 4]. Maintaininig of the LES tonic pressure is a complex and poorly explained phenomenon [5], while a recent hypothesis says that the LES tonus results from the balance of excitatory (cholinergic and substances P) and inhibitory (vasoactive intestinal peptide and nitric monoxide) effects [3, 6]. Thus, achalasia could be taken as nitrinergic neuritis that leads to late LES relaxation with swallowing [4].

It is not possible to restore motility of esophagus with achalasia, so the options in achalasia treatment are of palliative type either conservative or surgical [5]. It seems that the only way to improve esophageal emptying is to reduce the resistance to the level of LES [7, 8]. Several methods are available for the treatment of achalasia, namely medicamentous (nitrites, calcium antagonists, botulinum toxin), dilatation and surgical treatment including laparascopic cardiomyotomy [9–11].

Most often performed conservative method for the treatment of achalasia is dilatation. Wether to initially use surgery or dilatation in achalasia treatment is a not yet resolved dilemma [12–16].

It is known that many factors affect the efficacy of baloon dilatation in achalasia treatment. The aim of this study was to examine the possibility to rise efficacy and reduce complications in a patients with achalasia by the use of a modified baloon dilatation.

Methods

A total of 57 patients were treated by the use of balloon dilatation in a 16-year period. The average follow-up period was 8 years and 2 months. The diagnosis of achalasia was confirmed in all the patients on the basis of clinical examination, endoscopy, radiography, manometric and scintigraphic findings. Children, psychotic and uncooperative patients were excluded from the study. Dilatation was performed also in the patients with the law Karnofsky status, while those with serious cardiovascular diseases, such is unstable angina pectoris, were excluded from the study. The patients with tortuous, "sigmoid" esophagus, as well as those with hiatal hernia were also treated.

The basic standardized principles of the dilatation technique suggested by the National Medical Center, Betheseda, USA were applied including no premedication with diazepam, midazolam, pethidine, atropine, nor any other medications; endoscopic and radiographic positioning of a balloon (baloon widening with hydrosoluble contrast agent), and balloon widening up to above the pain threshold were signalled by a patient.

Dilatation was performed by the use of a Regiflex dilatator (Boston, USA), made of a special plastic material filled with a gas or liquid, affecting radially a reduced part of the esophagus.

Dilatation efficacy degree was estimated with the symptom score suggested by Kim et al. [9]. The symptom score for dysphagia, regurgitation, chest pain and heartburn (pyrosis) was calculated by multiplying the frequency of symptoms and their intensity. On the basis of the total symptom score the patients were divided into three groups regarding the response to balloon dilatation: the group I with excellent an good results (implying the total symptom score reduction by 50% or more as compared with the initial value), the group II with the result improvement (the total symptom score reduced by 50% to 25%), and the group III with the bad result (the total symptom score not reduced by 25% or less).

Results

Out of 57 analysed patients, there were 32 (57%) males and 25 (43%) females, the ratio being 1.2 : 1 (Figure 1).

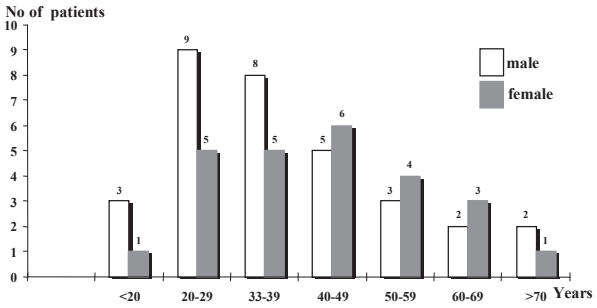

Fig. 1 – Age of the patients with achalasia.

The disease was most common in the males from the age group 20–30 years, and the females from the age group 40–49 years, the average age being 43 years. Up to 40, there were 31 patients, while above 40 there were 26 patients. The youngest patient was 16, and the oldest 83. Ther was no significant correlation found between the efficacy of balloon dilatation and sex distribution of the patients.

There was a correlation found between the efficacy of balloon dilatation and the age of the patients. The patients above 40 had better prognosis regarding dilatation success as compared to those below 40 years of age (Table 1).

The effect of dilatation evaluated by the use of symptom score suggested excellent (42) and good results (8) in 50 (89%) of the patients regarded as a complete recovery from the disease, while in 7 (11%) of the patients the results were bad including two patients with a perforation.

The majority of patients had symptoms for 1–5 years. In three patients symptoms were present for more than 12

Table 1

Long-standing results of dilatation in the patients with achalasia under 40 and above 40 years of age

Age of patients (years)	Dilatation efficacy			
	excellent	good	poor	total
< 40	21 (36.84)	5 (8.77)	5 (8.77)	31 (54.38)
> 40	21 (36.84)	3 (5.26)	2 (3.50)	26 (45.61)
Total	42 (73.68)	8 (14.03)	7 (12.28)	57 (100)

Data are present as number (%) of patients.

years, although radiographically it was decompensated achalasia. In the younger patients there was a shorter period of symptoms prior to dilatation. Out of the 10 patients with symptoms more than 10 years, 9 were above 40.

There was no significant correlation found between the efficacy of balloon dilatation and the period of symptoms present prior to dilatation. The duration of symptoms was found not to have a prognostic significance for a final outcome of dilatation. A few excellent and good results were achieved in the patients with a longer disease presence, and a few bad results in the patients with a short period of symptoms presence (Table 2).

Loss in body weight is the most common sign of the disease. The highest number of the patients lost 10 kg of body weight (Table 3).

A total of 54 patients showed loss in body weight. Six months after the dilatation the majority of the patients (n = 30) gained 1–10 kg of body weight. The three patients gained even more than 20 kg of body weight, while in 11 of the patients there was no increase in body weight (Table 4).

There was a significant correlation between the efficacy of balloon dilatation and the increase of body weight in the patients after the dilatation. Body weight increase is regarded to be an objective parameter for monitoring the efficacy of dilatation and suggests a final outcome of the therapy.

The majority of patients had esophagus lumen width of 3.5 cm to 6 cm in esophagogram, while in 13 of the patients it was more than 6 cm, implying that they were in decompensation stage (Table 5).

Table 2

Association of symptoms duration and dilatation efficacy

Duration of symptoms (years)	Dilatation efficacy			
	excellent	good	poor	total
< 1	6 (15.53)	2 (3.51)	1 (1.75)	9 (15.79)
1–5	19 (33.33)	3 (5.26)	2 (3.51)	24 (42.11)
5–10	8 (14.03)	2 (3.51)	2 (3.51)	12 (21.05)
> 10	9 (15.79)	1 (1.75)	2 (3.51)	12 (21.05)
Total	42 (73.68)	8 (14.03)	7 (12.28)	57 (100)

Data are present as number (%) patients.

Table 3

Association of body weight loss and dilatation efficacy

Weight loss (kg)	Dilatation efficacy			
	excellent	good	poor	total
No loss	3 (5.26)	1 (1.75)	1 (1.75)	5 (8.77)
< 5	12 (21.05)	2 (3.51)	2 (3.51)	16 (28.07)
5–10	14 (24.56)	3 (5.26)	2 (3.51)	19 (33.33)
> 10	13 (22.81)	2 (3.51)	2 (3.51)	17 (29.82)
Total	42 (73.68)	8 (14.03)	7 (12.28)	57 (100)

Data are present as number (%) of patients.

Table 4

Association of body weight increase after dilatation and dilatation efficacy

Results of dilatation	Dilatation efficacy			
	excellent	good	poor	total
Body weight increase (kg)				
no change	3 (5.26)	3 (5.26)	5 (88.78)	5 (8.78)
< 5	14 (24.56)	2 (3.51)	1 (1.75)	16 (28.07)
6–10	11 (24.56)	1 (1.75)	1 (1.75)	19 (33.33)
> 10	14 (19.30)	2 (3.51)	0 (0)	17 (29.82)
Total	42 (73.68)	8 (14.03)	7 (12.28)	57 (100)

Data are present as number (%) of patients.

There was no significant correlation found between the efficacy of balloon dilatation and the loss of body weight. The success od dilatation could not be predicted on the basis of body weight loss.

There was no significant correlation found between esophageal dilatation degree before the dilatation and the efficacy of balloon dilatation.

Table 5

Association of esophageal dilatation and dilatation efficacy

Esophageal dilatation width (cm)	Dilatation efficacy			
	excellent	good	poor	total
< 3.5	13 (22.81)	3 (5.26)	2 (3.51)	18 (31.59)
3.5–6	20 (35.09)	4 (7.02)	2 (3.51)	26 (45.60)
> 6	9 (15.79)	1 (1.75)	3 (5.26)	13 (22.81)
Total	42 (73.68)	8 (14.03)	7 (12.28)	57 (100)

Data are present as number (%) of patients.

Esophagus scintigraphy is a non-invasive, simple and reliable method which in physiological manner provides a direct quantification of esophageal motor function, that is esophageal clearance (Table 6, Figures 2 and 3).

There was a significant correlation found between balloon dilatation efficacy and esophageal emptying measured by the use of scintigraphy.

Table 6

Association of radionuclide discharge and dilatation efficacy

Radionuclide discharge (%)	Dilatation efficacy			
	excellent	good	poor	total
> 50	23 (56.09)	0 (0)	0 (0)	23 (56.09)
< 50	8 (19.51)	1 (2.44)	4 (9.76)	13 (31.71)
No change	0 (0)	4 (9.76)	1 (2.44)	5 (12.20)
Total	31 (75.60)	5 (12.20)	5 (12.20)	41 (100)

Data are present as number (%) of patients.

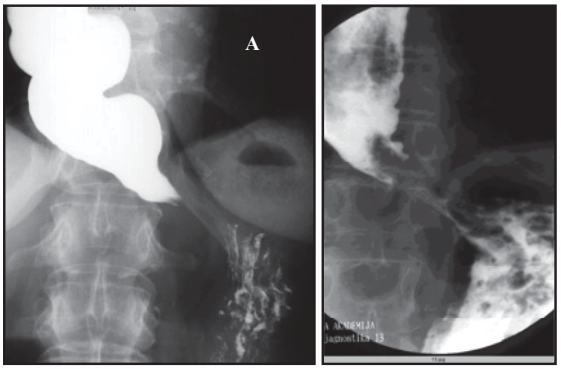

Fig. 2 – Typical radiological image of achalasia before (left) and after (right) successful dilatation.

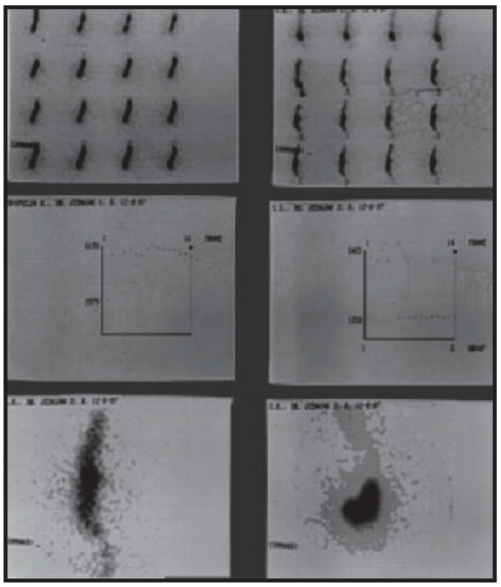

Fig. 3 – Radionuclide imaging in achalasia before (left) and after (right) dilatation.

In 40 (70%) of the patients one dilatation was performed, in 14 (25%) two, while in three (5%) of the patients three dilatations were done, thus a total of 74 dilatations were performed in 57 patients. Dilatation was repeated not earlier than three months after the previous one. The majority of patients were motivated for dilatation repetition, while the one was referred to esophagomyotomy due to failure in the first dilatation (Table 7).

Excellent and good results were obtained in two thirds of the patients after first dilatation, indicating best results of first dilatation. Second and third dilatations were justified by the fact that another 9 (15%) of the patients showed excellent results after repeated dilatation. Final excellent and good results were shown by 50 out of the total of 57 patients, and dilatation success rate was increased from 67% to 89%.

Esophageal perforation is the most common complication of balloon dilatation causing morbidity that could lead to death.

In 2 (3.57%) dilated patients there was a perforation, that is in 2.60% out of all dilatations. The diagnosis in both patients was made immediatelly after dilatation, then they were successfully operated on. There were no lethal outcomes. In 2 (3.57%) of the patients submucosal damage was registered. They were conservatively treated. In 23 (40%) of the patients there was blood on a balloon dilatator indicating mucosal damage and dilatation efficacy. It should not be considered as complication.

Early complications (prolonged pain, feaver, gastrointestinal bleeding) were present in 7 of the patients, but only temporary. A total of 3 patients had prolonged chest pain for 8–20 h. Esophagogram was repeated with no perforations found. Anxiolytics, not analgetics, were used for treatment. In 3 patients there was temperature increase above 38°C, and in one melena with hematocrit reduction to 0.08%.

Late complications were registered in 8 of the patients. They were mostly manifested by stage 1 esophagitis, and in 2 of the patients by stage 2, and in 1 by stage 3 esophagitis.

Table 7

Association of the number of dilatations and dilatation efficacy

Number dilatation	Dilatation efficacy			
	excellent	good	poor	total
One	33 (57.89)	7 (12.28)	17 (29.82)	57 (76.00)
Two	8 (14.03)	2 (3.50)	6 (10.52)	16 (28.07)
Three	1 (1.75)	1 (1.75)	1 (1.75)	3 (3.95)
Total	42 (73.67)	10 (8.77)	24 (41.09)	76 (100)

Data are present as number (%) patients.

There was no carcinoma found in any patients treated by dilatation, indicating good evaluation of the disease prior to dilatation.

Discussion

Sir Thomas Willis was the first one to report on achalasia in 1672, and then to perform dilatation on the same patient by the help of a whale bone [1]. Three and a half centuries later there are no significant changes except for technical improvements of the method [16–20]. Today achalasia treatment methods are still palliative, while esophageal emptying completely depends upon gravitation [21–23].

Medicaments such as nitroglycerin, isosorbide dinitrate, calcium antagonists are advised to patients with mild symptoms [24, 25]. Botulinum toxin in achalasia treatment was reported first in Lancet in 1993 [26]. Application of botulinum toxin in achalasia is safe, simple and efficient, and till now indicative in patients with a high risk for dilatation or cardiomyotomy [27].

Today there are two options of basic approach to the treatment of achalasia: dilatation and surgery including numerous modifications of both methods. Research for alternative endoscopic modalities for achalasia treatment is under way all the time. Reducing pressure of diffuse esophageal spasm (DES) by ethanolamine, used in scleroterapy of esophageal varices, has not found wider application, and the results have been followed up in short-term at the level of dilatation [28].

In 1991 laparoscopic myotomy as possible option in achalasia treatment was introduced while the results were shown later [29, 30]. Excellent results in 88% of patients indicate that laparoscopic myotomy is a method of choice in achalasia management [31]. In his study, Richter [32] tried to solve the dilemma whether to use laparoscopic myotomy or dilatation in achalasia management.

Initial achalasia treatment method is a personal choice of the physician, attitude of a medical institution and capability of teams for surgery or dilatation [1]. Here, we exclusively used dilatation as an initial method in achalasia treatment.

The second question to answer is what dilatation technique to use for achalasia treatment. Balloon dilatation is a traditional method for non-surgical achalasia treatment with the aim to mechanically cut muscle fiber of DES. Vantreppen and Hellemans [5] gave the greatest contribution to the promotion of this method. Many dilator types were used in the past: Brown-McHardy, Hurst, Tucker, Mosher, Rider-Moller etc. In 1981 the results obtained by dilators positioned under endoscopic monitoring were published [1]. Dilators with polyurethane baloon (Rigiflex) came into use 15 years ago. One of Rigiflex balloon most significant advantages is its possibility to be inflated only up to a clearly set radius. Richter [32] comes to a conclusion that the use of one or the other dilator depends more upon the endoscopist's experience than on the instrument type itself. Pneumatic dilatation is considered by the majority of authors to be the most efficient nonsurgical treatment of achalasia [33–36]. Dilatation technique has not yet been standardized in spite of its wide application in achalasia treatment [37–39].

Values of insufflation pressure that cause muscle fibres splitting have not been determined so far. Insufflation pressure ranging from 200 mmHg to 300 mmHg (5 psi – pound square inch) is used in Europe and Japan, while 450–740 mmHg (9–15 psi) is used in the USA. The higher the pressure, the efficient the method, but also the most frequent perforation. It is advisible to determine the pressure under which the efficacy increases with acceptable range of complications. By analysing 270 perforations, Borotto et al. [40] conclude that the upper limit of 11 psi allows a balloon insufflation with no higher risk for perforation.

The dilemma about dilatation balloon width has not been resolved, as well. Vantreppen and Helllemans [5] suggest a balloon of 4 cm width, while others suggest to start dilatation with a 3 cm balloon and to performe repeated dilations by the use of wider diameters, but not wider than 4.5 cm [20, 41].

The mentioned dilemmas about defining insufflation pressure and balloon diameter we solved by insufflating balloon up to just above pain treshold since that is the pressure under which DES muscle fibers split. It is individual to each patient. In order not to change pain threshold, however, we do not perform premedication, which makes the said method less comfortable to patients.

Insufflation duration for one treatment takes 15–60 s in the USA, and 1–3 min in Europe and Japan. In a prospective study Kim et al.[9] came to a conclusion that insufflation taking more than 1 min do not affect the results of dilatation and that muscle fibers probably split within the first 5–10 s. Duration of maximal insufflation pressure do not affect significantly the results of dilatation, thus leaving to the therapist to make a choice [21]. Like the majority of authors, we decided for maximal insufflation pressure in one minute [42].

Balloon insufflation for one treatment has to be repeated at least once by rising insufflation pressure in the second dilatation or by widening the diameter of a balloon [5]. There are the authors who consider that dilatation has not to be repeated within one treatment [9, 43]. We repeat dilatations within a treatment up to above pain treshold since we suppose that a way to rise dilatation efficacy.

Richter [23] and Cohen et al. [44] consider fluoroscopy necessary, while the majority of authors consider it unnecessary in the control of dilatation and to be used only from time to time.

With the Witzel dilator which is introduced and positioned under endoscopic vision there is no need for fluoroscopy. Combining endoscopic/fluoroscopic vision makes it possible to take advantages of both methods and to minimize their disadvantages. We introduce a dilator under endoscopic vision which is very safe even in sigmoid esophagus, thus reducing exposition to radiography. Fluoroscopy allows good balloon positioning and its keeping in the correct position. The use of a contrast agent in balloon dilatation make it possible to mesure balloon width ant to register all that at radiography.

Esophagogram is required only in patients with simptoms indicating perforation. That is the way to avoid unnecessary radiation and to reduce costs of treatment [16]. The clinical images of both patients clearly indicated perforation and radiography just confirmed it. In spite of the fact that we did esophagogram in all of the patients immediately after the dilatation, the mentioned experience suggests radiography only in case of doubt in perforation.

The majority of authors come to a conclusion that achalasia equally affects both sexes which was confirmed by our study, so that the ratio males to females is 1.2 : 1. There are, however, opposite data, thus some authors claim that achalasia is two times as present in males than in females, while the others claim quite the opposite [42].

Balloon dilatation efficacy measured by the symptome score regarding sex had no statistical significance in our study which is in accordance with data presented by other authors [5, 38, 45–50].

According to our study, the disease is most frequent in the third decade of life, although in females it prevails at 40 to 50 years of age. The average age of our patients was 43 that also corresponds with data from the literature, while Kodakia and Wong [16] state 52, and Mikaeli et al. [49] 35.5 years. There is no significant difference in efficacy of dilatation regarding age. However, dilatation results are worse in patients under 40 with the significance of $p < 0.05$. There is no a generally accepted attitude, however, the majority of authors report worse results in younger patients [1, 38].

Ever since introducing dilatation into the treatment of achalasia, numerous authors had tried to define risk factors that could anticipate the outcome of dilatation and in so doing sellect the patients that would have good response and the others treat surgically.

It is reported most frequently that there is no correlation of the duration of symptoms with good response [20]. In our study we did not find a significant correlation of the duration of symptoms before dilatation with the efficacy of dilatation.

The majority of authors confirmed no correlation of body weight reduction with the efficacy of dilatation, which is also confirmed in our study [5, 51, 52]. In our study, there were patients with a significant body weight loss and excellent results, as well as a low body weight loss and bad results. Higher loss in body weight within a short time period suggests the need to exclude malignacy and perform additional diagnostics not standard for achalasia diagnostics (computed tomography, echo endosonography). These procedures could predict cancer due to perineural myenteric esophageal plexus infiltration by pancreatic and suprarenalis cancers [38].

Vantreppen and Hellemans [5] were the first to point out that monitoring of body weight rise could estimate dilatation efficacy [5]. Body weight loss together with dysphagia is the major symptom of achalasia, thus it seems logical that monitoring of body weight rise could suggest dilatation outcome. In our series, 92% of the patients had body weight loss prior to dilatation, while 80% of the patient had body weight loss after dilatation. Body weight rise directly correlates with dilatation efficacy. So, by monitoring body weight, both physicians and patients could estimate dilatation efficacy in a simple, objective, measurable an acceptable way.

There is a controversy of predicting dilatation outcome on the basis of esophageal lumen width. Ponce et al. [50] reports such correlation having a high significance, while other authors conclude that there is no significant correlation of esophageal lumen width prior to dilatation with dilatation efficacy [9, 20, 41]. In our study there was no significant correlation of esophageal lumen width prior to dilatation which is logically to expect since dilatation is paliative and irreversible.

There is no predictive model which could be used for identification of patients who might have bad dilatation results and refer them to surgical treatment. The majority of authors conclude that worse results could be expected in patients younger than 20 years, esophageal width less than 3 cm, esophageal basal pressure higher than 15 mmHg, and DES pressure higher than 30 mmHg [9, 20, 50, 53].

Some authors state that esophageal scintigraphy could not replace manometry of the esophagus in the diagnostics of motor skill disorder due to high number of false positive findings [53–55]. Our study confirmed that scintigraphy of the esophagus can most objecively estimate dilatation effect in esophageal achalasia.

How many dilatations should be performed to be able to definitively estimate the treatment of achalasia by dilatation? If dilatation is unsuccessful, Vantrepen and Hellemans [5] consider that dilatation efficacy significantly rises by favorable dilatations, and recommend maximally four repeated dilatations. Richter [23] and the American Association of Gastrointestinal Endoscopy recommend two dilatations, and than refer a patient to surgery if dilatation was not efficient. Kodakia and Wong [16] state that increasing the number of dilatations does not significantly increase dilatation efficacy. Lake and Wong [42] come to a conclusion that dilatation efficacy rises up to two reinterventions, and that higher number of dilatations is not justified also due to treatment costs. Our study confirmed that dilatation efficacy rises with one or two redilatations. We did not have patients with more than three dilatations. In about two thirds of the patients excellent results were obtained after first dilatation, while after repeated dilatations the results were excellent or good in 89% of the patients. In other words, if repeated dilatations were not performed, the 12 more patients would have been operated on.

Perforation is the major complication of dilatation in achalasia affecting 2% to 6% of dilated patients. There were two perforations in our study, both in males, of which one occured in first and one in repeated dilatation. They were lacalized above DES to the left in the form of longitudinal rupture of 2–3 cm. Borotto et al. [40] analysed eight perforations con-

cluding that they are more frequent in patients with less body weight loss and high amplitude of esophageal contraction. Other authors conclude that there are no clearly defined risk factors for perforation, making it impossible to identify patients with a high risk of perforation [1, 5, 40, 44]. Contrary to the fact that the literature tells that the majority of perforations are treated conservatively, both of our patients were operated on.

The application of botulinum toxin remains as alternative for patients with risky operation or dilatation or in those patients who do not accept dilatation for any reason [56–65].

The most recent studies suggest that laparoscopy has good results and that its application increases leaving conventional surgery as alternative [66–68].

Peroral endoscopic myotomy (PEM) was developed by Inoue et al. [68] to ensure less invasive approach to achalasia treatment.

Conclusion

The use of modified balloon dilatation in achalasia treatment resulted in excellent and good results in 88% of the patients. The patients above 40 years as compared to younger ones showed better clinical response. Perforation was recorded in 3.67% of the patients without lethal outcome. A modified dilatation technique is efficious and safe method in the initial achalasia treatment.

R E F E R E N C E S

1. *Kahrilias PJ, Pandolfino JE.* Esophageal neuromuscular function and motilyti disorders. In: *Sleisenger MH, Fordtran JS*, editors. Sleisenger and Fordtran's Gastrointestinal and Liver Disease - Pathophysiology, Diagnosis, Management. 9th ed. Philadelphia: W. B. Saunders; 2010. p. 677−704.
2. *Ruiz-de-León A, Mendoza J, Sevilla-Mantilla C, Fernández AM, Pérez-de-la-Serna J, Gónzalez VA,* et al. Myenteric antiplexus antibodies and class II HLA in achalasia. Dig Dis Sci 2002; 47(1): 15−9.
3. *Spechler SJ.* AGA technical review on treatment of patients with dysphagia caused by benign disorders of the distal esophagus. Gastroenterology 1999; 117(1): 233−54.
4. *Mearin F, Mourelle M, Guarner F, Salas A, Riveros-Moreno V, Moncada S,* et al. Patients with achalasia lack nitric oxide synthase in thegastro-oesophageal junction. Eur J Clin Invest 1993; 23(11): 724−8.
5. *Vantrappen G, Hellemans J.* Treatment of achalasia and related motor disorders. Gastroenterology 1980; 79(1): 144−54.
6. *Bruley des Varannes S, Chevalier J, Pimont S, Le Neel JC, Klotz M, Schafer KH,* et al. Serum from achalasia patients alters neurochemical coding in the myenteric plexus and nitric oxide mediated motor response in normal human fundus. Gut 2006; 55(3): 319−26.
7. *Eckardt VF, Stauf B, Bernhard G.* Chest pain in achalasia: patient characteristics and clinical course. Gastroenterology 1999; 116(6): 1300−4.
8. *Li Y, Tesson BM, Churchill GA, Jansen RC.* Critical reasoning on causal inference in genome-wide linkage and association studies. Trends Genet 2010; 26(12): 493−8.
9. *Kim CH, Cameron AJ, Hsu JJ, Talley NJ, Trastek VF, Pairolero PC,* et al. Achalasia: prospective evaluation of relationship between lower esophageal sphincter pressure, esophageal transit, and esophageal diameter and symptoms in response to pneumatic dilation. Mayo Clin Proc 1993; 68(11): 1067−73.
10. *Bravi I, Nicita MT, Duca P, Grigolon A, Cantù P, Caparello C,* et al. A pneumatic dilation strategy in achalasia: prospective outcome and effects on oesophageal motor function in the long term. Aliment Pharmacol Ther 2010; 31(6): 658−65.
11. *Csendes A, Braghetto I, Burdiles P, Korn O, Csendes P, Henríquez A.* Very late results of esophagomyotomy for patients with achalasia: clinical, endoscopic, histologic, manometric, and acid reflux studies in 67 patients for a mean follow-up of 190 months. Ann Surg 2006; 243(2): 196−203.
12. *Mikaeli J, Bishehsari F, Montazeri G, Mahdavinia M, Yaghoobi M, Darvish-Moghadam S,* et al. Injection of botulinum toxin before pneumatic dilatation in achalasia treatment: a randomized-controlled trial. Aliment Pharmacol Ther 2006; 24(6): 983−9.
13. *Moses PL, Ellis LM, Anees MR, Ho W, Rothstein RI, Meddings JB,* et al. Antineuronal antibodies in idiopathic achalasia and gastro-oesophageal reflux disease. Gut 2003; 52(5): 629−36.
14. *Kroupa R, Hep A, Dolina J, Valek V, Matyasova Z, Prokesova J,* et al. Combined treatment of achalasia - botulinum toxin injection followed by pneumatic dilatation: long-term results. Dis Esophagus 2010; 23(2): 100−5.
15. *van Herwaarden MA, Samsom M, Smout AJ.* Prolonged manometric recordings of oesophagus and lower oesophageal sphincter in achalasia patients. Gut 2001; 49(6): 813−21.
16. *Kadakia SC, Wong RK.* Pneumatic balloon dilation for esophageal achalasia.Gastrointest Endosc Clin N Am 2001; 11(2): 325−46, vii.
17. *Hulselmans M, Vanuytsel T, Degreef T, Sifrim D, Coosemans W, Lerut T,* et al. Long-term outcome of pneumatic dilation in the treatment of achalasia. Clin Gastroenterol Hepatol 2010; 8(1): 30−5.
18. *Eckardt VF.* Clinical presentations and complications of achalasia. Gastrointest Endosc Clin N Am 2001;11(2): 281−92, vi.
19. *Vaezi MF.* Quantitative methods to determine efficacy of treatment in achalasia. Gastrointest Endosc Clin N Am 2001; 11(2): 409−24, viii-ix.
20. *Kadakia SC, Wong RK.* Graded pneumatic dilation using Rigiflex achalasia dilators in patients with primary esophageal achalasia. Am J Gastroenterol 1993; 88(1): 34−8.
21. *Becker K, Biesenbach S, Erckenbrecht JF, Frieling T.* Effect of balloon compliance on symptomatic success of pneumatic dilation in achalasia patients. Z Gastroenterol 2001; 39(10): 831−6.
22. *West RL, Hirsch DP, Bartelsman JF, de Borst J, Ferwerda G, Tytgat GN,* et al. Long term results of pneumatic dilation in achalasia followed for more than 5 years. Am J Gastroenterol 2002; 97(6): 1346−51.
23. *Richter JE.* Comparison and cost analysis of different treatment strategies in achalasia. Gastrointest Endosc Clin N Am 2001; 11(2): 359−70, viii.
24. *Vaezi MF, Baker ME, Achkar E, Richter JE.* Timed barium oesophagram: betterpredictor of long term success after pneumatic dilation in achalasia than symptom assessment. Gut 2002; 50(6): 765−70.
25. *Alonso P, González-Conde B, Macenlle R, Pita S, Vázquez-Iglesias JL.* Achalasia: the usefulness of manometry for evaluation of treatment. Dig Dis Sci 1999; 44(3): 536−41.
26. *Pasricha PJ, Rai R, Ravich WJ, Hendrix TR, Kalloo AN.* Botulinum toxin for achalasia: long-term outcome and predictors of response. Gastroenterol 1996; 110(5): 1410−5.
27. *Bassotti G, D'Onofrio V, Battaglia E, Fiorella S, Dughera L, Iaquinto G,* et al. Treatment with botulinum toxin of octo-nonagerians with oesophageal achalasia: a two-year follow-up study. Aliment Pharmacol Ther 2006; 23(11): 1615−9.
28. *Moretó M, Ojembarrena E, Rodríguez ML.* Endoscopic injection of ethanolamine as a treatment for achalasia: a first report. Endoscopy 1996; 28(7): 539−45.
29. *Deb S, Deschamps C, Allen MS, Nichols FC 3rd, Cassivi SD, Crownhart BS,* et al. Laparoscopic esophageal myotomy for achalasia:

factors affecting functional results. Ann Thorac Surg 2005; 80(4): 1191−4; discussion 1194−5.
30. *Finley CJ, Kondra J, Clifton J, Yee J, Finley R.* Factors associated with postoperative symptoms after laparoscopic Heller myotomy. Ann Thorac Surg 2010; 89(2): 392−6.
31. *Esposito PS, Sosa JL, Sleeman D, Santelices AA.* Laparoscopic management of achalasia. Am Surg 1997; 63(3): 221−3.
32. *Richter JE.* Surgery or pneumatic dilatation for achalasia: a head-to-headcomparison. Now are all the questions answered? Gastroenterology 1989; 97(5): 1340−1.
33. *Lambroza A, Schuman RW.* Pneumatic dilation for achalasia without fluoroscopic guidance: Safetyand efficacy. Am J Gastroenterol 1995; 90(8): 1226−9.
34. *Wehrmann T, Jacoby V, Jung M, Lembcke B, Caspary WF.* Pneumatic dilatation in achalasia with a low-compliance balloon: Results of a 5-year prospective evaluation. Gastrointest Endosc 1995; 42(1): 31−6.
35. *Mearin F, Armengol JR, Chicharro L, Papo M, Balboa A, Malagelada JR.* Forceful dilatation under endoscopic control in the treatment of achalasia: a randomisedtrial of pneumatic versus metallic dilator. Gut 1994; 35(10): 1360−2.
36. *Vaezi MF, Baker ME, Achkar E, Richter JE.* Timed barium oesophagram: better predictor of long term success after pneumatic dilation in achalasia than symptom assessment. Gut 2002; 50(6): 765−70.
37. *Molina EG, Stolman N, Grauer L, Reiner DK, Barkin JS.* Conservative management of esophageal nontrasmural tears after pneumatic dilatation for achalasio.Am J Gastroentrol 1996; 91(1): 15−8.
38. *Smout AJ.* Back to the whale bone?. Gut 1999 44(2): 149−50.
39. *Eckardt VF, Gockel I, Bernhard G.* Pneumatic dilation for achalasia: late results of a prospective follow up investigation. Gut 2004; 53(5): 629−33.
40. *Borotto E, Gaudertic M, Danel B, Samama J, Quartier G, Chaussade S,* et al. Risik factors of oesophageal perforation during pneumatic dilatation for achalasia. Gut 1996; 39(1): 9−12.
41. *Zerbib, F, Thetiot, V, Richy, F, Benajah DA, Message L, Lamouliatte H.* Repeated pneumatic dilations as long-term maintenance therapy for esophageal achalasia. Am J Gastroenterol 2006; 101(4): 692−7.
42. *Lake, JM, Wong, RK.* Review article: the management of achalasia - a comparison of different treatment modalities. Aliment Pharmacol Ther 2006; 24(6): 909−18.
43. *Wong RC Maydonovivith C.* Utility of parameters measred during pneumatic dilatataion as predictors of successful dilatation. Am J Gastroentrol 1996; 91(6): 1126−9.
44. *Cohen S, Parkman HP.* Tretment of achalasia: from whalebone to botulinum toxin. N Engl J Med 1995; 332(12): 815−6.
45. *Lange, O, Bigalke, H, Dengler, R, Wegner F, deGroot M, Wohlfarth K.* Neutralizing antibodies and secondary therapy failure after treatment with botulinum toxin type A: much ado about nothing?. Clin Neuropharmacol 2009; 32(4): 213−8.
46. *Hirota WK, Zuckerman MJ, Adler DG, Davila RE, Egan J, Leighton JA*, et al. ASGE guideline: the role of endoscopy in the surveillance of premalignant conditions of the upper GI tract. Gastrointest Endosc 2006; 63(4): 570−80.
47. *Fioranza V, Messner J, Zfass AM.* Dalayed esophageal perforation follwing pneumatic dilation for achalasia. Gastrointest Endosc 1988; 34(4): 365−6
48. *Pandolfino, JE, Kwiatek, MA, Nealis, T, Bulsiewicz W, Post J, Kahrilas PJ.* Achalasia: a new clinically relevant classification by high-resolution manometry. Gastroenterology 2008; 135(33): 1526−33.
49. *Mikaeli J, Malekzadeh R, Khatibain M, Vahedi R, Ansari R, Soleimani H,* et al. Graded pneumatic dilatation without fluoroscopy in the treatment of achalasia. MJIRI 2000; 14(1): 15−8.
50. *Ponce J, Garrigues V, Pertejo V, Sala T, Berenguer J.* Individual prediction of reponse to pneumatic dilatataion in patients with achalasia. Dig Dis Sci 1996; 41(11): 2135−41.
51. *Abid S, Champin G, Richter JE, McElvien R, Slaughter RL, Koehler RE.* Treatment of achalasia: the best of both worlds. Am J Gastroentrol 1994; 89(7): 979−85.
52. *Vela MF, Richter JE, Khandwala F, Blackstone EH, Wachsberger D, Baker ME,* et al. The long-term efficacy of pneumatic dilatation and Heller myotomy for the treatment of achalasia. Clin Gastroenterol Hepatol 2006; 4(5): 580−7.
53. *Holloway RH, Krosin G, Lange RC, Bane AE, McCallum RW.* Radionuclide esophageal emptying of a solid meal to quantitate result of therapy in achalasia. Gastroenterology 1983; 84(4): 771−6.
54. *Solomon MJ, McLeod RS.* Should we be performing more randomized controlled trials evaluating surgical operations? Surgery 1995; 118(3): 459−67.
55. *DeCaestecker JS, Blackwel JN, Adam RD, Hannan WJ, Brown J, Heading RC.* Clinical value of radionuclide oesophageal transit measurement. Gut 1986; 27(6): 659−66.
56. *Annese V, Bassotti G, Coccia G, Dinelli M, D'Onofrio V, Gatto G,* et al. A multicentre randomised study of intrasphincteric botulinum toxin in patients with oesophageal achalasia. GISMAD Achalasia Study Group. Gut 2000; 46(5): 597−600.
57. *Vaezi MF, Richter JE, Wilcox CM, Schroeder PL, Birgisson S, Slaughter RL,* et al. Botulinum toxin versus pneumatic dilatation in thetreatment of achalasia: a randomised trial. Gut 1999; 44(2): 231−9.
58. *National Institutes of Health Consensus Development Conference Statement, November 12-14, 1990.* Clinical use of botulinum toxin. Arch Neurol 1991; 48(12): 1294−8.
59. *Annese V, Basciani M, Lombardi G, Caruso N, Perri F, Simone P,* et al. Perendoscopic injection of botulinum toxin is effective in achalasia after failure of myotomy or pneumatic dilation. Gastrointest Endosc 1996; 44(4): 461−5.
60. *Doder R, Lukacević S, Perisić N, Jović J, Bozović C.* Botulinum toxin in the treatment of achalasia. Vojnosanit Pregl 1999; 56(3): 315−20. (Serbian)
61. *Fishman VM, Parkman HP, Schiano TD, Hills C, Dabezies MA, Cohen S,* et al. Symptomatic improvement in achalasia after botulinum toxin injection of the lower esophageal sphincter. Am J Gastroenterol 1996; 91(9): 1724−30.
62. *Smith, CD, Stival, A, Howell, DL, Swafford V.* Endoscopic therapy for achalasia before Heller myotomy results in worse outcomes than heller myotomy alone. Ann Surg 2006; 243(5): 579−84; discussion 584−6.
63. *Jankovic J, Brin MF.* Therapeutic use of botulinum toxin. N Engl J Med 1991; 324(17): 1186−94.
64. *Mac Iver R, Liptay M, Johnson Y.* A case of mediastinitis following botulinum toxin type A treatment for achalasia. Nat Clin Pract Gastroenterol Hepatol 2007; 4(10): 579−82.
65. *Rakita S, Bloomston M, Villadolid D, Thometz D, Zervos E, Rosemurgy A.* Esophagotomy during laparoscopic Heller myotomy cannot be predicted by preoperative therapies and does not influence long-term outcome. J Gastrointest Surg 2005; 9(2): 159−64.
66. *Ancona E, Anselmino, Zaninotto G, Costantini M, Rossi M, Bonavina L,* et al. Ecophageal achalasi: laparoscopic versus conventional open Heller-Dor operation. Am J Surg 1995; 170 (3): 265-70.
67. *Ferguson MK, Reeder LB, Olak J.* Results of myotomy and partial fundoplication after pneumatic dilatation for achalasia. Ann Thorac Surg 1996; 62(62): 327−30.
68. *Inoue H, Minami H, Kobayashi Y, Sato Y, Kaga M, Suzuki M*, at al. Peroral endoscopic myotomy (POEM) for esophageal achalasia. Enoscopy 2010; 42(4): 265−71.

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Size of the lower third molar space in relation to age in Serbian population

Zavisnost veličine donjeg retromolarnog prostora od uzrasta u srpskoj populaciji

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Abstract

Background/Aim. It is considered that the shortage of space is the major cause of the third molar impaction. The aim of this study was to establish the frequency of insufficient lower third molar eruption space in Serbian population, to question the differences in this frequency in the subjects of different age, to determine the influence of the lower third molar space (retromolar space) size on third molar eruption, and to investigate a possible correlation between the size of gonial angle and the space/third molar width ratio. **Methods.** Digital orthopantomograms were taken from 93 patients divided into two groups: early adult (16–18 years of age) and adult (18–26) patients. Retromolar space, mesiodistal third molar crown width, gonial angle and eruption levels were measured. **Results.** The space/third molar width in early adult subjects was smaller ($p < 0.0001$) and insufficient space was significantly more frequent ($p = 0.0003$) than in adult patients. Considerably more third molars erupted in case of enough space in both age groups ($p < 0.0001$). There was no difference between the means of gonial angle size in relations to the available space. **Conclusions.** The retromolar space/third molar width ratio is more favorable in adult subjects. Gonial angle is not in correlation with the retromolar space/third molar width ratio.

Key words:
molar, third; tooth eruption; tooth impaction; adolescent; adult; serbia.

Apstrakt

Uvod/Cilj. Smatra se da je nedostatak prostora glavni uzrok ukleštenja trećeg kutnjaka. Cilj ove studije bio je da se ustanovi učestalost nedovoljnog prostora za nicanje umnjaka u srpskoj populaciji, da se ispitaju razlike u ovoj učestalosti kod mlađih odraslih i odraslih ispitanika, da se odredi uticaj veličine retromolarnog prostora na nicanje umnjaka, kao i da se ispita povezanost između veličine ugla mandibule i odnosa između veličine retromolarnog prostora i meziodistalne širine umnjaka. **Metode.** U istraživanje su bila uključena 93 ispitanika podeljena u dve starosne kategorije: mlađi odrasli (16–18 godina) i odrasli (18–26 godina) ispitanici. Kod svakog pacijenta na digitalnom ortopantomogramu mereni su: retromolarni prostor, meziodistalna širina umnjaka, nivo izniklosti umnjaka i ugao mandibule. **Rezultati.** Odnos između veličine retromolarnog prostora i meziodistalne širine umnjaka bio je statistički značajno manji ($p < 0.0001$) kod mlađih ispitanika. Takođe, nedostatak prostora sretao se značajno češće u istoj starosnoj kategoriji ($p = 0.0003$). Prilikom poređenja nivoa izniklosti u obe starosne kategorije nađena je visoka statistička značajnost ($p < 0.0001$) u korist grupe sa dovoljnim prostorom za nicanje umnjaka. **Zaključak.** Značajno više umnjaka ima mesta za pravilno smeštanje u zubni niz nakon 18 godina života što navodi na zaključak da rast retromolarnog prostora nije završen u 16. godini. Ugao mandibule nije u korelaciji sa odnosom retromolarnog prostora i meziodistalnog promera umnjaka.

Ključne reči:
umnjak; zub, nicanje; zub, impakcija; adolescencija; odrasle osobe; srbija.

Introduction

Surgical extraction of impacted third molar is among the most frequently performed oral–surgical procedures [1]. It was reported that the lower third molar is the second most commonly impacted tooth in the human jaw [2–4]. Insufficient jaw development will primarily affect the eruption space of wisdom teeth, as they are the last ones to erupt into the oral cavity. In addition to inappropriate inclination of the lower third molar, the lack of space is considerate as main cause of

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its impaction [5]. Because of this, consideration of these teeth is a part of overall dental examination and treatment plan.

In the lower jaw, the lower third molar space (retromolar space) borders are well defined – the distal surface of the second molar crown and the anterior border of the mandibular ramus. The mesiodistal crown width of the third molar should be smaller than this space if its eruption is to be expected. Ganss et al. [6] claimed that in this case, almost 70% of wisdom teeth would erupt. However, this space is insufficient in a significant number of individuals.

It was considered that the growth of lower retromolar space should not be expected after the age of 16 [5, 7]. On the other hand, Chen et al. [8] reported that there is a significant expansion of this space between the age of 16 and 18. This issue is clinically significant, since possibility to predict impaction of lower third molar in an early stage would favor the decision to remove it easily before the roots are fully formed. However, if such prediction is based on a wrong assumption that retromolar space will not enlarge in the future, some of those surgical procedures would not be justified.

Several researchers also investigated the correlation between the size of gonial angle and the retromolar space width, as both variables are dependent on mandibular growth [9–11]. As the results are conflicting [9, 11, 12], it is interesting to evaluate if size of the gonial angle might be used as a predictor of the lower third molar impaction.

It can be assumed that facial growth, jaw size and tooth size differ among races and populations. Since there have been very few research articles on this issue based on Serbian population [13], it might be interesting to compare some of those variables in our material with results from studies reported for other populations.

Therefore, the aims of this study was to establish the frequency of insufficient space for lower third molar eruption in Serbian population, to determine the influence of this fact on third molar eruption, to investigate whether there are differences in this variable between different age groups and to analyze the relationship between the retromolar space and the gonial angle size.

Methods

A total of 93 subjects (41 males and 52 females) between 16 and 26 years and with no history of previous orthodontic treatment were included in this study. Exclusion criteria were previous extraction or hypodontia of any tooth and some particular angulations of the lower third molar (buccooral position and distal angulations for more than 10 degrees). The study took place at The Clinic of Orthodontics, School of Dentistry, University of Belgrade. The participants were divided into two age groups: the early adult group – subjects from 16 to 18 years of age and the adult group – subjects from 18 to 26 years.

The total sample consisted of 164 lower third molars, 85 on the left and 79 on the right side. The early adult group included 62 third molars (23 from males and 39 from females), and the adult group included 102 third molars (45 from males and 57 from females).

Digital orthopantomograms (Planmeca, Promax; performed at 66–70 kV; 11–14 mA; 6.2 s exposure time; pulse x-ray) were taken and, on acetate paper attached to radiographs, the following planes, lines, and angles were drawn (Figure 1): occlusal plane (OP) – line connecting midpoint of the vertical overlap of the central incisors and the most distal contact point of upper and lower teeth; mesiodistal crown width of the lower third molar (MW) – measured as the greatest diameter of the crown; tangent line (TL) – drawn through the most distal points on the crown and root of the second molar; retromolar space (RS) – measured as a length of the line drawn along the occlusal plane from the point it bisects TL to the point it bisects the anterior border of the ramus; space/third molar width ratio – calculated by dividing RS with MW; gonial angle formed between the tangent line to the posterior border of the mandibular ramus and the tangent line to the lower border of the mandibular corpus; eruption level – measured according to the classification of Pell and Gregory [14]: A level – the occlusal surface of the third molar is leveled or nearly leveled as the occlusal surface of the second molar, B level – the occlusal surface of the third molar is between the occlusal surface of the second molar and its cervical line, C level – the occlusal surface of the third molar is below the cervical line of the second molar.

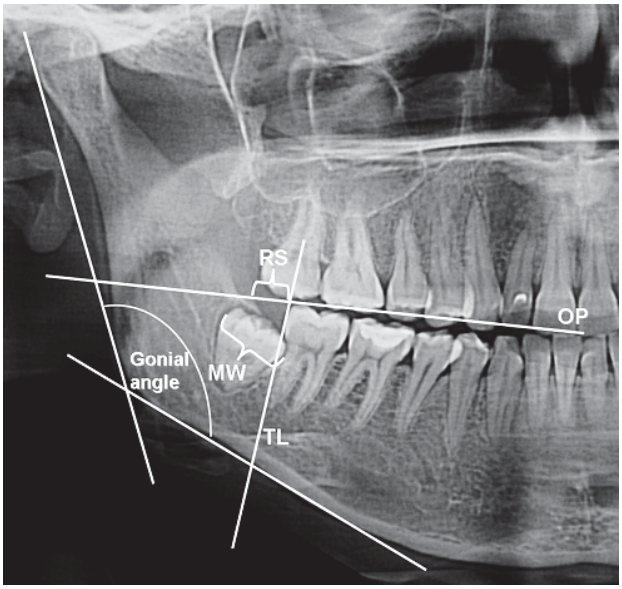

Fig. 1 – Linear and angular measurements on orthopantomogram
RS – retromolar space; MW – mesiodistal width of the third molar; OP – occulasal plane; TL – tangent line.

After calculating space/third molar width ratio, both age groups were divided into two subgroups the ES subgroup with enough space for third molar eruption (space/width ratio ≥ 1), and the NS subgroup with no enough space for third molar eruption (space/width ratio < 1).

All orthopantomograms were interpreted by the same examiner.

The arithmetic mean and standard deviation were calculated for each continuous variable. The frequency and percentages were displayed for categorical variables. Compari-

son of the continuous variables between genders and sides was made using the Student's *t*-test and Mann Whitney's test. Statistical differences between frequencies were tested with Pearson's χ^2 test and Fisher's test. Statistical analyses were performed in R 2.11 statistical software package (R Foundation, Vienna, Austria).

Results

In the early adult group the majority (more than 80%) of investigated third molars did not have enough space for eruption. However, in the adult group, this was the case with about half of the third molars (Table 1).

Table 1
Distribution of lower third molars in two age groups in relation to the available space for eruption

Patients	Subgroups of patients		*p*
	NS n (%)	ES n (%)	(χ^2 test)
Male			
early adult	18 (78.26)	5 (21.74)	0.04
adult	24 (53.33)	21 (46.67)	
Female			
early adult	34 (87.18)	5 (12.82)	0.003
adult	34 (59.65)	23 (40.35)	
Total			
early adult	52 (83.87)	58 (56.86)	0.0003
adult	10 (16.13)	44 (43.13)	

Early adult – subjects aged 16 to 18 years; Adult – subjects older than 18 years; ES – third molars with enough space for their eruption [RM (retromolar space)/MD (mesiodistal crown with) ≥ 1]; NS – third molars without enough space for its eruption (RM/MD < 1).

These differences proved to be statistically significant, both in the whole sample and when data on genders were extrapolated. Comparisons between genders and between the left and right side showed no significant differences. Comparing male and female subjects within the these age groups, the same results were obtained.

In order to confirm these results, mean values of the space/third molar width ratio for early adult and adult subjects were calculated and the differences between them were tested (Table 2). The results showed significantly smaller space/third molar width ratio in younger patients ($p < 0.0001$). Comparing the means of this parameter between males and females, no significant difference was observed.

Table 2
Age dependence of the space/third molar crown width ratio in males and females

Patients	Space/crown ratio ($\bar{x} \pm SD$)	*p* (*t*-test)
Male		
early adult	0.62 ± 0.44	0.0007
adult	1.01 ± 0.43	
Female		
early adult	0.67 ± 0.26	0.006
adult	0.84 ± 0.37	
Total		
early adult	0.64 ± 0.32	< 0.0001
adult	0.92 ± 0.40	

Early adult – subjects aged 16 to 18 years; Adult – subjects older than 18 years; space/crown ratio – RM (retromolar space) divided by MD (mesiodistal crown width).

In the patients from the early adult group, the highest number of third molars was in the C-position, according to the Pell-Gregory classification. This was particularly the case in the third molars with enough space for their eruption in the NS subgroup, in contrast to the third molars with enough space for their eruption in the ES subgroup where more of the third molars were in the A-position (Table 3). On the other hand, in the adult group, the highest number of the third molars was in the A-position, clearly indicating their eruption over time. Despite this, in the NS subgroup more than half of the investigated teeth were in the C position while almost 90% of the third molars reached the occlusal plane in the ES subgroup. Differences between ES and NS subgroups were statistically significant in both age groups.

There were no differences between the mean values of the gonial angle size in relation to the available space (Table 4). The average mandibular angle for the whole group was 124.39 on the left and 123.45 degrees on the right side ($p > 0.05$). There were no significant differences in mean values of this angle between genders and between left and right sides.

Table 3
Third molar eruption level in relation to the available space in the mandible in two age groups

Patients	Level of eruption (the Pells Gregory classification), n (%)			*p*
	A	B	C	(χ^2 test)
Early adult				
NS	8 (15.38)	15 (28.85)	29 (55.77)	0.008
ES	6 (60.00)	1 (10.00)	3 (30.00)	
Adult				
NS	14 (24.14)	10 (17.24)	34 (58.62)	< 0.0001
ES	39 (88.64)	1 (2.27)	4 (9.09)	
Total				
NS	22 (20.00)	25 (22.72)	63 (57.27)	< 0.0001
ES	45 (83.33)	2 (3.70)	7 (12.96)	

Early adult – subjects aged 16 to 18 years; Adult – subjects older than 18 years; ES – third molars with enough space for its eruption [RM (retromolar space)/MD (mesiodistal crown with) < 1]; NS – third molars without enough space for its eruption (RM/MD < 1).

Table 4

Gonial angle size in relation to the available space in the mandible in two age groups

Mandible side	Early adult		Adult	
	($\bar{x}$ ± SD)	p*	($\bar{x}$ ± SD)	p*
Left				
NS	126.4 ± 6.63	0.16	125.4 ± 8.02	0.06
ES	123.2 ± 13.03		121.1 ± 7.90	
Right				
NS	126.4 ± 6.79	0.80	120.8 ± 7.2	0.50
ES	127.8 ± 13.66		122 ± 7.76	

Early adult – subjects aged 16 to 18 years; Adult – subjects older than 18 years; ES – third molars with enough space for its eruption [(RM (retromolar space)/MD (mesiodistal crown with) < 1]; NS – third molars without enough space for its eruption (RM/MD < 1); *Mann-Whitney test .

Discussion

The lack of space in human jaws has been a topic of interest for a long time. The mandibular retromolar space is one of the most investigated parameters for two reasons: the lower third molars are the second most frequently impacted teeth [2–4] and the lack of space is considered to be the major cause of this[9]. Therefore, the analysis of this space should be carefully performed, especially in young patients.

Two main methods have been used for estimation of the available retromolar space: measurement of the distance between the center of the ramus (Xi point) and the distal aspect of the lower second molar [15, 16], and measurement of the distance between the anterior edge of the ramus and the distal surface of the lower second molar [6, 12, 17]. Olive and Basford [17] reported that the use of the first method could not be supported.

Many studies have demonstrated that orthopantomography can give reliable measurements of the skeletal and dental structures as can lateral cephalogram [6, 18–21]. The advantage of the orthopantomogram is evident when measuring right and left side because there is no superimposition, which is present at lateral cephalograms. Furthermore, digital technology gives more clear radiograms and analysis on them is easier. However, possible distortions and magnifications in the molar region can lead to unreliable linear measurements on the orthopantomogram [6, 20, 22]. Therefore, the space/third molar width ratio was used as a parameter for space analyses because these irregularities will affect the retromolar space width as well as the third molar width, but the ratio will remain constant. Moreover, Olive and Basford [17] concluded that the space/width ratio provides reliable assessment of the available retromolar space for the third molar eruption and that orthopantomogram gives the best estimation of the required ratio, while the lateral cephalogram is uncertain. Lerheim and Svanses [20] showed that orthopantomogram does not change the size of the gonial angle and Mattila et al. [21] concluded that it is more obvious choice for determination of the gonial angles than lateral cephalograms.

It is considered that the shortage of space is the major cause of the third molar impaction [11]. Kahl et al. [23] found that the majority (97.40%) of impacted teeth did not have enough space. After 7 years of observation, Ganss et al. [6] concluded that, if the space/third molar width ratio is larger than 1, most of wisdom teeth would ultimately enter the arch (almost 70%). Many authors supported this observation. Bjork et al. [12] reported that the third molar space was reduced in 90% of cases of its impaction. Hattab and Alihaija [9] found that the space/third molar width ratio was significantly larger in the group of teeth that had erupted than in the impacted group. In addition, in the impacted group, in approximately 80% of investigated teeth, this ratio was smaller than 1, whereas in the erupted group, in 69% it was larger than 1 [9]. Olive and Basford [17] concluded that prognosis for the third molar eruption is favorable if the ratio is equal or greater than 1, while Uthman [10] found even smaller minimum values for successful eruption (0.88 for males and 0.83 for females).

Our results showed significantly more erupted third molars in the enough space (ES) subgroups, regardless of patients age (Table 3). In the early adult group, the difference reached the significance of $p = 0.008$ and in the adult group it was even higher ($p < 0.0001$). It is interesting that these differences proved to be statistically significant even in the early adult group, although it is the period of life in which third molars just begin to erupt. Altogether these results are in agreement with previous studies, thus supporting the opinion that the lack of space can delay or disable the third molar eruption and enough space, among other factors, favors its eruption.

One of the aims of this study was to investigate the frequency of insufficient retromolar space in Serbian population as it is considered the main cause of third molar impaction. Although, there are differences between early adult and adult subjects, high prevalence of shortage of retromolar space was evident (Table 1).

The question we also posed was weather the third molar space can be measured in the age of 16 without making wrong assessment about the future outcomes. Ganss et al. [6] reported that the space/width ratio remained almost constant between 16 and 20 years of age in the impacted group and increased insignificantly in the erupted group. The investigation of Bjork [24] showed no increase of posterior dental arch after the age of 14 for girls, and the age of 16 for boys. Ledyard [7] also found no expanding of this area after the age of 16. Niedzielska et al. [5] confirmed this observation and concluded that eruption or non-eruption can be adequately predicted in young adults.

Nevertheless, it was also shown that some significant changes can happen in the size of retromolar space after the age of 16 [8]. It was reported that total increases from 13 to 18 years

of age were 5.12 mm for girls and 5.79 mm for boys. Also, significant annual increase for boys between 16 and 17 years of age (average 1.20 ± 0.02 mm) and for girls between 17 and 18 years of age (1.32 ± 0.04 mm) was found. We found that this increasing is important and we consider that the retromolar space size cannot be adequately assumed in the age of 16.

Our results show that in early adult patients lack of space is significantly more frequent than in adults ($p = 0.04$ in male and $p = 0.009$ in female subjects) (Table 1). Moreover, the means of the space/third molar width ratio were significantly larger in older subjects (Table 2). For such strong statistical significance, we find no other explanation than the fact that retromolar space grows after the age of 16. This growth will, during time, lead to an improvement of the space/third molar width ratio. We tested the differences between means of space/third molar width ratio and frequencies of insufficient space in younger and older subjects, so it could be more obvious that decision concerning third molar removal can be unreliable in early adulthood.

Chen et al. [8] found differences between genders, but this was not observed in our study. However, we divided subjects in 16–18 years of age as the early adult and from 18–26 years of age as the adult group and compared differences between them. Chen et al. [8] analyzed differences between genders annually and found significant retromolar growth for girls at the age 17 and for boys at the age 16. This was not observed in our study as both male and female subjects showed significant growth between the age of 16 and 18 (in our study – early adults).

Average gonial angle in our sample was 123.45 degrees on the right and 124.39 degrees on the left side, whereas in Finish population, it was 128.3 degrees [25]. In Jordanian population, Hattab and Alihaija [9] reported smaller average gonial angle (120.8 degrees). Richardson [11] and Bojrk et al. [12] had reported that smaller gonial angle was more common among subjects with impacted third molars. On the other hand, Hattab and Alihaija [9] concluded that there was no relationship between the size of the gonial angle and impaction of the third molars. If the size of the gonial angle is different in subject with impacted than in those with erupted lower third molars, than the impaction is caused by insufficient space as these two parameters depend on mandibular growth. Therefore, we compared sizes of gonial angle of the NS and ES subgroup, without concerning the eruption status. Our findings show that the size of gonial angle cannot be an indicator of future outcomes of the space/third molar width ratio because there was no relationship between these two parameters (Table 4).

Conclusion

The retromolar space/third molar width ratio differs between subjects aging from 16 to 18 years and subjects older than 18 years. Insufficient space was more frequent in younger group and the mean value of the space/third molar width ratio was significantly smaller in the same group. Therefore, the decision about the removal of the third molar in young adults should be made with caution.

Gonial angle size was not in correlation with the retromolar space/third molar width ratio and the use of this parameter as a predicting factor for future outcomes of this ratio cannot be recommended.

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REFERENCES

1. *Mercier P, Precious D.* Risks and benefits of removal of impacted third molars. A critical review of the literature. Int J Oral Maxillofac Surg. 1992; 21(1):17−27.
2. *Bishara SE, Anreasen G.* Third Molars: a review. Am J Orthod 1983; 83(2): 131−7.
3. *Dachi SF, Howell FV.* A survey of 3, 874 routine full-month radiographs. II. A study of impacted teeth. Oral Surg Oral Med Oral Pathol 1961; 14: 1165−9.
4. *Grover PS, Lorton L.* The incidence of unerupted permanent teeth and related clinical cases. Oral Surg Oral Med Oral Pathol 1985; 59(4): 420−5.
5. *Niedzielska IA, Drugacz J, Kus N, Kreska J.* Panoramic radiographic predictors of mandibular third molar eruption. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006; 102(2): 154−8; discussion 159.
6. *Ganss C, Hochban W, Keilbassa AM, Umstad HE.* Prognosis of third molar eruptrion Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1993; 76(6): 688−93.
7. *Ledyard BC Jr.* A study of the mandibular third molar area. Am J Orthod 1953; 39: 366−9.
8. *Chen LL, Xu TM, Jiang JH, Zhang XZ, Lin JX.* Longitudinal changes in mandibular arch posterior space in adolescents with normal occlusion. Am J Orthod Dentofac Orthop 2010; 137(2): 187−93.
9. *Hattab FN, Alihaija ES.* Radiographic evaluation of mandibular third molar eruption space Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999; 88(3): 285−91.
10. *Uthman AT.* Retromolar space analysis in relation to selected linear and angular maesurments for an Iraqi sample Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007; 104(4): e76−e82.
11. *Richardson ME.* The etiology and prediction of mandibular third molar eruption. Angle Orthod 1977; 47(3): 165−72.
12. *Bjork A, Jensen E, Palling M.* Mandibular growth and third molar impaction. Acta Odont Scand 1956; 14: 231−72.
13. *Nedeljkovic N, Stamenkovic Z, Tatic Z, Racic A.* Possibilty of the lower third molar eruption - radiographic analysis. Vojnosanit Pregl 2006; 63(2): 159–62. (Serbian)
14. *Pell GJ, Gregory GT.* Impacted mandibular third molars: classification and modified technique for removal. Dent Digest 1933: 39: 330−8.

15. *Ricketts RM, Turley S, Chaconas S, Schulhof RJ.* Third molar enucleation: diagnosis and technique. J Calif Dent Assoc 1976; 4(4): 52−7.
16. *Forsberg CM, Vingren B, Wesslen U.* Mandibular third molar eruption in relation to available space as assessed on lateral cephalograms. Swed Dent J 1989; 13(1−2): 23−31.
17. *Olive R, Basford K.* Reliability and validity of lower third molar space- assessment techniques. Am J Orthod 1981; 79(1): 45−53.
18. *Haavikko K, Altonen M, Mattila K.* Predicting angulational development and eruption of the lower third molar. Angle Orthod 1978; 48(1): 39−48.
19. *Uthman AT.* Estimation of some linear and angular measurements of the mandible by orthopantomograph. Iraqi Dent J 2002; 30: 215−20.
20. *Lerheim TA, Svanses DB.* Reproducibility of rotational panoramic radiography: mandibular linear dimensions and angles. Am J Orthod Dentofacial Orthop 1986; 90(1): 45−51.
21. *Mattila K, Altonen M, Haavikko K.* Determination of the gonial angle from the orthopantomogram. Angle Orthod 1977; 47(2): 107−10.
22. *Laster WS, Ludlow JB, Bailey LJ, Hershey HG.* Accuracy of measurements of mandibular anatomy and prediction of asymmetry in panoramic radiographic images. Dentomaxillofac Radiol 2005; 34(6): 343−9.
23. *Kahl B, Gerlach KL, Hilgers RD.* A long-term, follow-up, radiographic evaluation of asymptomatic impacted third molars in orthodontically treated patients. Int J Oral Maxillofac Surg 1994; 23(5): 279−85.
24. *Bjork A.* Mandibular growth and third molar impaction. Eur J Orthod 1956; 32: 164–97.
25. *Altonen M, Haavikko K, Mattila K.* Developmental position of lower third molar in relation to gonial angle and lower second molar. Angle Orthod 1977; 47(4): 249−55.

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Reliability of conventional shade guides in teeth color determination

Pouzdanost primene konvencionalnih ključeva za određivanje boje zuba

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Abstract

Background/Aim. Color matching in prosthodontic therapy is a very important task because it influences the esthetic value of dental restorations. Visual shade matching represents the most frequently applied method in clinical practice. Instrumental measurements provide objective and quantified data in color assessment of natural teeth and restorations. In instrumental shade analysis, the goal is to achieve the smallest ΔE value possible, indicating the most accurate shade match. The aim of this study was to evaluate the reliability of commercially available ceramic shade guides. **Methods.** VITA Easyshade spectrophotometer (VITA, Germany) was used for instrumental color determination. Utilizing this device, color samples of ten VITA Classical and ten VITA 3D – Master shade guides were analyzed. Each color sample from all shade guides was measured three times and the basic parameters of color quality were examined: ΔL, ΔC, ΔH, ΔE, ΔElc. Based on these parameters spectrophotometer marks the shade matching as good, fair or adjust. **Results.** After performing 1,248 measurements of ceramic color samples, frequency of evaluations adjust, fair and good were statistically significantly different between VITA Classical and VITA 3D Master shade guides (p = 0.002). There were 27.1% cases scored as adjust, 66.3% as fair and 6.7% as good. In VITA 3D – Master shade guides 30.9% cases were evaluated as adjust, 66.4% as fair and 2.7% cases as good. **Conclusion.** Color samples from different shade guides, produced by the same manufacturer, show variability in basic color parameters, which once again proves the lack of precision and nonuniformity of the conventional method.

Key words:
prosthesis coloring; spectrophotometry; esthetics, dental.

Apstrakt

Uvod/Cilj. Određivanje boje zuba u protetskoj terapiji predstavlja veoma važan zadatak jer utiče na prirodan izgled i estetsku vrednost zubnih nadoknada. Vizuelni metod određivanja boje zuba najčešće se koristi u kliničkoj praksi. Instrumentalna merenja pružaju objektivne i kvantifikovane podatke u proceni boje prirodnih zuba i restauracija. U instrumentalnoj analizi boje cilj je da se postigne najmanja moguća vrednost ΔE, što predstavlja najtačniji izbor nijanse. Cilj ovog istraživanja bio je da se utvrdi pouzdanost najčešće korišćenih ključeva za određivanje boje zuba. **Metode.** Za instrumentalni izbor boje korišćen je *VITA Easyshade* spektrofotometar (*VITA*, *Germany*). Uz pomoć ovog uređaja, analizirani su uzorci boja 10 *VITA Classical* i 10 *VITA* 3D – *Master* ključeva boja. Svaki uzorak boje analiziran je tri puta i ispitivani su osnovni parametri kvaliteta boje: ΔL, ΔC, ΔH, ΔE, ΔElc. Stepen poklapanje boje nadoknade sa ciljnom nijansom spektrofotometar izražava kroz tri ocene kvaliteta: *good*, *fair* i *adjust*. **Rezultati.** Nakon izvršenih 1 248 merenja keramičkih uzoraka boje, frekvencije ocena *adjust*, *fair* i *good* statistički su se značajno razlikovale između *VITA Classical* i *VITA* 3D – *Master* ključeva boja (p = 0.002). U *VITA Classical* ključu boja bilo je 27,1% ocene *adjust*, 66,3% *fair* i 6,7% ocene *good*. U *VITA* 3D – *Master* ključu boja bilo je 30,9% ocene *adjust*, 66,4% *fair* i 2,7% ocene *good*. **Zaključak.** Uzorci boje iz različitih ključeva boja proizvedenih od istog proizvođača, pokazuju varijabilnost u osnovnim parametrima boje, što ukazuje na nepreciznost i neuniformnost konvencionalne metode.

Ključne reči:
zubna proteza, boja; spektrofotometrija; zub, estetika.

Introduction

Color matching in prosthodontic therapy is a very important task because it influences the natural appearance and esthetic outcome of dental restorations. According to the research of Kawaragi et al. [1], over 80% of patients are not satisfied with the color of metal-ceramic crowns in esthetic region compared to natural tooth.

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Color is a special type of psychophysical sensation in the eye caused by visible light [2]. Color perception depends on four levels: light source, an observed object, the eye and the brain. Without light and proper illumination, color can be neither accurately perceived nor correctly evaluated. The human eye can perceive only the wavelengths of light from the visible light spectrum, in physical terms 400–700 nm [3]. Colorimetry, the science of color, has been developed to quantify and describe physically the human color perception. The only internationally recognized system for color measurement is Commision Internationale de l'Eclairage (CIE) system established in 1931 [4].

There are two color matching methods in dentistry: visual (conventional) and instrumental. Visual shade determination, when comparing to patient's tooth with color standard, is the most frequently applied method in clinical dentistry [5]. However, visual shade matching is unreliable, inconsistent and considered highly subjective. This is the result of multiple factors such as individual's physiological and psychological responses to radiant energy stimulation, aging, fatigue, emotions, lighting conditions, object and illumination position, previous eye exposure and metamerism [6, 7]. Furthermore, human eye can detect very small differences in color, the range of available shades in the shade guides is inadequate and it is not possible to translate results into CIE color specifications. Technology-based color matching has been developed to minimize color mismatches during visual color estimation [8, 9]. Most often used instruments are: tristimulus colorimeters, spectroradiometers, digital cameras and spectrophotometers [10]. Most of these instruments use CIELAB color system to determine the color differences (ΔE) between a tooth to be matched and a chosen shade. With CIELAB colorimetry, color can be expressed in terms of three coordinate values (L*, a*, b*), which locate object in a three-dimensional color space. The L* coordinate characterizes the brightness of a color, a* represents the red-green axis and b* value represents the yellow or blue chroma [11]. The ΔE is the shortest distance in the CIEL*a*b* color space between the colors being compared and is given by following equation: $\Delta E = (\Delta L^{*2} + \Delta a^{*2} + \Delta b^{*2})^{1/2}$ (Figure 1) [12].

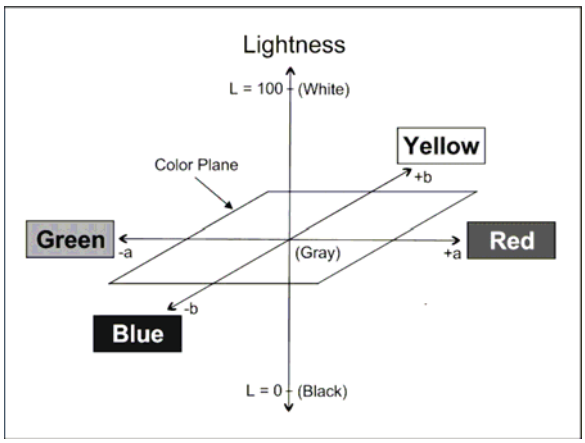

Fig. 1 – *Commision Internationale de e'Eclairage* (CIE) system which locates object in three demensional (brightness of color – L, red green axis-a*, yelow or blue axis – b*) color space.

The aim of this study was to determine the reliability of the most commonly used dental shade guides.

Methods

For instrumental shade selection a VITA Easyshade spectrophotometer (VITA Zahnfabrik Germany; Software version: 11R(b), light source D65, 2° observer) has been used. This device analyzed color samples of randomly selected ten unused VITA Classical and ten VITA 3D – Master shade guides (VITA Zahnfabrik, Germany). The middle third of the shade guide tab was selected for all readings. To ensure an identical position of all samples we made a transparent silicone mold as an attachment on the instrument's probe tip (Zhermack Elite Transparent, Italy). Prior to all the measurements, the instrument was calibrated according to manufacturers' recommendations. Each color sample from all shade guides was fixed and measured 3 separate times and the basic parameters of color quality were being examined: ΔL, ΔC, ΔH, ΔE, ΔElc. We observed these parameters individually and within four groups of colors of VITA Classical shade guides (A–D) and five groups of colors of VITA 3D – Master shade guides [1–5]. The instrument's software is programmed to provide results as differences (ΔE, ΔL, ΔC, ΔH, ΔE_{lc}) from color values, incorporated in the instrument database. There are three components of color: value (L) – the color brightness, chroma (C) – saturation or intensity of color, hue (H) – color itself or "name" of the color. Delta E (ΔE) is the color difference between two shade specimens, while ΔE_{LC} represents ΔE calculated excluding hue.

The degree to which the restoration matches the target shade is given by 3 color quality marks: good, fair and adjust. In this case "good" indicates that the base color of the restoration has very little or no color distinction from the target shade to which it has been established. "Fair" signifies that the base color of restoration may have visible but adequate distinction to which it has been verified. However, this might be unacceptable for an anterior restoration. "Adjust" indicates that the base color of the restoration has visible differences from the target shade from which it has been verified, and the restoration needs to be adjusted to acceptable shade match.

The obtained data were tested for normal distribution by the Kolmogorov-Smirnov test. Quantitative variables were compared (between observed groups of colors) using the Kruskal Wallis nonparametric test. The differences between two groups were assessed by the Mann-Whitney U-test. Qualitative data have been compared using the χ^2 test. The level of $p < 0.05$ was considered statistically significant. Statistical analysis was done using the SPSS 11.0.

Results

The basic parameters of color quality (ΔL, ΔC, ΔH, ΔE, ΔElc) for VITA Classical shade guides were statistically significantly different among the observed four groups of colors (Table 1).

Table 1

VITA Classical shade guide comparisons among the observed four groups of colors

Parameters	Colors	Colors		
		b	c	d
ΔL [a]*	a	* *[b]	*	*
	b		*	*
	c			*
ΔC *	a	* *	*	* *
	b		*	* *
	c			*
ΔH *	a	*	*	*
	b		*	*
	c			*
ΔE *	a	*	*	*
	b		*	*
	c			*
ΔE_{lc} *	a	*	*	*
	b		*	*
	c			*

[a]**Kruskal Wallis test (comparisons among all five color groups);** [b]**Mann Whitney U-test (multiple comparisons);** *__statistically significant;__ *__not statistically significant; L – color brightness; C – chroma saturation; H – "name" of the color; ΔE – color difference between two shade specimens;** ΔE_{lc} **– ΔE calculated excluding hue (H).**

The highest value of ΔL parameter was observed in the group C of colors and the lowest in the group D (Figure 2). The lowest values of ΔE were observed in the group C and the highest in the group D of colors (Figure 3). For all the other observed parameters the results are shown in Table 2 and Figures 4, 5 and 6. Table 2 shows the value of these parameters for all colors of VITA Classical shade guides.

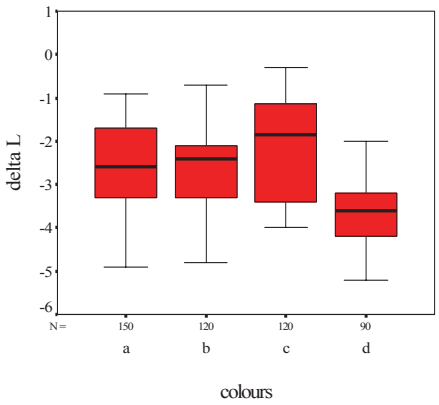

Fig. 2 – Color brightness difference (ΔL).

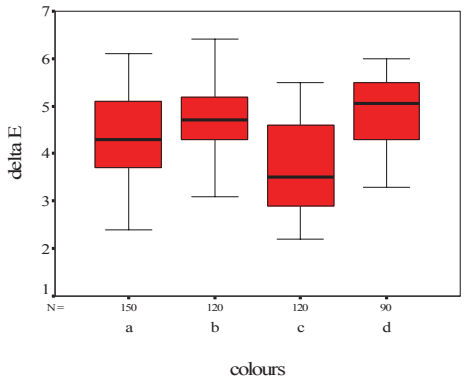

Fig. 3 – Color difference between two shade specimens (ΔE).

Comparisons of basic parameters of color quality (ΔL, ΔC, ΔH, ΔE, ΔElc) between the observed five groups of colors in VITA 3D – Master shade guides, showed statistically significant differences. Table 3 shows the results of multiple comparisons among the observed five groups of colors. ΔL parameter had the highest values in the group 5 of colors, and the

Table 2

VITA Classical shade guide – prameters of color quality

Colors	ΔL	ΔC	ΔH	ΔE	ΔE_{lc}
A1	-3,57 ± 0,74	-3,50 ± 0,43	1,60 ± 0,75	5,07 ± 0,52	5,05 ± 0,52
A2	-2,74 ± 0,44	-3,04 ± 0,64	1,73 ± 0,52	4,20 ± 0,33	4,18 ± 0,34
A3	-3,39 ± 0,60	-4,14 ± 0,39	2,28 ± 0,40	5,41 ± 0,57	5,36 ± 0,56
A3,5	-1,37 ± 0,26	-3,02 ± 0,69	2,14 ± 0,21	3,41 ± 0,61	3,33 ± 0,63
A4	-1,76 ± 0,24	-3,03 ± 0,29	4,15 ± 0,24	3,76 ± 0,33	3,54 ± 0,39
B1	-4,16 ± 0,37	-2,13 ± 1,39	1,27 ± 0,50	4,88 ± 0,39	4,87 ± 0,40
B2	-1,90 ± 0,48	-4,01 ± 0,80	4,36 ± 0,63	4,60 ± 0,79	4,44 ± 0,82
B3	-2,51 ± 0,48	-3,47 ± 3,55	2,84 ± 0,62	4,43 ± 0,55	4,32 ± 0,57
B4	-2,30 ± 0,31	-4,16 ± 0,67	3,72 ± 0,52	4,98 ± 0,63	4,77 ± 0,67
C1	-3,54 ± 0,38	-2,65 ± 0,38	-0,96 ± 3,19	4,43 ± 0,47	4,42 ± 0,46
C2	-3,06 ± 0,44	-3,74 ± 0,74	2,81 ± 0,81	4,82 ± 0,45	4,74 ± 0,47
C3	-1,32 ± 0,24	-2,16 ± 1,22	2,34 ± 0,92	2,86 ± 0,34	2,76 ± 0,32
C4	-0,84 ± 0,33	-2,74 ± 0,29	2,13 ± 0,67	2,97 ± 0,33	2,89 ± 0,34
D2	-3,73 ± 0,64	-3,45 ± 0,45	-1,40 ± 1,83	5,07 ± 0,52	5,11 ± 0,53
D3	-4,15 ± 0,23	-3,45 ± 0,57	1,50 ± 1,09	5,44 ± 2,89	5,43 ± 0,28
D4	-3,09 ± 0,40	-3,44 ± 0,24	0,33 ± 0,70	4,20 ± 0,38	4,62 ± 0,36

Note: results presented as mean ± standard deviation
L – color brightness; C – chroma saturation; H – "name" of the color; ΔE – color difference between two shade specimens; ΔE_{lc} **– ΔE calculated excluding hue (H).**

Table 3

VITA 3D – Master shade guide – comparisons between observed five groups of colors

Parameters	Colors	Colors 2	3	4	5
ΔL [a]*	1	* [b]	*	*	*
	2		*	*	*
	3			*	*
	4				*
ΔC *	1	*	*	*	*
	2		*	*	*
	3			*	*
	4				*
ΔH *	1	*	*	* *	*
	2		*	*	*
	3			*	*
	4				*
ΔE *	1	* *	*	*	*
	2		*	*	*
	3			*	*
	4				* *
ΔE_{lc} *	1	* *	*	*	*
	2		*	*	*
	3			*	*
	4				*

[a]Kruskal Wallis test (comparisons among all five color groups); [b]Mann Whitney U-test (multiple comparisons);*statistically significant;**not statistically significant; L – color brightness; C – chroma saturation; H – "name" of the color; ΔE – color difference between two shade specimens; ΔE_{lc} – ΔE calculated excluding hue (H).

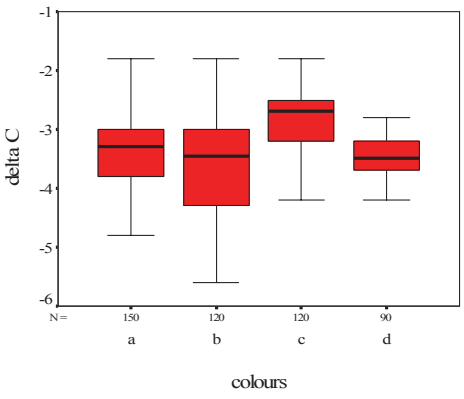

Fig. 4 –Intensity of color difference (ΔC) parameter.

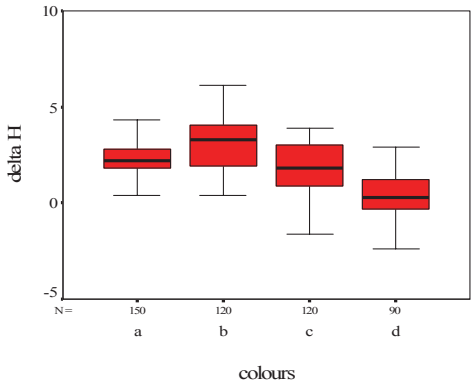

Fig. 5 –Color itself difference (ΔH) parameter.

lowest in the group 1 (Figure 7). For ΔE, the lowest values were observed in the groups 4 and 5 (in this two groups the value of ΔE was similar) and the highest in the group 2 of colors (Figure 8). Figures 9, 10 and 11 show the results of measurements for all the other observed parameters.

Frequencies of adjust, fair and good score were statistically significantly different between the VITA Classical and Vita 3D – Master shade guides (p = 0.002). In the VITA Classical shade guides, there were 27.1% cases scored as adjust, 66.3% had score fair and 6.7% score good. In the VITA 3D – Master shade guides 30.9% cases were evaluated as adjust, 66.4% as fair and 2.7% cases as good (Figure 12, Table 4).

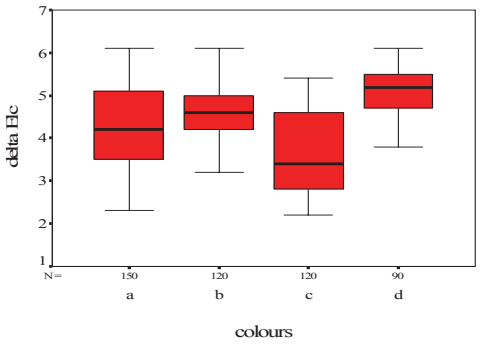

Fig. 6 – Color difference between two shade specimens (ΔE) parameter calculated excluding hue (H).

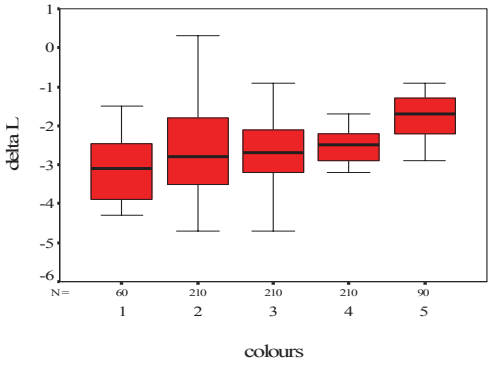

Fig. 7 – Color brightness difference (ΔL) parameter.

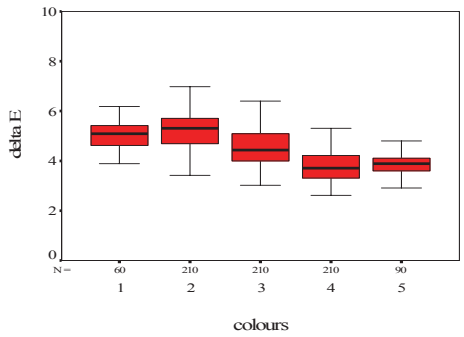

Fig. 8 – Color difference between two shade specimens (ΔE) parameter.

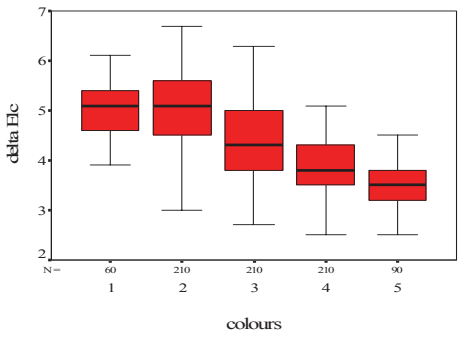

Fig. 11 – Color difference between two shade specimens (ΔE) parameter calculated excluding hue (H).

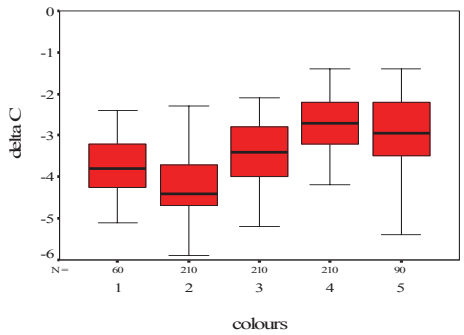

Fig. 9 – Intensity of color difference (ΔC) parameter.

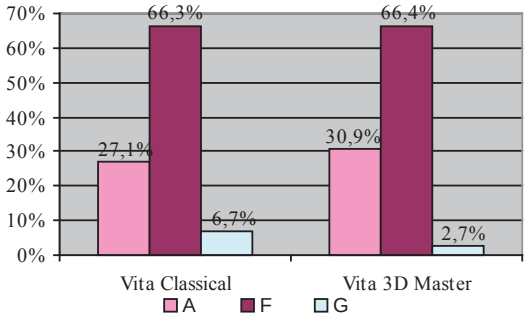

Fig. 12 – Color quality evaluated by two conventional shade guides (A – adjust; F – fair; G – good).

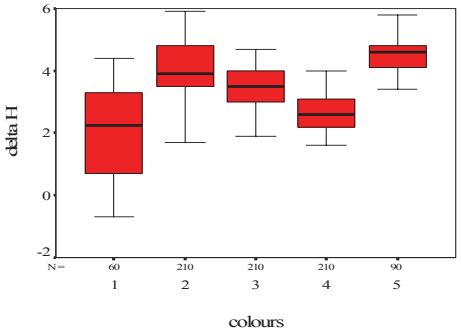

Fig. 10 – Color itself difference (ΔH) parameter.

stances [14]. It is also a color measurement instrument with both reliability and accuracy values grater than 90% [15].

In instrumental shade analysis, the goal is to achieve the smallest ΔE value possible, indicating the most accurate shade match. The ΔE value provides the quantification of the shade difference between the selected shade and the shade to be matched and it does not indicate whether one shade is darker or lighter than another. Brightness might be the most important component of color and must be prioritized during shade selection. Mostly, if the value and chroma are correct, the restoration will be clinically acceptable, even if the hue is slightly off. A hue is not of critical importance during shade selection because of the low concentration of hue in dental

Table 4

ΔE VITA Classical *versus* VITA 3D – Master shade guide

Shade guides	x̄	Med	SD	Min	Max	95%CI
VITA Classical	4,49	4,50	0,93	2,10	8,70	4,43-4,56
VITA 3D Master	4,41	4,50	0,92	2,20	6,40	4,33-4,49

x̄ = mean; Med = median; SD = standard deviation; min = minimum; max = maximum; 95 % CI = 95 % confidence interval for mean.

Discussion

Color determination is a delicate procedure considered to have the mayor role in clinical success of prosthodontic treatment. Previous studies showed that computer-assisted shade analysis is more accurate and more consistent compared with visual shade matching, while spectrophotometers are the most reliable standard for color matching studies [10, 13]. Dozić et al. [14] found VITA Easyshade spectrophotometer the most reliable instrument in both *in vitro* and *in vivo* circumshades. The ΔL (value) is the most significant parameter because human eye perceives changes in value faster than changes in hue. Clinically acceptable color matching shows a ΔL less than 2.0 and a total ΔE of less than 4.0 [16, 17]. For many years the VITA Classical shade guide has been considered the reference, one among all available guides for ceramic systems. Results of some studies showed, on the other hand, that VITA Classical shade guide is too low in chroma and to high in value when compared to extracted tooth samples [18–20]. In our study, the highest values of ΔL parameter

among VITA Classical samples were observed in C and the lowest in D group of colors (Figure 2). The best value of ΔE got color C3 and the worst color D3 (Table 2, Figure 3).

The VITA 3D – Master shade guide was developed to overcome the disadvantages of the VITA Classical shade guide. It was found to have broader color range, better color distribution and smaller coverage error when compared to other shade guides [21]. As shown, the best values of ΔE were obtained in the groups 4 and 5 and the worst in group 2 of colors (Figure 8). VITA 3D – Master shade guide demonstrated lower average ΔE when compared to VITA Classical, but both shade guides showed the average value of this parameter higher than clinically acceptable (Table 4). It was expected that based on increased shade range selection of 26 3D shades rather than the familiar 16 VC shades as well as new 3D shade guide design, 3D – Master shade guide would have better results [22].

Problem of shade guides technology production has been present for many years, so there has been an attempt to design them using predefined average ΔE [23]. Analoui et al. [24] found that it is possible to design a shade guide for target average ΔE. As the target average ΔE decreases, the number of shade tabs will increase. Even though human observer can detect under controlled conditions ΔE 1.0, clinically acceptable values are much higher. The American Dental Association (ADA) has set the limit of ΔE 2, as the tolerance for shade guides and ΔE 3.7 as the average color difference between teeth and matched shade tabs in the oral environment [25, 26].

Conclusion

According to our results and similar studies, technology-based color matching has advantages over visual, because it is an objective method that provides quantified and reproducible data without the influence of surroundings and lighting conditions. Shade tabs, produced by the same manufacturer, may vary in the observed parameters within and among several guides witch, once again, proves the lack of precision and nonuniformity of a conventional method. Reasons can be found in a large human influence factor in the production of shade guides. It is therefore necessary to use some of the instrumental methods for shade selection or to change technology of shade guides production.

R E F E R E N C E S

1. *Kawaragi C, Ishikawa S, Miyoshi F, Furakawa K, Ishibashi K.* Evaluations by dentists and patients concerning the color of porcelain-fused-to-metal restoration. Dent J Iwate Med Univ 1990; 15: 9−17.
2. *Gayton CS, Hall EJ.* Medical physiology. Beograd: Savremena administracija; 1999. (Serbian)
3. *Chu SJ, Devigus A, Mieleszko AJ.* Fundamentals of color. Carol Stream, IL: Quintessence Publishing Co, Inc; 2004.
4. *Commision Internationale de l'Eclairage* (CIE). CIE Technical Report: Improvement to Industrial Color-Difference Evaluation. CIE Pub No 142-2001.Vienna, Austria: Central Bureau of the CIE; 2001.
5. *Berns RF.* Billmeyer and Saltzman's principles of color technology. 3rd ed. New York: John Wiley; 2000.
6. *Judd DB, Wzsyecki G.* Color in business, science and industry. 3rd ed. New York: John Wiley; 1975.
7. *Hunter RS.* The measurement of appearance. New York: John Willey; 1975.
8. *Corciolani G, Vichi A, Goracci C, Ferrari M.* Color correspondence of a ceramic system in two different shade guides. J Dent 2009; 37(2): 98−101.
9. *Wee AG, Kang EY, Johnston WM, Seghi RR.* Evaluating porcelain color match of different porcelain shade-matching systems. J Esthet Dent 2000; 12(5): 271−80.
10. *Lu H, Roeder LB, Powers JM.* Effect of polishing systems on surface roughness of microhybrid composites. J Esthet Restor Dent 2003; 15(5): 297−303.
11. *Commision International de l'Eclarirage.* Colorimetry, Official Recommendations of the International Commision on Illumination [Publication CIE No. 15 (E-1.3.1)]. Paris: Bureau Central de la CIE ; 1971.
12. *JJL Technologies LLC.* Vita Easyshade Technology. Bad Sackingen: Vita Zahnfabrik GmbH; 2003.
13. *Brewer JD, Wee A, Seghi R.* Advances in color matching. Dent Clin North Am 2004; 48(2): v, 341−58.
14. *Dozić A, Kleverlaan CJ, El-Zohairy A, Feilzer AJ, Khashayar G.* Performance of five commercially available tooth color-measuring devices. J Prosthodont 2007; 16(2): 93−100.
15. *Kim-Pusateri S, Brewer JD, Davis EL, Wee AG.* Reliability and accuracy of four dental shade-matching devices. J Prosthet Dent 2009; 101(3): 193−9.
16. *Paul S, Peter A, Pietrobon N, Hammerle CH.* Visual and spectrophotometric shade analysis of human teeth. J Dent Res 2002; 81(8): 578−82.
17. *Paul SJ, Peter A, Rodoni L, Pietrobon N.* Conventional visual vs spectrophotometric shade taking for porcelain-fused-to-metal crowns: a clinical comparison. Int J Periodontics Restorative Dent 2004; 24(3): 222−31.
18. *Miller LL.* A scientific approach to shade matching. In: *Preston JD,* editor. Perspectives in Dental Ceramics. Chicago, Ill: Quintessence Publishing; 1988. p. 193−208.
19. *Miller LL.* Shade matching. J Esthet Dent 1993; 5(4): 143−53.
20. *Miller LL.* Shade selection. J Esthet Dent 1994; 6(2): 47−60.
21. *Paravina RD, Powers JM, Fay RM.* Color comparison of two shade guides. Int J Prosthodont 2002; 15(1): 73−8.
22. *Della Bona A, Barrett AA, Rosa V, Pinzetta C.* Visual and instrumental agreement in dental shade selection: Three distinct observer populations and shade matching protocols. Dent Mater 2009; 25(2): 276−81.
23. *Cocking C, Helling S, Oswald M, Rammelsberg P, Reinelt G, Hassel AJ.* Using discrete optimization for designing dental shade guides. Col Res Appl 2010; 35(3): 233−9.
24. *Analoui M, Papkosta E, Cochran M, Matis B.* Designing visually optimal shade guides. J Prosthet Dent 2004; 92(4): 371−6.
25. *Wozniak WT.* Proposed guideline for the acceptance program for dental shade guides. Chicago: American Dental Association; 1987.
26. *Johnston WM, Kao EC.* Assessment of appearance match by visual observation and clinical colorimetry. J Dent Res 1989; 68(5): 819−22.

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Prevalence and quality of life in high school pupils with acne in Serbia

Prevalencija i kvalitet života srednjoškolaca sa aknama u Srbiji

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Abstract

Background/Aim. Acne is a common problem in adolescent children with considerable emotional and psychological effects. The aim of this study was to determine the self-reported prevalence of acne and to assess its impact on the quality of life in high school pupils in Serbia. **Methods.** The cross-sectional study was conducted in May 2011 in two medical high schools in Serbia. Only pupils who gave a written informed consent to participate in the study (n = 440) were asked to fill in two questionnaires: short demographic questionnaire and Cardiff Acne Disability Index (CADI), a disease-specific questionnaire measuring disability induced by acne. Internal consistency (tested by Cronbach's alpha) and item-total score correlations (Spearman's correlation analysis) were used for reliability analyses. **Results.** The study population consisted of 440 pupils, 281 from Belgrade and 159 from Užice. Among them 371 (84.3%) were girls and 69 (15.7%) boys, with similar sex distribution in Belgrade and Užice. The total mean age of pupils was 16.48 years (SD = 0.55). Out of 440 pupils 228 (51.8%) self-reported their acne. The acne prevalence was significantly higher in pupils from Užice (73.6%) than in those from Belgrade (39.6%). The overall mean CADI score for the whole sample was 2.87 ± 2.74, with the similar quality of life impairment in adolescents from Belgrade and from Užice. The mean Cronbach's alpha was 0.82. **Conclusion.** This study shows that the quality of life impairment due to acne is mild for the majority of the affected pupils. The Serbian version of the CADI is a reliable, valid, and valuable tool for assessing the impact of acne on the quality of life.

Key words:
acne vulgaris; adolescent; shcools; serbia; prevalence; quality of life; questionnaires.

Apstrakt

Uvod/Cilj. Akne predstavljaju često oboljenje adolescenata, sa značajnim emocionalnim i psihološkim uticajem. Cilj ovog istraživanja bio je da se proceni prevalencija akni i njihov uticaj na kvalitet života srednjoškolaca u Srbiji. **Metode.** U maju 2011. godine sprovedena je studija preseka u dve srednje medicinske škole u Srbiji. Samo učenici koji su dostavili pisanu saglasnost za učešće u studiji (n = 440) zamoljeni su da popune dva upitnika: kratak opšti standardni upitnik i Kardifov indeks nesposobnosti u vezi akni (CADI), specifični upitnik za procenu kvaliteta života obolelih od akni. Za analizu pouzdanosti CADI upitnika korišćeni su Kronbahov koeficijent alfa (za testiranje unutrašnje konzistentnosti upitnika) i Spirmanova korelaciona analiza. **Rezultati.** Studijsku populaciju sačinjavalo je 440 učenika, 281 iz Beograda i 159 iz Užica. Među njima je bilo 371 (84,3%) devojčica i 69 (15,7%) dečaka, sa sličnom distribucijom po polu u oba grada. Ukupan prosečni uzrast učenika bio je 16,48 godina (SD = 0,55). Od 440 učenika njih 228 (51,8%) navelo je postojanje akni. Prevalencija akni bila je značajno viša kod učenika iz Užica (73,6%) nego kod onih iz Beograda (39,6%). Ukupni prosečni CADI skor za ceo uzorak bio je 2,87 ± 2,74, sa sličnim smanjenjem kvaliteta života kod adolescenata u Beogradu i Užicu. Kronbahov koeficijent alfa iznosio je 0,82. **Zaključak.** Studija je pokazala da je kod većine učenika sa aknama umereno narušen kvalitet života. Srpska verzija CADI upitnika je pouzdana, validna i korisna za procenu uticaja akni na kvalitet života adolescenata.

Ključne reči:
akne; adolescenti; škole; srbija; prevalenca; kvalitet života; upitnici.

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Introduction

Acne vulgaris is one of the most common skin diseases. Almost every individual has some degree of acne during puberty, with spontaneous resolution occurring in early adult life. Occasionally, the disease persists longer or even remains a lifelong problem [1].

Although skin diseases are sometimes thought as unimportant, even trivial, acne has a considerable psychological impact on affected individuals [2]. Previous studies on the psychosocial impact of acne have documented dissatisfaction with the appearance, embarrassment, self-consciousness and lack of self-confidence in acne patients [3, 4]. Social dysfunctions have also been observed, including concerns regarding social interactions with the opposite gender, appearances in public, interactions with strangers and reduced employment opportunities [5, 6]. The levels of social, psychological and emotional impairments in acne may be compared with chronic diseases such as asthma, epilepsy, diabetes and arthritis and do not necessarily follow positive correlation with dermatological damage and real cosmetic problems [7]. Because of that, it is imperative to evaluate both the psychological impact of acne on the adolescents and its repercussion on patients' quality of life. It seems that adolescents are more influenced by the psychosocial effects of acne than older patients [8]. Many teenagers with acne may suffer for years before being given effective therapy and the majority even do not seek any professional advice for managing acne [9], although it has been proven that effective treatment results in improvement of quality of life (QoL) measurement [10].

The aim of this study was to determine the self-reported prevalence of acne, its psychosocial impact and repercussion on quality of life in high school pupils in Serbia.

Methods

The cross-sectional study was conducted in May 2011 in two medical high schools in Serbia, one in Belgrade and another in Užice, the town in the central part of Serbia. Pupil participation was voluntary and anonymous and the written informed consent was obtained by their parents. The percentage of the second class pupils who agreed to partcipate in the study was somewhat higher in Užice (159/210; 75.7%) than in Belgrade (281/376; 74.7%). All 440 pupils (281 from Belgrade and 159 from Užice) were asked to fill in two questionnaires: short demographic questionnaire and the Cardiff Acne Disability Index – CADI [11].

A short demographic questionnaire included questions on the presence of acne, disease duration, treatment, presence of any other coexisting skin disease and family history of acne.

The CADI is a disease-specific questionnaire measuring disability induced by acne. It is a short, 5-item questionnaire. The response to each of five questions is scored from 0 to 3, with a total maximum score of 15. The higher score means that more quality of life is impaired in affected individuals. We used the Serbian version of the CADI [12] to asses the impact of acne on the pupils' quality of life.

Written informed consent was obtained from pupils' parents.

Statistical analysis

Categorical variables were expressed as counts and percentages while continuous variables were presented as mean ± standard deviation. The differences between variables were assessed by χ^2 or *t*-test. Internal consistency (tested by Cronbach's alpha) and item-total score correlations (Spearman's correlation analysis) were used for reliability analyses. Statistical analysis was performed with the Statistical Package for the Social Sciences, SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). A two-tailed probability value of 0.05 or less was considered significant.

Results

The study population consisted of 440 pupils (281 from Belgrade and 159 from Užice. Among them 371 (84.3%) were girls and 69 (15.7%) boys, with similar sex distribution in Belgrade and Užice. The total mean age of pupils was 16.48 years (SD = 0.55 years). Out of 440 pupils 228 (51.8%) self-reported their acne. The acne prevalence was significantly higher in Užice (117/159, 73.6%) than in Belgrade (111/281, 39.6%). It was more prevalent in boys (41/69, 59.4%) than in girls (187/228, 50.4%).

Demographic and disease characteristics of 228 adolescents with acne are presented in Table 1. The majority of them were girls 187 (82%) and only 41 (18%) were boys with similar sex distribution in Belgrade and Užice. Pupils with acne from Užice were older compared to those from Belgrade.

Among affected pupils 22 (9.8%) also suffered from skin diseases other than acne and 101 (44.7%) had positive family history of acne. The majority of adolescents who reported acne in both cities had tried some kind of acne therapy. Acne duration was less than one year in 112 (51.4%) and more than one year in 106 (48.6%) of pupils, without significant difference between pupils from two cities.

The overall mean CADI score for the whole sample was 2.87 ± 2.74, with the similar quality of life impairment in adolescents from Belgrade and from Užice (Table 2). We found a statistically significant positive correlation between every simple question and overall mean CADI score, which was in range 0.599–0.787 (Table 2). The highest correlation was found between the 4th question (patient's psychological state) and overall score.

In general, although the overall mean CADI score was low and the majority of affected pupils did not have psychological and social consequences of acne (Table 3), 8 (3.9%) of them became more aggressive, frustrated or embarrassed as a result of having acne. Also, a small, but important minority 25 (12.2%) of pupils with acne were concerned about the appearance of their skin most of the time, and 9 (4.4%) pupils felt very depressed and miserable.

The Serbian version of CADI questionnaire showed high internal consistency (the mean Cronbach's alpha was 0.82).

As presented in Table 4, quality of life impairment due to acne was mild for the majority of affected adolescents

Table 1

Characteristics of pupils with acne

Pupils characteristics	Total (n = 228)	Belgrade (n = 111)	Užice (n = 117)	*p*
Gender, n (%)				
males	41 (18.0)	22 (19.8)	19 (16.2)	ns*
females	187 (82.0)	89 (80.2)	98 (83.8)	
Age, years (mean ± SD)	16.49 ± 0.53	16.35 ± 0.50	16.62 ± 0.53	< 0.001†
Family history of acne, n (%)				
yes	101 (44.7)	53 (48.6)	48 (41.0)	ns*
no	125 (55.3)	56 (51.4)	69 (59.0)	
Other skin disease, n (%)				
yes	22 (9.8)	11 (10.3)	11 (9.4)	ns*
no	202 (90.2)	96 (89.7)	106 (90.6)	
Therapy for acne				
yes	157 (70.1)	80 (74.8)	77 (65,8)	ns*
no	67 (29.9)	27 (25.2)	40 (34.2)	
Duration of acne (in years), n (%)				
< 1	112 (51.4)	46 (43.8)	66 (58.4)	
≥ 1	106 (48.6)	59 (56.2)	47 (41.6)	< 0.05*

***χ^2 test; †*t*-test; ns – no significant.**

Table 2

CADI questionnaire – mean scores and item correlation

Item	Mean score (± SD)	Max possible score	Min/max score	Item total correlation*
1	0.57 ± 0.75	3	0/3	0.737
2	0.37 ± 0.66	3	0/3	0.636
3	0.30 ± 0.67	3	0/3	0.599
4	0.80 ± 0.82	3	0/3	0.787
5	0.83 ± 0.69	3	0/3	0.768
Total score	2.87 ± 2.74	15	0/15	1.00

***Spearman's rho ; CADI – Cardiff Acne Disability Index.**

Table 3

CADI questionnaire – participants' answers

	CADI items	Answers	n (%)
1	As a result of having acne, during the last month have you been aggressive, frustrated or embarrassed?	Very much indeed	8 (3.9)
		A lot	9 (4.4)
		A little	75 (36.4)
		Not at all	114 (55.3)
2	Do you think that having acne during the last month interfered with your daily social life, social events or relationships with members of the opposite sex?	Severely, affecting all activities	6 (2.9)
		Moderately, in most activities	3 (1.5)
		Occasionally, in some activities	51 (24.9)
		Not at all	145 (70.7)
3	During the last month have you avoided public changing facilities or wearing swimming costumes because of your acne?	All of the time	5 (2.4)
		Most of the time	9 (4.4)
		Occasionally	28 (13.6)
		Not at all	164 (79.6)
4	How would you describe your feelings about the appearance of your skin over the last month?	Very depressed and miserable	9 (4.4)
		Usually concerned	25 (12.2)
		Occasionally concerned	88 (42.9)
		Not bothered	83 (40.5)
5	Please indicate how bad you think your acne is now:	The worst it could possibly be	4 (1.9)
		A major problem	22 (10.7)
		A minor problem	116 (56.3)
		Not a problem	64 (31.1)

CADI – Cardiff Acne Disability Index.

Table 4

CADI scores distribution

CADI score	Number of students n (%)
< 5	165 (80.9)
5–9	34 (16.7)
10–15	5 (2.4)
Total	204 (100.0)

CADI – Cardiff Acne Disability Index.

(80.9%). Only 5 (2.4%) pupils were severely affected by acne in terms of impairment of their quality of life, with the maximum reported CADI score of 15 (100% impairment) in just one affected pupil.

Discussion

Acne vulgaris is a common, distressing dermatosis with the prevalence reaching up to 80% during adolescence [13]. Because the disease occurs in a psychologically labile period during adolescence and causes a change in appearance, acne may have negative effects on the psychological status of sufferers [14, 15], with considerable impact on their emotional health, sexual relationships and social life.

Self-reported acne occurred in 51.8% of the Serbian teenagers involved in this study. This result is in accordance with the finding of a Greek study (59.2%) [16], but it is significantly lower than in several other studies with the range from 70.0% to over 90% [9, 17–20]. We have to mention that a significantly higher acne prevalence was in Užice (73.6%) than in Belgrade (39.6%), without any reasonable explanation for this finding. Like in several other studies [9, 21] we found that acne was more frequent in boys (59.4%) than in girls (50.4%). Among the affected pupils positive family history of acne was found in 44.7%. According to Kubota et al. [22] 56.8% of Japanese adolescents reported a family history of acne. The prevalence of other skin diseases was 9.2%, which is in agreement with the findings of the previous studies [18, 20]. Hince our study was a self-reported study, it is possible that the pupils may have overlooked minor cutaneous problems, such as warts, or not considered them as skin problems.

Almost one half of the pupils with acne (48.6%) of both sexes reported acne duration longer than one year, with a significantly longer duration of acne among the pupils from Belgrade than those from Užice. According to the results of a Japanese study 23.4% of adolescents who reported having acne estimated acne duration of 1–2 years and 29.5% estimated duration of acne that was longer than 2 years [22].

The consequences of having a skin disease, including acne vulgaris, may be more profound concerning the patients' quality of life. The impact of acne on the quality of life, has been recognized for over 30 years.

In this cross-sectional study the Serbian version of the CADI, a disease-specific questionnaire, was used to asses the impact of acne on the quality of life in affected adolescents. The CADI is a well-known acne disability measure and has been used in some studies to assess the burden of living with acne on a patient's experience of disability [20, 23–25].

The Serbian version of the CADI questionnaire showed a high internal consistency (the mean Cronbach's alpha was 0.82). This finding indicates that Serbian version of the CADI questionnaire is reliable to measure the impact of acne on the quality of life in Serbian-speaking patients. Moreover, with only 5 questions, the CADI is also easy to administer and thus a practical tool to use in routine clinical practice.

The overall mean score of the CADI in our study for the whole sample was 2.9, which is lower in comparison with Serbian study conducted in 2010 where total CADI score was 3.6 [20], but somewhat higher than in Scottish study with the CADI score of 1.9 [18]. The fact that the pupils replied together in the same classrooms with their friends being able to read their answers could prevent some of them to express how they really felt.

Although the majority of the affected pupils did not have psychological and social consequences of acne, almost 20% of pupils were moderately to severely affected by acne in terms of impairment of their quality of life that was higher than in previous similar studies conducted among the pupils [18, 20].

We found a statistically significant positive correlation between every simple question and a total CADI score. Like in the Scottish study [18] the higher scoring questions in our study pertained to the feelings about the skin appearance and patient's assessment of their current acne severity, while the lower scoring questions were related to social consequences of acne and to avoidance of sport activities, public changing facilities and clothing restrictions. Acne is associated with a greater psychological burden than a variety of disparate chronic disorders [5] and has a demonstrable association with depression, anxiety, and feelings of social isolation. It affects personality, emotions, self-image, self-esteem, and the ability to form relationships [26, 27]. Gupta and Gupta [28] showed that acne is associated with higher depression scores than other dermatologic conditions. Even suicidal ideation was found to be around 6–7% in acne patients [7, 28, 29]. Acne in adolescents appears to have a considerable impact on emotional health [21] and affects self-image and assertiveness, factors that are important in forming friendship and personality traits [8].

In our study a small, but important minority of the pupils with acne 3.9% became more aggressive, frustrated or embarrassed as a result of having acne, 4.4% felt very depressed and miserably, and 12.2% were concerned about the appearance of their skin most of the time. This suggests that the impact of acne can be more serious for the patients than most clinicians think it would be and thus, it is very important to focus on the subjective perception in managing acne patient, irrespective of their objective severity.

As delay in obtaining adequate treatment increases the risk of scarring, both cutaneous as well as psychological, it is important to educate teens about the availability of effective acne therapy and to encourage them to consult with dermatologist in order to stop further increase of psychological problems, reversing disability and thus to achieve a better quality of life of affected individual.

The strength of this study was the large number of adolescents surveyed from the general population (high schools), thus excluding the possibility of referral bias and overestimation of psychometric morbidity with hospital-based data. On the other side, the QoL data from only two districts, may not be generalised to other settings in the country. The reliability of self-reported QoL data cannot be guaranteed.

Conclusion

Our study shows that acne is associated with decrease in quality of life in affected pupils. The Serbian version of the CADI questionnaire is valid and reliable to assess different aspects of quality of life among people with acne who speak Serbian language. As there are a wide variations in an individual response to having acne, quality of life scales, primarily the CADI questionnaire, may help dermatologists to understand the impact of acne on the quality of life and to take it into consideration when treating acne.

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Conflict of interest

There is no conflict of interest.

REFERENCES

1. *Wolff H*. Diseases of Hair. In: *Burgdorf WH, Plewig G, Wolff HH, Landthaler M,* editors. Braun-Falco's Dermatology. 3rd ed. Berlin: Springer; 2009; p. 1050−2.
2. *Khoo J*. The psychological impact of acne: patients' perceptions. J Am Acad Dermatol 1995; 32(5): S26–S30.
3. *Mulder MM, Sigurdsson V, van Zuuren EJ, Klaassen EJ, Faber JA, de Wit JB,* et al. Psychosocial impact of acne vulgaris. Evaluation of the relation between a change in clinical acne severity and psychosocial state. Dermatology 2001; 203(2): 124−30.
4. *Tallab TM*. Beliefs, perceptions and psychological impact of acne vulgaris among patients in the Assir region of Saudi Arabia. West Afr J Med 2004 23(1): 85–7.
5. *Tan JK*. Psychosocial impact of acne vulgaris: evaluating the evidence. Skin Therapy Lett 2004; 9(7): 1–3.
6. *Magin P, Adams J, Heading G, Pond D, Smith W*. Psychological sequelae of acne vulgaris: results of a qualitative study. Can Fam Physician 2006; 52(8): 978–9.
7. *Mallon E, Newton JN, Klassen A, Stewart-Brown SL, Ryan TJ, Finlay AY*. The quality of life in acne: a comparison with general medical conditions using generic questionnaires. Br J Dermatol 1999; 140(4): 672–6.
8. *Lewis-Jones MS, Finlay AY*. The Children's Dermatology Life Quality Index (CDLQI): Initial validation and practical use. Br J Dermatol 1995; 132(6): 942–9.
9. *Uslu G, Sendur N, Uslu M, Savk E, Karaman G, Eskin M*. Acne: prevalence, perceptions and effects on psychological health among adolescents in Aydin, Turkey. J Eur Acad Dermatol Venereol 2008; 22(4): 462–9.
10. *Thomas DR*. Psychosocial effects of acne. J Cutan Med Surg 2004; 8(Suppl 4): 3–5.
11. *Motley RJ, Finlay AY*. Practical use of a disability index in the routine management of acne. Clin Exp Dermatol 1992; 17(1): 1–3.
12. *Jankovic S, Vukicevic J, Djordjevic S, Jankovic J, Marinkovic J, Basra MK*. The Cardiff Acne Disability Index (CADI): linguistic and cultural validation in Serbian. Qual Life Res 2012; 22(1): 161−6.
13. *Lello J, Pearl A, Arroll B, Yallop J, Birchall NM*. Prevalence of acne vulgaris in Auckland senior high school students. N Z Med J 1995; 108(1004): 287–9.
14. *Hull PR, D'Arcy C*. Acne, depression, and suicide. Dermatol Clin 2005; 23(4): 665–74.
15. *Gurel MS, Yanik M, Simsek Z, Kati M, Karaman A*. Quality of life instrument for Turkish people with skin diseases. Int J Dermatol 2005; 44(11): 933–8.
16. *Rigopoulos D, Gregoriou S, Ifandi A, Efastathiou G, Georgala S, Chalkias J,* et al. Coping with acne : beliefs and perceptions in sample of secondary school Greek pupils. J Eur Acad Dermatol Venereol 2007; 21(6): 806–10.
17. *Yosipovitch G, Tang M, Dawn AG, Chen M, Goh CL, Chan YH,* et al. Study of Psychological Stress, Sebum Production and Acne Vulgaris in Adolescents. Acta Derm Venereol 2007; 87(2): 135–9.
18. *Walker N, Lewis-Jones MS*. Quality of life and acne in Scottish adolescent schoolchildrend: use of the Children's Dermatology Life Quality Index (CDLQI) and the Cardiff Acne Disability Index (CADI). J Eur Acad Dermatol Venereol 2006; 20(1): 45–50.
19. *Do JE, Cho SM, In SI, Lim KY, Lee S, Lee ES*. Psychosocial aspects of acne vulgaris: a community based study with Korean adolescents. Ann Dermatol 2009; 21(2): 125–9.
20. *Janković S, Vukićević J, Djordjević S, Janković J, Marinković J*. Quality of life among schoolchildren with acne: results of a cross-sectional study. Indian J Dermatol Venereol Leprol 2012; 78(4): 454−8.
21. *Smithard A, Glazebrrook C, Williams HC*. Acne prevalence, knowledge about acne and psychological morbidity in mid-adolescence: a community based study. Br J Dermatol 2001; 145(2): 274–9.
22. *Kubota Y, Shirahige Y, Nakai K, Katsuura J, Moriue T, Yoneda K*. Community-based epidemiological study of psychosocial effects of acne in Japanese adolescents. J Dermatol 2010; 37(7): 617–22.
23. *Salek MS, Khan GK, Finlay AY*. Questionnaire techniques in assessing acne handicap: Reliability and validity study. Qual Life Res 1996; 5(1):131–8.
24. *Oakley AM*. The Acne Disability Index: usefulness confirmed. Australas J Dermatol 1996: 37(1): 37–9.
25. *Agheai S, Mazaharinia N, Jafari P, Abbasfard Z*. The Persian version of the Cardif Acne Disability Index. Reliability and validity study. Saudi Med J 2006; 27(1): 80–2.
26. *Lasek RJ, Chren MM*. Acne vulgaris and the quality of life of adult dermatology patients. Arch Dermatol 1998; 134(4): 454–8.
27. *Urpe M, Pallanti S, Lotti T*. Psychosomatic Factors in Dermatology. Dermatol Clin 2005; 23(4): 601–8.
28. *Gupta MA, Gupta AK*. Depression and suicidal ideation in dermatology patients with acne, alopecia areata, atopic dermatitis and psoriasis. Br J Dermatol 1998; 139(5): 846–50.
29. *Picardi A, Mazzoti E, Pasqiuni P*. Prevalence and correlates of suicidal ideation, among patients with skin disease. J Am Acad Dermatol 2006; 54(3): 420–6.

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Psychosocial characteristics and motivational factors in woman seeking cosmetic breast augmentation surgery

Psihosocijalne karakteristike i motivacioni faktori kod žena koje žele estetsko uvećanje grudi

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Abstract

Background/Aim. There are various opinions regarding the factors motivating women to undergo breast augmentation. The aim of this study was to estimate motivation for augmentation mammaplasty (AM), self-esteem and body image perception in breast augmentation patients. **Methods**. This prospective study involved AM patients operated in the Clinical Center of Vojvodina during a 3-year period. A total of 45 patients responded to our package of questionnaires designed to assess motivation for surgery, self-esteem level and body image perception. Those patients were compared to the control group of women who did not want to change their breast size, and who were similar in their age, social status and education level. Our package of questionnaires included a general questionnaire, Photographic Figure Rating Scale (PFRS) and Rosenberg's Self-Esteem Scale. **Results.** Differences in marital status, educational level, habitation and employment status were statistically insignificant, but there was a significantly lower body mass index (BMI) in the operated women. Considering motives for surgery, a few factors were distinguished: desire to feel more feminine (82.2%), confident (75.5%) and attractive (73.3%), to feel less shy with men (64.4%), to improve their sex life (46.5%), teasing history (42.2%) and easier to find a partner (11.1%) and job (2.2%). Both groups demonstrated a high self-esteem level, but in the the AM group results were lower than in the control group. The mean current self-rating by the PFRS in the group AM was lower than in the control group (4.28 ± 1.3 *vs* 5.12 ± 1.23, respectively) and this coincided with lower BMI in the AM group. The women in the AM group had chosen significantly smaller body size as maximally attractive, and had chosen a narrower attractive body size range than the women in the control group. **Conclusion.** Preoperative evaluation of patients' motives for surgery can help surgeons to exclude woman with unrealistic expectations and different psychological problems.

Key words:
esthetics; mammaplasty; psychology; personality assessment; questionnaires.

Apstrakt

Uvod/Cilj. Postoje različita mišljenja o činiocima koji motivišu žene da se podvrgnu operaciji uvećanja grudi. Cilj ove studije bio je da se procene motivi za operaciju uvećanja grudi, nivo samopouzdanja kod tih pacijentkinja i lični doživljaj sopstvene slike tela. **Metode.** Ova prospektivna studija obuhvatila je pacijentkinje kojima je urađena augmentaciona mamoplastika (grupa AM) u Kliničkom centru Vojvodine u toku tri godine. Na paket upitnika koji je osmišljen da se procene motivi za operaciju, nivo samopouzdanja i lični doživljaj slike tela odgovorilo je 45 pacijentkinja. Kontrolnu grupu činile su žene sličnog životnog doba, socijalnog statusa i nivoa obrazovanja koje nisu želele da menjaju veličinu grudi. U istraživanju su korišteni opšti upitnik, Rozenbergov upitnik za procenu samopoštovanja i *Photographic Figure Rating Scale* (PFRS) test. **Rezultati.** Nisu utvrđene statistički značajne razlike između dve grupe žena u sociodemografskim varijablama (bračnom statusu, nivou obrazovanja, mestu stanovanja i zaposlenju), ali je utvrđen značajno niži indeks telesne mase (BMI) kod žena koje su želele uvećanje grudi. Najčešće navođeni motivi za operaciju bili su: želja za povećanjem ženstvenosti (82,2%), samopouzdanja (75,5%) i atraktivnosti (73,3%), zatim smanjenje stidljivosti u kontaktu sa muškarcima (64,4%), poboljšanje seksualnih odnosa (46,5%) i smanjeno zadirkivanje zbog izgleda grudi od strane okoline (42,2%), kao i lakše nalaženje partnera (11,1%) i posla (2,2%). Obe grupe pokazale su visok nivo samopouzdanja, ali su dobijene vrednosti testa bile značajno niže u grupi AM. Srednja vrednost dobijena u samoprocenjivanju slike tela po PFRS skali bila je značajno niža u grupi AM nego u kontrolnoj grupi (4,28 ± 1,3 *vs* 5,12 ± 1,23), što koincidira sa vrednostima BMI. Žene u grupi AM pokazale su statistički značajno niže vrednosti u proceni najmršavije i najdeblje atraktivne figure prema PFRS skali, i imale su uži raspon procene atraktivnosti figura. **Zaključak.** Preoperativna procena činilaca koji upućuju žene da se odluče za uvećanje grudi treba da pomogne hirurzima da isključe one sa nerealnim očekivanjima i različitim tendencijama ka psihičkim poremećajima.

Ključne reči:
estetika; mamaplastika; psihologija; ličnost, procena; upitnici.

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Introduction

Augmentation mammaplasty (AM) is one of the commonest aesthetic surgical procedures being sought by women preoccupied with their breast size and shape. Actually, the American Society for Aesthetic Plastic Surgery (ASAPS) published in their 15th annual statistical report that there was an increase of 213.2% in AM procedures from 1997 to 2011 with AM being the second rated aesthetic surgical procedure after liposuction in 2011[1].

There are different opinions concerning the reasons and motivations for this surgery. The fact that these women are ready to undergo surgery in order to solve an aesthetic problem, accepting the risk of postoperative pain and possible side effects and paying often significant amounts of money, tells us that there is a strong underlying motivation for this decision. It is very important for plastic surgeons to understand these motives and get an insight into women's expectations in order to be able to fulfill their wishes and arrive to the best solution for the patient whether or not that in fact involves surgery.

The idea of the idealized image offered by media and entertainment industry in the 21st century on how women should look, think, feel and behave should not be underestimated. Media images depict an unrealistic image of ultra thin, forever young women with ideal proportions. On the other hand, people often tend to associate that 'perfect' image with the competence and social desirability. This image certainly contributes to drastic increase in cultural expectations for attractiveness. Actually, this social pressure set unattainable standards of attractiveness by which we evaluate ourselves. Although important, these factors are not the only ones influencing positive attitudes toward cosmetic surgery.

There is an accumulating evidence that body image is the most relevant factor that predicts an interest in cosmetic surgery [2]. A basic component of body image is appearance evaluation which represents the judgmental beliefs regarding the body, commonly in terms of body dissatisfaction. The second aspect of body image is investing in appearance, a measure of how much importance individuals place on their looks and how much they pay attention to their appearance. Actually, investing in appearance suggests the importance of appearance to self worth [3]. Various researches show that women interested in breast augmentation report greater investment in their appearance, greater distress about their appearance in a variety of situations, and more frequent appearance related teasing [4].

Other common factors that may lead women to consider cosmetic surgery are body image dissatisfaction [5], low self-rated attractiveness [6], lack of confidence and a feeling of embarrassment and insecurity [7, 8]. Desire to feel more feminine and more attractive to men is a common motive for cosmetic surgery that could be seen in the literature [9]. Typically, cosmetic surgery is desirable for women when it enhances youthfulness and beauty. Specifically, it is considered "normal" for women to have cosmetic surgery in order to become or remain attractive to the opposite sex [10].

The relation of psychological problems or different profiles of patients and aesthetic surgery is well-known both in practice and the literature [11, 12]. A recent review notes that among 7 and 15 percent of patients who undergo cosmetic procedures meet the diagnostic criteria for the presence of body dysmorphic disorder (BDD), and considering that they should not be operated [13]. Also, results published after introduction of psychological service in some plastic surgery units in the United Kingdom reveal that 42% referrals receive psychological instead of surgical recommendation [14]. Unrecognized problems, such as BDD, eating disorders or any unrealistic expectations can affect an outcome of operation, compromise postoperative rehabilitation and lead to poor patient compliance and the patient dissatisfaction in general [15].

Despite the growing popularity of cosmetic surgery, our knowledge about the factors that influence attitudes toward these procedures is still humble. The aim of this study was to estimate motivation for AM, psychological status and body image dissatisfaction in breast augmentation patients.

Methods

This prospective study involved 52 patients who were operated in the Clinic for Plastic and Reconstructive Surgery, Clinical Center of Vojvodina, during a 3-year period, from 2008 to 2010. Those patients were asked to participate in the study during initial consultation at the Clinic. Those who agreed to participate (50 of them), were asked to sign an informed consent and fulfill a package of questionnaires, and return them on the day of surgery. Forty five patients responded completely to the packet of questionnaires designed to assess motivation for surgery, current psychological status, body image dissatisfaction (the AM group). The control group consisted of 70 women, similar in their age, social status and education level, but who did not want to change their breast size.

Our package of questionnaires included three questionnaires: general questionnaire, the Photographic Figure Rating Scale (PFRS) and Rosenberg's Self-Esteem Scale.

General questionnaire provided data on age, highest educational qualification, marital status, employment, motivation for surgery, teasing history.

The PFRS was used as a body image assessment scale that consists of ten photographic images of real women who presented the 5 established body mass index (BMI) categories, from emaciated to obese (BMI: Image 1 – 12.51, Image 2 – 14.72, Image 3 – 16.65, Image 4 – 18.45, Image 5 – 20.33, Image 6 – 23.09, Image 7 – 26.94, Image 8 – 29.26, Image 9 – 35.92, Image 10 – 41.23) [16]. The women were asked to self rate their body image, most attractive body figure, largest and thinnest figure they found attractive, in order to calculate body dissatisfaction score (a difference between the current self-rated body size image and ideal body size image) and attractiveness range (thinnest figure subtracted from the largest attractive figure).

The Rosenberg's Self-Esteem Scale was used to assess a self esteem level in both groups [17]. It is most widely used, self-report measure of self esteem. The scale was scored as Likert's scale on four points (1 – strongly agree to 4 –

strongly disagree). The results were interpreted in a way that the high score indicated high self-esteem, and the final score was accepted as low, medium or high.

The statistical package SPSS for Windows (ver. 16) was used for statistical analysis. To test the significance of differences between the two groups of women, *t*-test was used for parametric and χ^2 test for nonparametric categories. Statistical significance was accepted at the level of $p < 0.05$.

Results

The majority of patients requesting AM at the Clinical Center of Vojvodina, 45 (86.5%) women, agreed to participate in this investigation.

The sociodemographic characteristics of the patients were shown in Table 1. The mean age of the female respondents in the breast augmentation group (the AM group) was 28.7 ± 5.82 (age range 18 to 40) years. Out of all patients, 46.7% were married, 11.1% were divorced, and 42.2% were single. In terms of the highest education level 71.1% had secondary school and only 26.7% of women had a postgraduate degree. In the AM group, 31.1% lived with parents, 57.8% lived with a partner and only 8.9% lived alone. Out of all women in the AM group 26.7% were unemployed. The mean BMI was 19.85 ± 1.92 (from 15.6 to 26.3 kg/m^2) which was considered normal.

The motivation for surgery is shown in Table 2. Concerning motivation for surgery, most women, 34 (75.5%) of them, said that an important reason for seeking surgery was to feel more confident. They also stressed the desire to feel more feminine [37 (82.2%)], and less shy with men [29 (64.4%)]. Most of them thought that they would be or might be more attractive to men after breast augmentation [33 (73.3%)].

Table 2
Motivational factors for breast augmentation in the group of women with augmentation mammaplasty (AM)

Motivational factor	Patients (%)
To feel more feminine	82.2
To feel more confident	75.5
To be more attractive	73.3
To feel less shy with men	64.4
To improve their sex life	46.5
Teasing history	42.2
Easier to find a partner	11.1
To help them to get a job	2.2

The AM group was divided in three subgroups: women who always had small or no breast and wanted them "normal" (the subgroup I – 19 women), women who referred to their breast size as "normal" but wanted to have them big (the subgroup II – 11 women) and women who considered their breast "damaged" with breast feeding or weight loss and wanted them to look as they were before (the subgroup III – 15 women). Only one (2.2%) woman answered that augmenting breast would help her to get a better job. Only 6 (13.3%) women said that after AM they wanted to correct some other part of her body.

Table 1
Sociodemographic characteristics of women who underwent augmentation mammaplasty (AM) and the control group

Characteristics	AM group (%)	Control group (%)
Married	46.7	58.6
Divorced	11.1	8.6
Single	42.2	32.8
Secondary school education	71.1	
Postgraduate education	26.7	22.86
Employment	83.3	64.8
Live with parents	31. 1	29.3
Live with partner	57.8	62.1
Live alone	8.9	7
BMI ($\bar{x}$ ± SD)	19.85 ± 1.92	22.71 ± 3.14

BMI – body mass index.

The control group included 70 women who addressed Clinic for Plastic and Reconstructive Surgery as they had some other, but non aesthetic problems in a field of plastic surgery, who were in the same age range as the AM group (from 18 to 40 years), who did not have any aesthetic operations before and who did not want to change their breast appearance. The mean age in this group was 30.2 ± 5.2. More than half women of the control group, 41 (58.6%), were married, 6 (8.6 %) divorced and 23 (32.8%) single. There were 35.2% unemployed women. In the control group, 29.3% lived with their parents, 62.1% with a partner and 7% alone. Most of the women in this group had secondary education level [54 (77.14%)]. Further analysis showed that there was not a statistically significant difference in marital status, educational level, cohabiting and employment status (χ^2 test, $p > 0.05$). The mean BMI was 22.71 ± 3.14 kg/m^2. There was a statistically significant difference in BMI (*t*-test, $p < 0.05$).

We further found that 53.5% of women did not expect that augmenting breast would improve their sex life and 88.9% did not think that it would make them easier to find a partner. Feelings of embarrassment that lead to avoidance of sex were present in 12 (26.7%) of patients.

Psychometric measures addressed self-esteem and appearance-related teasing.

The Rosenberg's Self Esteem Scale showed that both groups of women had high self-esteem. The AM group had

lower results than the control group, the mean value was 22.54 ± 4.99 in the AM group and 25.14 ± 4.7 in the control group, and this difference was statistically significant ($p < 0.01$). A statistically significant difference was found between the subgroup I of the AM women (women who always had small or no breast and wanted them "normal") and the control group, as those women had lowest results with the average value of 20.16 ± 2.62 (*t*-test, $p < 0.01$).

Considering teasing history in the subgroup I of the AM women, teasing history was a significant motive for seeking surgery and it was present in 12 (63.15%) women which were more than in the other two subgroups and the complete AM group of 45 (42.2%) women. Teasing history was not present in the control group.

The results of PFRS are represented in Table 3. Mean current self-rating by PFRS in the AM group is lower than in the control group, (4.28 ± 1.3 *vs* 5.12 ± 1.23, respectively) and this coincided with lower BMI in the AM group. Image number 4 represented an underweight group in the PFRS scale (15–18.5 kg/m^2 BMI), while a picture number 5 was considered normal weight women (18.5–24.9 kg/m^2 BMI).

Table 3

Photographic Figure Rating Scale in the women with augmentation mammaplasty (the AM group) and the control group

Parameter	AM group ($\bar{x}$ ± SD)	Control group ($\bar{x}$ ± SD)	*p*
Mean current self rating	4.28 ± 1.3	5.12 ± 1.23	< 0.05
Ideal body size	3.04 ± 0.63	3.52 ± 0.81	< 0.05
Body dissatisfaction rate	1.24 ± 1.07	1.6 ± 1.22	> 0.05
Thinnest attractive figure	2.91 ± 0.42	3.07 ± 0.35	> 0.05
Largest attractive figure	4.93 ± 0.62	5.8 ± 0.76	< 0.05

The mean ideal body size, represented by the chosen image number in the PFRS scale, was lower in the AM group than in the control one (3.04 ± 0.63 *vs* 3.52 ± 0.81, respectively). Body dissatisfaction rate was higher in the control group (1.6 ± 1.22 *vs* 1.24 ± 1.07), but this was not statistically significant (*t*-test, $p > 0.05$).

Women in the AM group had chosen significantly smaller body size as maximally attractive, and a narrower attractive body size range than women in the control group. Interestingly, the women in the control group accepted the largest body size as still attractive with the average upper limit of 5.8 ± 0.76 while 20% of them accepted image 7 as an upper limit. Nobody in the AM group answered that image 7 was still attractive body size. The average upper limit in the AM group was 4.93 ± 0.62. Between the two groups there was statistically significant difference in upper body attractive limits (*t*-test, $p < 0.01$), but there was not in thinnest attractive figure.

Discussion

The benefits of aesthetic surgery operations are numerous. Results of those procedures could not be measured just by a change in the breast volume. Scientific studies underline far-reaching influence that this procedure has on a woman's life; from highly significant improvement in the patients self-confidence, significantly improved level of sexual satisfaction after surgery to even modified body posture with retropositioning of the head and anterior positioning of the pelvis [18, 19]. Data from the literature say that hypomastia is often associated with kyphosis as women are trying to hide what they consider a deficiency [19]. These postural changes after breast augmentation are believed to happen mostly because of psychological changes in women after surgery, as they feel more confident and more satisfied with their own body image.

Although in a waste world of surgery, aesthetic surgery is often considered less important and sometimes a little bit frivolous as it is "just" making people look beautiful, it has to be kept in mind that changing patients' appearance is changing his/her life, touching his/her soul and often giving him/her a completely new beginning. By correcting disfigurement and restoring harmonic appearance, the surgeon improves patients' self-esteem, social and psychological functioning and significantly influences the quality of life [20]. In all societies and through different cultures, a physical beauty has been socially appreciated and this gives a special impulse to people to look for a surgical solution to sometimes non-surgical problems.

Aesthetic surgery in general, and AM as one of the most often done procedures, is often sought to relieve marital, psychosexual and interpersonal problems. Even though surgery is influencing different segments of a woman's life, expectations can be unrealistic and that can create postoperative problems both to the patient and the surgeon.

Data analysis revealed different factors associated with a decision making process. It was found that most often seen motives for seeking breast augmentation were the following: dissatisfaction with size and shape of breasts, a wish to feel more confident, more feminine, less shy with men, more attractive to men. These reasons coincide with the motives for surgery found in the literature. A feeling of embarrassment that leads to avoidance of sex was present in 26.7% of women. It was noticed that dissatisfaction with body in general was not a motive for surgery in the AM group as dissatisfaction with the specific body region, in this case breasts. Literature data show that cosmetic surgery patients generally do not differ from non-patients in body satisfaction, but that they rather express dissatisfaction with specific feature considered for surgery [21, 22]. Only 13.3% of the AM women expressed dissatisfaction with some other parts of the body as well, and they wanted to do more surgeries in the future.

We did not find many unrealistic expectations as only 13.3% answered that having this surgery would solve their marital problems or easy job getting (2.2%). Teasing history was strongly associated with an interest in the breast augmentation, especially in the subgroup I (63.15%) as we could

see in some other studies [23–25]. In this study, as in the literature [25], knowing someone who had previous breast augmentation, was a factor that eased making a decision to undergo surgery in 60% of women.

Motivations for all forms of the cosmetic surgery, including breast augmentation, can be classified as internal or external. An example of an internal motivation would be undergoing breast augmentation to improve body image or boost confidence. In contrast, an external motivation would undergo the surgery for a secondary reason, such as to please another (e.g. a romantic partner), to decrease stress factors (life crisis) or career planning.

It is found that the most frequent motivation (or a goal) for breast augmentation is related to a desire to feel more attractive, more feminine and more confident. Actually, it could be said that internal motivation factors are prevalent in the group of AM women. Many researches show that internally motivated women are thought to be more likely to achieve their goals for surgery [26]. If it is known that the ultimate goal of plastic surgery is the improvement of the patient's well being, then understanding and processing motivational factors in preoperative counseling becomes even more important.

Previous studies revealed that women with breast augmentation had a higher divorce rate, but even though in the AM group of this study divorce rate was higher, this difference was not statistically significant [27]. Although some investigations found that low education level was a strong predictor of an interest in breast augmentation, we did not notice any difference in education levels in the two groups [28]. Women in the AM group had mostly secondary education level (71.1%) as it could be seen in the control group (77.14%) and in Serbian general population.

Women in the AM group appear to have lower BMI than women in the control group and below average body weight. This could implicate greater prevalence of eating disorders in breast augmentation patients. They have not been inquired in that direction, but this would be interesting, since the data from literature often suggest that distorted eating attitude is a significant predictor of an interest in some types of cosmetic surgery [11, 29]. Eating disorders, like increase in cosmetic surgery operations, could be a consequence of western beauty concept where being thin and young is an imperative. As eating disorders are one of the manifestations of some psychological problems, diagnosing them could be useful for a plastic surgeon as a warning that this patient requires a psychological help prior or instead of an aesthetic surgery.

The hypothesis that patients seeking aesthetic surgery operations have low self-esteem, altered perception of their body and often even psychiatric disorders could be seen earlier in the literature. It could be expected that women who have aesthetic problems consider so important that they should address a plastic surgeon, have low self-esteem. In our study it was found that women seeking AM had a high score in the Rosenberg Self-Esteem Test indicating that they had positive orientation toward themselves and their worth. This coincided with the data from other studies [11, 30, 31]. The subgroup of women with small or "no breasts" and wanted them normal (not big) had the lowest self-esteem, and this is understandable. As breasts are often considered an important symbol of femininity, "not having" them can create a sense of insecurity in women and decreased her self-esteem, as it is seen in the study.

The results of the PFRS should be interpreted carefully considering all limitations of this study designed to see if women who want to do breast augmentation have different physical attractiveness perception than other women. We did not correlate those results with potential differences in personality traits in the two groups which might lead to interesting conclusions. Also as the PFRS can be useful for assessing perception of body size, it would be interesting to see how those results correlate with Multidimensional Body Self Relations questionnaire results, or some other standardized tests used for body image disorder assessment used in this population. This should be done in future studies. As current self rating of body weight based on the PFRS according to the authors strongly correlate with participants BMI, and could be used for assessing perception of body size, we compared BMI of operated women and their current self-rating body size image in order to see if there will be any big discrepancy.[16] In the AM group, like in the control one, women mostly marked their body size accurately or one picture up or down, and there were no any great discrepancies that would implicate distorted body image, so it was not considered that significant. As the aim of this study was not to detect women with BDD, no other test was used for body perception disorders, and therefore it was not possible to present any valid conclusions considering this point.

A "perfect" candidate for the surgery has a healthy body image, and the desire to improve upon a specific feature (e.g. breasts), not the entire body and mind. There is a big difference between the idea of self-improvement with aesthetic surgery and narcissistic, unhealthy fixation with beauty.

Initial psychiatric evaluations of an aesthetic surgery patient conceptualized the desire for cosmetic surgery in terms of unconscious motivations, involving the symbolic meaning of body parts and unresolved sexual conflicts. Contemporary opinion has largely refuted these notions, stating that motivation for aesthetic surgery is not derived from the psychiatric pathology, but rather represents a normal patients attempting to remedy an inconsistency between general and specific body-part esteem [32]. Many researchers have found that cosmetic surgery results in an increased satisfaction with the specific body part that alter, and potentially a slight overall increase in self-confidence [33, 34]. In that respect, it would be interesting to conduct a follow-up study with women of the AM group in order to check whether they achieved their goals, and follow the long-term effects, as well. Some investigations propose that the quality of life and body image measures are probably the most important components of patient's satisfaction and, therefore, they are the most appropriate means addressing the issue of measuring patient's satisfaction in cosmetic surgery [32].

The strength of this study is in various non-surgical aspects that were addressed, and which should provide better overall understanding of patients seeking aesthetic surgery. Different approaches to surgical problems in specific fields

of plastic surgery lead to interesting results. There are of course some limitations of the study that we have to underline. All our patients were from one region, all Caucasian race, all Christian, so the results could not be generalized.

Conclusion

Preoperative evaluation could help surgeons to exclude women with nonrealistic expectations, motivations that are not correlated with real aesthetic problems or those with different body image disorders. Unlike other necessary surgeries, women are often driven to consider cosmetic surgery from a combination of social and emotional factors. Thorough preoperative patients evaluation, not only physical check-up and breast measurement, but also psychological analysis will allow the surgeon to create a good relationship with them, create realistic plans and do good surgery with satisfying outcomes for both sides.

R E F E R E N C E S

1. The American Society for Aesthetic Plastic Surgery. !5th annual Cosmetic Surgery National Data Bank Statistics 2011. Available from: http/ /www.surgery.org/media/statistics
2. *Sarwer DB, Pertschuk M J, Wadden, TA, Whitaker LA.* Psychological investigations in cosmetic surgery: A look back and a look ahead. Plast Reconstr Surg 1998; 101(4): 1136−42.
3. *Cash TF, Melnyk SE, Hrabosky JI.* The assessment of body image investment: An extensive revision of the Appearance Schemas Inventory. Int J Eat Disord 2004; 35(3): 305–16.
4. *Sarwer DB, LaRossa D, Bartlett SP, Low DW, Bucky LP, Whitaker LA.* Body Image Concerns of Breast Augmentation Patients. Plast Reconstr Surg 2003; 112(1): 83−90.
5. *Henderson-King D, Henderson-King E.* Acceptance of cosmetic surgery: Scale development and validation. Body Image: An Int J Res 2005; 2(2): 137−49.
6. *Brown A, Furnham A, Glanville L, Swami V.* Factors that affect the likelihood of undergoing cosmetic surgery. Aesthet Surg J 2007; 27(5): 501–8.
7. *Rubin LR, Klassen A, Cano SJ, Pusic AL.* Motivations for breast surgery: a quantitative comparison study of breast reconstruction, augmentation and reduction patients. Breast J 2009; 15(6) 666−7.
8. *Crerand CE, Infield AL, Sarwer DB.* Psychological considerations in cosmetic breast augmentation. Plast Surg Nurs 2007; 27(3): 146−54.
9. *Solvi AS, Foss K, von Soest T, Roald HE, Skolleborg KC, Holte A.* Motivational factors and psychological processes in cosmetic breast augmentation surgery. J Plast Reconstr Aesthet Surg 2010; 63(4): 673−80.
10. *Bazner J.* Attitudes About Cosmetic Surgery: Gender and Body Experience. GVSU McNair Scholars J 2002; 6(1): 11−6.
11. *Alagoz MS, Basrerzi AD, Uysal AC, Tüzer V, Unlü RE, Sensöz O,* et al. The Psychiatric View of Patients of Aesthetic Surgery: Self-Esteem, Body Image and Eating Attitude. Aesth Plast Surg 2003; 27(5): 345−8.
12. *Sarwer DB.* Psychological consideration in cosmetic surgery. In: *Gloduyn RM, Cohen MN,* editors. The Unfavorable Result in Plastic Surgery. 3rd ed. Philadelphia. Lippincott Wiliams & Wilkins; 2001. p. 14−23.
13. *Crerand CE, Franklin ME, Sarwer DB.* Body dysmorphic disorder and cosmetic surgery. Plast Reconstr Surg 2006; 118(7): 167e−80e.
14. *Kellett S, Clarke S, McGill P.* Outcome from psychological assessment regarding recommendation for cosmetic surgery. J Plast Reconstr Aesthet Surg 2008; 61(5): 512−7.
15. *Borah G, Rankin M, Wey P.* Psychological complication in 281 plastic surgery practices. Plast Reconstr Surg 1999; 104(5): 1241−9.
16. *Swami V, Salem N, Furnham A, Tovee MJ.* Initial examination of the validity and reliability of the female photographic figure rating scale for body image assessment. Personal Individ Differen 2008; 44: 1752−61.
17. *Rosenberg M.* Society and the Adolescent Self-Image. Revised ed. Middletown, CT: Wesleyan University Press, 1989.
18. *Bruck JC, Klenschmidt A, Ottomann C.* Invreased self-confidence and decreased sexual discomfort after subpectoral mammaplasty. Handchir Mikrochir Plast Chir 2011; 43(2): 112−8. (German)
19. *Mazzocchi M, Dessi LA, Iodice P, Saggini R, Scuderi N.* A study of postural changes after breast augmentation. Aesthetic Plast Surg 2012; 36(3): 570−7.
20. *McGregor FC.* Social, psychological and cultural dimensions of cosmetic and reconstructive plastic surgery. Aesth Plast Surg 1989; 13(1): 1−8.
21. *Simis KJ, Verhulst FC, Koot HM.* Body image, psychosocial functional, and personality: How different are adolescents and young adults applying for plastic surgery? J Child Psychol Psychiatry 2001; 42(5): 669−78.
22. *Sarwer DB, Crerand CE.* Body image and cosmetic medical treatments. Body Image 2004; 1(1): 99−111.
23. *Didie ER, Sarwer DB.* Factors that influence the decision to undergo cosmetic breast augmentation surgery. J Womens Health (Larchmt) 2003; 12(3): 241−53.
24. *Javo IM, Sorlie T.* Psychosocial predictors of an interest in cosmetic surgery:a population-based study. Plast Reconstr Surg 2009; 124(6): 2142−8.
25. *von Soest T, Kvalem IL, Skolleborg KC, Roald HE.* Psycholosocial factors predicting the motivation to undergo cosmetic surgery. Plast Reconstr Surg 2006; 117(1): 51−62; discussion 63−4.
26. *Honigman R, Phillips KA, Castle DJ.* A review of psychosocial outcomes for patients seeking cosmetic surgery. Plast Reconstr Surg 2004; 113(4): 1229−37.
27. *Birtchnell S, Whitfield P, Lacey JH.* Motivation factors in women requesting augmentation and reduction mammaplasty. J Psychosom Res 1990; 34(5): 509−14.
28. *Javo IM, Sorlie T.* Psychosocial characteristics of young norwegian women interested in liposuction, breast augmentation, rhinoplasty, and abdominoplasty:a population –based study. Plast Reconstr Surg 2010; 125(5): 1536−43.
29. *Levine JC, Anderson RC.* Preoperative assessment of eating disorders in plastic surgery patients. Plast Surg Nurs 2009; 29(1): 60−3.
30. *Burk J, Zelen SL, Terino EO.* More than skin deep: a self-consistency approach to the psychology of cosmetic surgery. Plast Reconstr Surg 1985; 76(2): 270−80.
31. *Ozgur F, Tuncali D Gursu G.* Life satisfaction, self-esteem and body image:a psychosocial evaluation of aesthetic an reconstructive surgery candidates. Aesthetic Plast Surg 1998; 22(6): 412−9.
32. *Shim C, Thoma A, McCabe RE, Antony M.* Measuring Outcomes in Aesthetic Surgery: A Comprehensive Review of the Literature. Plast Reconstr Surg 2003; 111(1): 469−80.

33. *Crerand CE, Cash TF, Whitaker LA.* Cosmetic surgery of the face. In: *Sarwer DB, Pruzinsky T, Cash TF, Goldwyn RM, Persing JA, Whitaker LA*, editors. Psychological Aspects of Reconstructive and Cosmetic Plastic Surgery: Empirical, Clinical, and Ethical Issues. Philadelphia, Pennsylvania: Lippincott Williams & Wilkins; 2006. p. 233−50.
34. *Sarwer DB, Didie ER, Gibbons LM.* Cosmetic surgery of the body. In: *Sarwer DB, Pruzinsky T, Cash TF, Goldwyn RM, Persing JA, Whitaker LA,* editors. Psychological Aspects of Reconstructive and Cosmetic Plastic Surgery: Empirical, Clinical, and Ethical Issues. Philadelphia, Pennsylvania: Lippincott Williams & Wilkins; 2006. p. 251−66.

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ORIGINAL ARTICLE

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Correlation between extraintestinal manifestations and clinical parameters with the histologic activity index in patients with inflammatory bowel diseases

Povezanost vancrevnih manifestacija i kliničkih parametara sa indeksom histološke aktivnosti kod bolesnika sa inflamatornim bolestima creva

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Abstract

Bacground/Aim. Crohn's disease (CD) and ulcerative colitis (UC) are chronic, idiopathic, inflammatory diseases of the digestive tract. The aim of this study was to determine a possible correlation between the clinical parameters of the disease activity degree and the presence of extraintestinal manifestations with disease activity histopathological degree, in patients presented with CD and UC. **Methods.** This cross-sectional study included 134 patients (67 with CD and UC, respectively) treated at the Clinic of Gastroenterology, Clinical Center of Serbia, Belgrade. After clinical, laboratory, endoscopic, histopathologic and radiologic diagnostics, the patients were divided into two groups according to their histopathological activity. The group I comprised 79 patients whose values of five-grade histopathological activity were less than 5 (45 with CD and 34 with UC), while the group II consisted of 55 patients with the values higher than 5 (22 with CD and 33 with UC). The CD activity index (CDAI) and Truelove and Witts' scale of UC were used for clinical evaluation of the disease activity. **Results.** CD extraintestinal manifestations were present in 28.9% and 63.6% of the patients in the groups I and II, respectively ($p < 0.05$). Comparison of the mean CDAI values found a significant difference between these two patients groups (the group I: 190.0 ± 83.0, the group II: 263.4 ± 97.6; $p < 0.05$). No correlation of extraintestinal manifestations of the disease, Truelove and Witts' scale and histological activity was found in UC patients ($p > 0.05$). **Conclusion.** In the patients presented with CD, the extraintestinal manifestations with higher CDAI suggested a higher degree of histopathological activity. On the contrary, in the UC patients, Truelove and Witts' scale and extraintestinal manifestations were not valid predictors of the disease histopathological activity.

Key words:
crohn disease; colitis, ulcerative; severity of illness index; signs and symptoms; histological techniques.

Apstrakt

Uvod/Cilj. Kronova bolest (*Crohn's disease* – CD) i ulcerozni kolitis (*ulcerative colitis* – UC) su hronične, idiopatske, zapaljenske bolesti digestivnog trakta. Cilj rada bio je da se utvrdi da li kod bolesnika sa CD i UC postoji uzajamni odnos između kliničkih pokazatelja stepena aktivnosti bolesti i prisustva vancrevnih manifestacija sa patohistološkim stepenom aktivnosti bolesti. **Metode.** Studija preseka obuhvatila je 134 bolesnika (67 sa CD i 67 sa UC) lečena u Klinici za gastroenterologiju Kliničkog centra Srbije u Beogradu. Nakon kliničke, laboratorijske, endoskopske, patohistološke i radiološke dijagnostike, bolesnici su na osnovu patohistološke aktivnosti bolesti podeljeni u dve grupe. U grupu I svrstano je 79 bolesnika čije su vrednosti petostepenog gradusa patohistološke aktivnosti bile manje od 5 (45 sa CD i 34 sa UC), dok je u grupi II bilo 55 bolesnika sa vrednostima većim od 5 (22 sa CD i 33 sa UC). Za kliničku procenu aktivnosti bolesti korišćen je indeks aktivnosti CD bolesti (CDAI) i Truelove i Wittsova skala za UC. **Rezultati.** Vancrevne manifestacije CD bile su prisutne kod 28,9% bolesnika grupe I i 63,6% bolesnika grupe II ($p < 0,05$). Upoređivanjem srednjih vrednosti CDAI uočena je statistički značajna razlika između dve grupe bolesnika (grupa I: 190,0 ± 83,0, grupa II: 263,4 ± 97,6; $p < 0,05$). Kod bolesnika sa UC nije utvrđena veza između prisustva vancrevnih manifestacija bolesti, Truelove i Wittsove skale i patohistološke aktivnosti bolesti ($p > 0,05$). **Zaključak.** Kod bolesnika sa CD prisustvo vancrevnih manifestacija, zajedno sa višim CDAI, ukazuje na veći stepen patohistološke aktivnosti bolesti. Nasuprot tome, kod bolesnika sa UC, Truelove i Wittsova skala i prisustvo vancrevnih manifestacija nisu bili pouzdani prediktori histološkog stepena aktivnosti bolesti.

Ključne reči:
kronova bolest; kolitis, ulcerativni; bolest, indeks težine; znaci i simptomi; histološke tehnike.

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Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are idiopathic, chronic, inflammatory diseases of the digestive tract. Due to similar clinical manifestation, histopathological findings, diagnostics, complications and treatment, these diseases are both described as inflammatory bowel diseases (IBD).

In CD patients, changes are most usually localized in the terminal ileum and ascending colon, then in the colon or terminal ileum only, and the rarest location is only in the ileum and/or jejunum. The most characteristic histopathological finding is chronic inflammation which involves all intestinal wall layers, followed by deep ulcerations, frequently seen as linear fissures with "cobblestone" appearing mucosa between them [1].

On the contrary to CD, in UC patients changes always affect the rectum and may be continuously spread to the proximal colon all the way to the caecum. Mucosa is primarily involved, being uniformly hyperemic, edematous, ulcerated and fragile. In a long-term course of the disease, fibrosis and longitudinal retraction result in the loss of haustra, and X-ray finding demonstrates typical "lead-pipe" appearance of the colon [2].

There is no possibility to distinguish UC from CD, up to 10–20% of cases, what is a special clinical entity called indeterminate colitis. The majority of these patients is differentiated as UC patients over time. Indeterminate colitis is a histopathological term, meaning the condition where biopsy specimens of the colon have overlapping characteristics [3].

The commonest intestinal IBD symptoms are following: diarrhea, abdominal pain, hemorrhage, body weight loss and fever. Extraintestinal manifestations (EIM) are also significant, manifesting as: skin changes (erythema nodosum, vasculitis, pyoderma gangrenosum), arthralgia and arthritis, ankylosing spondylitis, uveitis, episcleritis, biliary lithiasis and urolithiasis. Additionally, IBDs are frequently associated with primary sclerosing cholangitis, thrombosis and embolies [4].

The aim of the study was to find out if there was a correlation between clinical parameters of the disease activity and the EIM presence with the histopathological activity index of the disease.

Methods

This cross-sectional study was conducted at the Clinic for Gastroenterology, Clinical Center of Serbia, Belgrade, including a period from December 2006 to January 2011. The study involved 134 patients (67 with CD and UC, respectively).

All the patients were analyzed for the following parameters: age, sex, localization of changes in the digestive tract, histopathological degree of the disease activity (five-grade activity), present EIM, Crohn's Disease Activity Index (CDAI) [5] and Truelove and Witts' scale for the assessment of the activity [6].

The investigation was based on the medical history data, physical examination and laboratory analyses used for CDAI (Table 1) and Truelove and Witts' scale (Table 2) calculations. All the patients underwent colonoscopy with histopathological verification. The patients with non-determined colitis were excluded.

Table 1

Crohn's Disease Activity Index – (CDAI)[5]

Parameter	Index
Number of liquid or soft stools in 7 days	× 2
Abdominal pain – pain score per day (0 = none, 1 = mild, 2 = moderate, 3 = severe)	× 5
General well-being – general well-being score per day (0 = generally well, 1 = slightly under par, 2 = poor, 3 = very poor, 4 = terrible)	× 7
Number of complications (presence or absence): arthritis or arthralgia iritis or uveitis anal fissure, fistula or abscess erythema nodosum, pyoderma gangrenosum, aphthous stomatitis other fistula fever over 37.8°C	× 20
Loperamide or diphenoxylate for diarrhea	× 30
Abdominal mass (none = 0, questionable = 2, definite = 5)	× 10
Hematocrit [males 47 (%), females 42 (%)]	× 6
Body weight: (1- Body weight/standard weight) × 100	× 1

Table 2

Truelove and Witts' index [6]

Parameter	Mild	Moderate	Severe
Bloody stools	< 4	≥ 4	≥ 6
Pulse rate	< 90/min	≤ 90/min	> 90/min
Temperature	< 37.5 °C	≤ 37.8 °C	> 37.8 °C
Hemoglobin	> 11.5 g/dL	≥ 10.5 g/dL	≥ 10.5g/dL
ESR/CRP	normal	≤ 30	> 30

ESR – erythrocyte sedimentation rate; CRP – C reactive protein.

The patients were divided into two groups according to the values of five-grade inflammation activity (FGA) by Geboes et al. [7], which is a numerical scale for evaluating the histological disease activity (Table 3).

Table 3

The histologic grading system according to Geboes et al. [7]

GRADE 0 – structural (architectural change)
0.0. No abnormality
0.1 Mild abnormality
0.2 Mild or moderate diffuse or multifocal abnormalities
0.3 Severe diffuse or multifocal abnormalities
GRADE 1 – Chronic inflammatory infiltrate
1.0 No increase
1.1 Mild but unequivocal increase
1.2 Moderate increase
1.3 Marked increase
GRADE 2 – Lamina propria neutrophils and eosinophils
2A Eosinophils
2A.0 No increase
2A.1 Mild but unequivocal increase
2A.2 Moderate increase
2A.3 Marked increase
2B Neutrophils
2B.0 None
2B.1 Mild but unequivocal increase
2B.2 Moderate increase
2B.3 Marked increase
GRADE 3 – Neutrophils in epithelium
3.0 None
3.1 < 5% crypts involved
3.2 < 50% crypts involved
3.3 > 50% crypts involved
GRADE 4 – Crypt destruction
4.0 None
4.1 Probable – local excess of the neutrophils in part of the crypt
4.2 Probable – marked attenuation
4.3 Unequivocal crypt destruction
GRADE 5 – Erosion or ulceration
5.0 No erosion, ulceration, or granulation tissue
5.1 Recovering epithelium + adjacent inflammation
5.2 Probable erosion focally stripped
5.3 Unequivocal erosion
5.4 Ulcer or granulation tissue

Descriptive and analytical statistical methods were used for data analysis: Mann-Whitney test for numerical characteristics and χ^2 test for categorical characteristics. The values of $p < 0.05$ were considered significant. SPSS for Windows v.17.0 (SPSS Inc. Chicago, IL) was used for statistical data processing.

Results

There were 45 CD patients in the group I, with the values of FGA < 5.0, while the group II included 22 patients with the values of FGA > 5.0. Among the UC patients, 34 patients with FGA < 5.0 were in the group I and 33 patients with FGA > 5.0 were in the group II.

The average age of the patients with CD was 37.1 ± 14.2 years, of which 28 (41.8%) were males and 39 (58.2%) females. Upon group analysis, no significant difference in age (Mann Whitney U Z= -1.094; $p = 0.274$) and sex ($\chi^2 = 0.010$; $p = 0.918$) was found in the CD patients (Table 4).

There was no statistical significance in relation to CD localization ($\chi^2 = 2.919$; $p = 0.232$). Ileocolitis was manifested in 24 (53.3%) patients with the lower histopathological activity index and 13 patients with FGA > 5 (59.1%), what is the most frequent localization of CD. Second by frequency was Crohn colitis presented in 12 (26.7%) patients with FGA < 5 and 8 (36.4%) patients with FGA > 5, while the localized disease of the terminal ileum was found in 9 (20%) patients with FGA < 5 and only in one (4.5%) with high histopathological activity index.

Comparison of the mean values of CDAI (in patients with FGA < 5 190.0 ± 83.0, and in the group with high histopathological activity 263.4 ± 97.6), showed a direct correlation and highly significant difference between (Mann Whitney UZ = -3.385; $p = 0.001$).

Out of a total number of patients, at least one EIM was reported in 39 (29.1%) patients (CD 40.3%; UC 17.9%). In the CD patients, EIMs were manifested in the forms of: arthralgia in 19 (28.4%), aphthous stomatitis in 5 (7.5%), ery-

Table 4

Distribution of patients with Crohn's disease (CD) and ulcerative colitis (UC) according to age, sex and five-grade inflammation activity (FGA)

Disease	FGA	Patients			
		age (years), $\bar{x} \pm SD$	*p*	sex (M/F), n	*p*
CD	< 5	38.8 ± 2.4 (n = 34)	0.274	19/26	0.918
	> 5	33.8 ± 2.4 (n = 30)		9/13	
UC	< 5	40.5 ± 3.7 (n = 35)	0.994	16/18	0.895
	> 5	40.4 ± 3.0 (n = 34)		15/18	

thema nodosum in 5 (7.5%), uveitis anterior in 2 (3%) and primary sclerosing cholangitis in 2 (3.0%) of the patients. In relation to histopathologic activity index of CD, EIM were present in 13 (28.9%) of the patients with a low histologic grade of the disease activity and 14 (63.6%) patients with FGA > 5 ($\chi^2 = 7.415$; $p = 0.009$) (Figure 1).

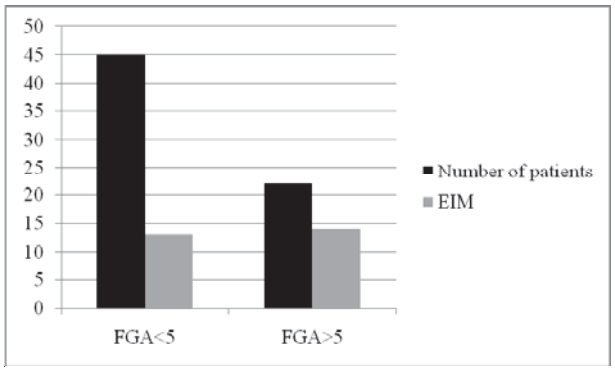

Fig. 1 – Distribution of patients with extraintestinal manifestations (EIMs) of Crohn's disease in relation to five grade inflammation activity (FGA) ($p = 0.009$).

In 67 patients with UC, the mean age was 40.5 ± 15.5 years, out of which 31 (46.3%) were males and 36 (53.7%) females. Group analysis failed to show any difference in age (Mann Whitney U Z = -0.007; $p = 0.994$) and sex ($\chi^2 = 0.017$; $p = 1.000$) of the patients with different velues of FGA (Table 4).

Comparison of the diseases distribution in patients with UC to the histopathological disease activity found a statistically significant difference ($\chi^2 = 9.439$; $p = 0.003$). A total of 12 (35.3%) patients with a moderate histological form of the disease were diagnosed with pancolitis, while the rest of 22 (64.7%) patients had "left side' distribution of the disease. In the patient group with FGA > 5, 24 (72.7%) patients had pancolitis, while others had "left side" colitis.

Testing the correlation of Truelove and Witts' scale and histopathological activity index failed to show any significant difference in the diseese distribution ($\chi^2 = 1.679$; $p = 0.432$) (Figure 2). The moderate form of disease was presented in 15 (44.1%) patients with low histopathological activity index and in 15 (45.5%) patients with FGA > 5. A severe form of the disease had 11 (32.4%) patients with FGA < 5 and 14 (42.4%) patients with FGA > 5, while a mild form of it was lightly represented in only 8 (23.5%) patients, whose FGA was lower than 5 and in 4 (12.1%) patients with FGA > 5.

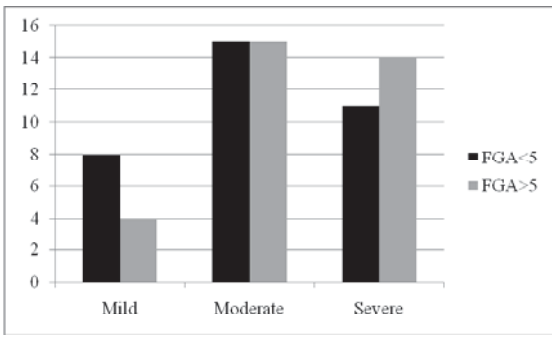

Fig. 2 – Distribution of patients with ulcerative colitis according to values of the Truelove and Witts' scale and five grade inflammation activity (FGA) of the disease ($p = 0.432$).

EIMs were verified in 7 (20.6%) of the patients with lower histopathological activity index of UC and in 5 (15.2%) patients with FGA > 5. Arthralgia and primary sclerosing cholangitis (PSC) were manifested in 5 (7.5%) patients, respectively, and pyoderma gangrenosum in 3 (4.5%) patients. In distinction from CD, UC patients were not verified with a significant difference between the EIM and the histopathological activity index ($\chi^2 = 0.337$; $p = 0.752$) (Figure 3).

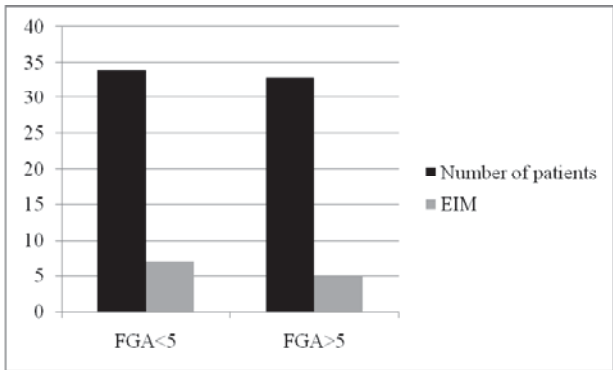

Fig. 3 – Distribution of patients with extraintestinal manifestations (EIMs) of ulcerative colitis in relation to five-grade activity (FGA) of the disease and ($p = 0.752$).

Discussion

The maximum age of the onset for both diseases is between 15 and 25 years. In some series, the second, lower peak of incidence occurs between 55 and 65 years. Most series show approximately equal incidence of both diseases in males and females. Some studies show CD incidence higher in females by 30%, while it may be somewhat higher among males [8, 9].

In our study, the majority of patients were between 35 and 45 years of age, what is compatible with literature data.

Most studies report that females are more affected with CD than males, contrary to UC where the incidence is higher in males. Also, a large study of Herrinton et al. [9] reported a higher incidence rate of CD in women than in men (1.2 times as frequent), and higher incidence rate of UC in men than in women (1.3 times as frequent).

Our study also confirmed higher incidence of CD in women. However, contrary to earlier articles, the incidence of UC was also higher in women than in men.

Younger age at diagnosis (< 20 years), compared with the older age (≥ 40), was associated with higher incidence of CD family history (29.9% *vs* 13.6%, respectively), greater small bowel involvement (88.7% *vs* 57.5%, respectively), more stricturing disease (45.8% *vs* 28.8%, respectively), and higher frequency of surgery (70.6% *vs* 55.3%, respectively). Older age *vs* yunger one at diagnosis was associated with higher incidence of colonic disease (84.8% *vs* 71.2%, respectively) and the inflammatory subtype (54.5% *vs* 34.4%, respectively) [10].

Epidemiological and family studies demonstrate that genetic factors play a role in the susceptibility to IBD. UC and CD may be heterogeneous polygenic disorders sharing some but not all susceptibility loci. Most likely, the disease phenotype is determined by several factors, including the interaction between allelic variants at a number of loci, as well as genetic and environmental influences [11]. Genome-wide scanning with microsatellite DNA markers has identified several genetic sites as being potentially associated with UC or CD [11]. Significant linkages have been reported on chromosomes 1, 3, 6, 7, 12, 14, 16, and 19 [12]. Detailed analysis has resulted in the identification of the nucleotide-binding oligomerization domain 2 (NOD2) gene and protein. NOD2 is also known as caspase activation and recruitment domain 15 (CARD15). This is a polymorphic gene, the product of which is involved in the innate immune system. It is estimated that defects in NOD2 account for 17% to 27% of CD cases [13].

In addition, pathogenic microbes such as: *Mycobacterium paratuberculosis, Listeria monocytogenes, Chlamydia trachomatis, Escherichia coli, Cytomegalovirus, Saccharomyces cerevisiae*, have been proposed as having a potential etiologic role [14]. Bacterial superinfection (most commonly *Clostridium difficile*, but also *Entamoeba histolytica, Campylobacter spp.*) is also able to elicit relapse of IBD. This hypothesis was confirmed in the study of Mylonaki et al. [15] 2004, where 10.5% of all relapses were associated with the enteric infections. In another study, 20% of all relapses were associated with *Clostridium difficile* [16].

In genetically susceptible host with IBD, other local factors in the colon with the antigen presenting cells may trigger an immune reaction to a shared antigen in the involved organs. This pathogenetic mechanism may explain the development of EIMs, which are observed in up to 20–40% of patients with IBD. Moreover, patients with CD are more susceptible to EIM than patients with UC [17].

EIMs may involve nearly any organ system including musculoskeletal, dermatologic, hepatopancreatobiliary, ocular, renal and pulmonary systems that can cause a significant challenge to physicians managing IBD patients [18]. Some of them are very rare: tracheobronchitis, acute respiratory distress syndrome, membranous glomerulonephritis, acute pancreatitis, lower extremity arterial occlusive disease, pericarditis or acute CNS white matter lesions.

Few studies have specifically examined how frequently EIM is a patient's presenting symptom or is present at the time of diagnosis *vs* occurring later in the disease course. In a retrospective study of 448 IBD patients Aghazadeh et al. [19] showed that 31.4% of UC patients and 40.4% of CD patients had 1 of the 5 major manifestations. A smaller percentage of patients had more than 1 EIM.

The study of Yüksel I et al. [20], included 352 patients. Among them, 34 (9.3%) patients presented with at least 1 cutaneous manifestation. The prevalence of erythema nodosum and pyoderma gangrenosum in IBD was 7.4% and 2.3%, respectively. Erythema nodosum was more common in CD (16/118) than UC (10/234) and was found to be related to disease activity of the bowel. In addition, they reported that the prevalence of arthritis was significantly higher in the IBD patients with erythema nodosum and pyoderma gangrenosum [20].

In a study of Vavricka et al. [21] 950 IBD patients were prospectively included from an adult clinical cohort in Switzerland. There were 580 (61%) cases with CD and 370 (39%) with UC. Out of these, 249 (43%) of CD and 113 (31%) of UC patients had one to five EIMs. The following EIMs were found: arthritis (CD 33%; UC 21%), aphthous stomatitis (CD 10%; UC 4%), uveitis (CD 6%; UC 4%), erythema nodosum (CD 6%; UC 3%), ankylosing spondylitis (CD 6%; UC 2%), psoriasis (CD 2%; UC 1%), pyoderma gangrenosum (CD and UC each 2%), and primary sclerosing cholangitis (CD 1%; UC 4%) [21].

In our study, the EIM incidence in CD patients was 40.3%, what is compatible with earlier reports. The frequency of arthralgia, aphthous stomatitis, erythema nodosum, uveitis anterior and primary sclerosing cholangitis did not deviate from other study data. However, in distinction from the aforementioned studies, the EIM incidence in the UC patients was 17.9%. A low EIM incidence in UC could be accounted for correlation between the EIM and histopathological disease activity found no in our study.

Mendoza et al. [22] described that EIM related to IBD occurred at least once in 46.6% of patients. Joint manifestations were the most common EIM (UC 51.5%; CD 42.2%). Hepatobiliary manifestations, venous thromboembolism and arthralgias were more frequent in UC than CD. Erythema nodosum and peripheral arthritis were more frequent in CD. The incidence of the ocular and the rest of joint manifestations were not different in relation to UC or CD.

Asymptomatic sacroiliitis may be actually seen in up to three-quarters of IBD patients. Careful survey may also reveal many patients with a history of swollen joints and other musculoskeletal symptoms, often preceding the diagnosis of IBD in several years. The prevalence of axial arthritis varies from 3% to 25% of patients with IBD and may or may not be associated with peripheral arthropathy [23]. Moreover, several

case studies have described acute idiopathic pancreatitis manifested many years before diagnosis of CD was made [24].

EIM sometimes impair the overall life quality much more than the bowel-related symptoms. Extraintestinal manifestations need to be distinguished from secondary diseases or complications of inflammatory bowel diseases, as they require different and specific treatment [25].

Conclusion

In patients with CD, EIMs together with higher CDAI indicate higher histopathological activity grade. On the contrary, in UC patients, Truelove and Witts' scale and EIMs were not valid predictors of histopathological activity of the disease.

REFERENCES

1. *Steinhardt HJ, Loeschke K, Kasper H, Holtermüller KH, Schäfer H.* European Cooperative Crohn's Disease Study (ECCDS): clinical features and natural history. Digestion 1985; 31(2−3): 97−108.
2. *Griffel LH, Das KM.* Ulcerative colitis: pathogenesis, diagnosis, and current treatment. J Assoc Acad Min Phys 1996; 7(3): 63–9.
3. *Van Assche G, Dignass A, Panes J, Beaugerie L, Karagiannis J, Allez M,* et al. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: Definitions and diagnosis. J Crohns Colitis 2010; 4(1): 7−27.
4. *Popović O, Vukčević V.* Inflammatory bowel diseases: Crohn's Disease and ulcerative colitis. In: *Manojlović D,* editor. Internal medicine I. Belgrade: Zavod za udžbenike i nastavna sredstva; 2006. p. 687–700. (Serbian)
5. *Best WR, Becktel JM, Singleton JW.* Rederived values of the eight coefficients of the Crohn's Disease Activity Index (CDAI). Gastroenterology 1979; 77(4 Pt 2): 843−6.
6. *Truelove SC, Witts LJ.* Cortisone in ulcerative colitis. Final report on a therapeutic trial. Br Med J 1955; 2(4947): 1041–8.
7. *Geboes K, Riddell R, Ost A, Persson T, Lofberg R.* A Reproducible grading scale for histological assessment of inflammation in ulcerative colitis. Gut 2000; 47(3): 404–9.
8. *Calkins BM, Lilienfeld AM, Garland CF, Mendeloff AI.* Trends in the incidence rates of ulcerative colitis and Crohn's disease. Dig Dis Sci 1984; 29(10): 913−20.
9. *Herrinton LJ, Liu L, Lewis JD, Griffin PM, Allison J.* Incidence and Prevalence of Inflammatory Bowel Disease in a Northern California Managed Care Organization, 1996–2002. Am J Gastroenterol 2008; 103(8): 1998–2006.
10. *Polito JM 2nd, Childs B, Mellits ED, Tokayer AZ, Harris ML, Bayless TM.* Crohn's disease: Influence of age at diagnosis on site and clinical type of disease. Gastroenterol 1996; 111(3): 580–6.
11. *Satsangi J, Morecroft J, Shah NB, Nimmo E.* Genetics of inflammatory bowel disease: scientific and clinical implications. Best Pract Res Clin Gastroenterol 2003; 17(1): 3–18.
12. *Hendrickson BA, Gokhale R, Cho JH.* Clinical aspects and pathophysiology of inflammatory bowel disease. Clin Microbiol Rev 2002; 15(1): 79–94.
13. *Hugot JP, Chamaillard M, Zouali H, Lesage S, Cezard JP, Belaiche J,* et al. Association of NOD2 leucine rich repeat variants with susceptibility to Crohn's disease. Nature 2001; 411(6837): 599–603.
14. *Lakatos PL, Fischer S, Lakatos L, Gal I, Papp J.* Current concept on the pathogenesis of inflammatory bowel disease-crosstalk between genetic and microbial factors: Pathogenic bacteria and altered bacterial sensing or changes in mucosal integrity take "toll"? World J Gastroenterol 2006; 12(12): 1829–41.
15. *Mylonaki M, Langmead L, Pantes A, Johnson F, Rampton DS.* Enteric infection in relapse of inflammatory bowel disease: importance of microbiological examination of stool. Eur J Gastroenterol Hepatol 2004; 16(8): 775–8.
16. *Meyer AM, Ramzan NN, Loftus EV Jr, Heigh RI, Leighton JA.* The diagnostic yield of stool pathogen studies during relapses of inflammatory bowel disease. J Clin Gastroenterol 2004; 38(9): 772–5.
17. *Agrawal D, Rukkannagari S, Kethu S.* Pathogenesis and clinical approach to extraintestinal manifestations of inflammatory bowel disease. Minerva Gastroenterol Dietol 2007; 53(3): 233–48.
18. *Larsen S, Bendtzen K, Nielsen OH.* Extraintestinal manifestations of inflammatory bowel disease: Epidemiology, diagnosis, and management. Ann Med 2010; 42(2): 97–114.
19. *Aghazadeh R, Zali MR, Bahari A, Amin K, Ghahghaie F, Firouzi F.* Inflammatory bowel disease in Iran: a review of 457 cases. J Gastroenterol Hepatol 2005; 20(11): 1691–5.
20. *Yüksel I, Başar O, Ataseven H, Ertuğrul I, Arhan M, Ibiş M,* et al. Mucocutaneous manifestations in inflammatory bowel disease. Inflamm Bowel Dis 2009; 15(4): 546–50.
21. *Vavricka SR, Brun L, Ballabeni P, Pittet V, Vavricka BM, Zeitz J,* et al. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. Am J Gastroenterol 2011; 106(1): 110–9.
22. *Mendoza JL, Lana R, Taxonera C, Alba C, Izquierdo S, Díaz-Rubio M.* Extraintestinal manifestations in inflammatory bowel disease: differences between Crohn's disease and ulcerative colitis. Med Clin (Barc) 2005; 125(8): 297–300. (Spanish)
23. *Meier C, Plevy S.* Therapy insight: how the gut talks to the joints-inflammatory bowel disease and the spondyloarthropathies. Nat Clin Pract Rheumatol 2007; 3(11): 667–74.
24. *Triantafillidis JK, Merikas E, Malgarinos G, Panteris V, Peros G.* Acute idiopathic pancreatitis preceding diagnosis of Crohn's disease. Description of three cases. Rev Med Chir Soc Med Nat Iasi 2009; 113(1): 97–102.
25. *Rogler G, Schölmerich J.* Extraintestinal manifestations of inflammatory bowel disease. Med Klin (Munich) 2004; 99(3): 123–30. (German)

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Combined spinal-epidural technique: single-space *vs* double distant space technique

Kombinovana spinalno-epiduralna tehnika: izvođenje u jednom prostoru i u dva udaljena prostora

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Abstract

Background/Aim. Several combined spinal-epidural (CSE) anesthesia techniques have been described. This study was designed to compare the single space ("needle-through-needle") technique (SST) and the double distant space technique (DDS) with regards to the time needed for the procedure, patient discomfort during the procedure and patient's preference technique. **Methods.** This prospective, randomized single-blind study included 156 patients undergoing colorectal surgery under general anesthesia and CSE. All neuraxial blocks were performed before general anesthesia induction. DDS group of patients had thoracic epidural catheter placed at T6–7 or T7–8, followed by subarachnoid injection at the L2–3 interspace. The SST group of patients had a single injection using the needle-through-needle technique (Espocan® needle) at L2–3. The epidural catheter was used for postoperative analgesia for 72 hours. Body habitus, spinal anatomy and spinal landmarks were assessed preoperatively. The number of epidural and spinal punctures, the feeling that the dura is perforated (dural perforation click) and the time needed to perform CSE were also recorded. Complications during epidural catheter placement and perioperative and postoperative epidural catheter function and patient preference for the anesthetic procedure were recorded. **Results.** Epidural and subarachnoid spaces were successfully identified in all the patients. Duration of CSE procedure, the number of spinal punctures, dural click feeling and the effects of test dose did not differ between the groups. The patients in both groups (90% of DDS and 87% of SST) would choose CSE as preferred method in the future. The CSE procedure was painful for 16% of DDS *vs* 20% of SST patients. A significant correlation between time needed for CSE technique performance and body habitus ($r = 0.338$, $p < 0.01$), spinal landmarks ($r = 0.452$, $p < 0.001$) and anatomy ($r = 0.265$, $p < 0.05$) was found in the SST group. There was no correlation between the number of epidural/spinal punctures and epidural bacteriological findings. There was no correlation between the patients' choice of the CSE technique and the number of spinal punctures, duration of CSE procedure and epidural catheter stay. **Conclusion.** The two CSE techniques did not differ with regards to the procedure time and patient's preference. Procedure time correlated with body habitus, spinal landmarks and the anatomy in the SST group.

Key words:
anesthesia, epidural; anesthesia, spinal; colorectal surgery; anesthesia, general.

Apstrakt

Uvod/Cilj. Opisano je više tehnika izvođenja kombinovane spinalno-epiduralne anestezije (KSE). Ova studija je sprovedena sa ciljem da se uporede tehnike u jednom prostoru „igla-kroz-iglu" (SST) i tehnika dva udaljena prostora (DDS) u smislu dužine trajanja procedure, bolnosti i izbora tehnike od strane bolesnika. **Metode.** Ova prospektivna, randomizovana, jednostruko slepa studija obuhvatila je 156 bolesnika koji su planirani za kolorektalnu hirurgiju. Svi neuroaksijalni blokovi su izvođeni pre uvoda u anesteziju. Ukoliko je izvođena DDS tehnika, prvo je postavljan epiduralni kateter (T6–7 ili T7–8), a nakon toga izvedena subarahnoidna punkcija na nivou L2–3 (spinalna igla 25G). SST je izvođena upotrebom Espocan® igle specijalno konstruisane za izvođenje KSE u nivou L2–3. Nakon identifikacije epiduralnog prostora, vršena je subarahnoidana punkcija. Epiduralni kateter korišćen je za terapiju postoperativnog bola u periodu od 72 časa. Preoperativno, ispitana je telesna građa bolesnika, spinalna anatomija i spinalni anatomski znaci. Beleženi su broj spinalnih i epiduralnih punkcija, postojanje osećaja probijanja dure i vreme neophodno za izvođenje KSE, pojava parestezija kao i problemi tumačenja epiduralne test doze. Beležene su komplikacije u toku postavljanja epiduralnog katetera, perio-

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perativno i postoperativno funkcionisanje epiduralnog katetera i mišljenje bolesnika da li bi prihvatio korišćenje iste tehnike za sledeći hirurški zahvat. **Rezultati.** Epiduralni i subarahnoidni prostori su uspešno indentifikovani kod svih bolesnika. Nije bilo razlika između grupa u pogledu dužine trajanja KSE procedure, broja spinalnih punkcija, osećaja probijanja dure i tumačenja test doze. KSE tehnika bi bila procedura izbora za terapiju bola u obe grupe (DDS 90.4%, SST 87%). Izvođenje KSE tehnike bilo je bolno kod 16% DDS i 20% SST bolesnika. U SST grupi ustanovljena je značajna korelacija u vremenu neophodnom za izvođenje KSE, telesnoj građi ($r = 0.338$, $p < 0.01$), spinalnim znacima ($r = 0.452$, $p < 0.001$) i anatomiji ($r = 0.265$, $p < 0.05$). Nije nađena korelacija između broja epiduralnih/spinalnih punkcija i pozitivnih bakterioloških kultura. Nije nađena korelacija između odluke za ponovni izbor tehnike i broja spinalnih punkcija, trajanja izvođenja KSE i dužine stajanja epiduralnog katetera. **Zaključak.** Nije nađena razlika u dužini trajanja između dve tehnike izvođenja KSE. U tehnici izvođenja KSE u jednom interspinalnom prostoru, dužina izvođenja procedure KSE bila je u korelaciji sa telesnom građom, spinalnim znacima i spinalnom anatomijom.

Ključne reči:
anestezija, epiduralna; anestezija, spinalna; hirurgija, kolorektalna, procedure; anestezija, opšta.

Introduction

Combined spinal-epidural-general anesthesia (CSE-GA) offers several advantages over general anesthesia alone [1]. Several CSE techniques are described [2], and several technical improvements have been proposed as attempts to improve the technique, and reduce the incidence of complications. According to previous studies, the separate needle technique is superior compared to the "needle-through-needle" techniques with regards to complications and effectiveness [2].

Single space "needle-through-needle" technique (SST) is performed using a modified Touhy needle that has a back eye, *ie* a hole at the Touhy needle bevel for spinal needle guidance. The lower number of skin punctures with the SST technique may decrease pain during the procedure, and may also reduce the risk of infection at the puncture site, especially skin-borne infections and hematomas [3].

Since special CSE kits became commercially available, the single space CSE technique has been the preferred technique, whereas the double space technique is rarely used, because it requires puncture at two different interspaces (one space for epidural catheter placement and a lower space for subarachnoid puncture). In this study we used the technique described in earlier publications, which includes epidural puncture for epidural catheter placement in the thoracic region, combined with spinal puncture and a single subarachnoid injection at a lumbar level (double distant space – DDS) [4, 5].

The aim of a study was to compare the single space "needle-through-needle" technique (SST) with the double distant space technique (DDS). Our hypothesis was that the SST could offer shorter procedural time, less patient discomfort and better patient satisfaction as compared to the DDS. The time needed to perform the CSE procedure was the primary study outcome. Patient discomfort during the procedure and patient preference for the CSE as the technique of choice for postoperative pain management were designated as secondary outcomes.

Methods

This prospective, randomized, single blinded clinical trial was approved by the University Expert Council for Medical Science, and written informed consent was obtained from all patients before they entered the study. In total, 160 the American Society of Anesthesiology (ASA) physical status 1–3 adult patients requiring rectal surgery for malignancy were recruited. Inclusion criteria were scheduled surgery for resection of rectal carcinoma, absence of metastatic disease, and the need for intraoperative and postoperative epidural analgesia. Exclusion criteria were: patient refusal to participate, significant cardiac, pulmonary, hepatic or renal comorbidity, preoperative opioid or non- steroidal antiinflammatory drugs (NSAID) use, drug addiction, psychiatric disorders, spinal problems, neurological problems, allergy to medications used in the study, and any contraindication to neuraxial anesthesia. Preoperative preparation included patient education, in order to explain the goals of the study, and familiarize patients with the anesthesia technique. A computer-generated randomization schedule was provided to two independent investigators who preformed all blocks: the investigator one performed all DDS procedures, while the investigator two performed all SST procedures. The patients were blinded to the group assignment.

All the patients received pre-medication with midazolam 2.5 mg *iv*, fluid preload with Hartman's solution 1 L, and antibiotic prophylaxis with ceftriaxone 2 g and metronidazole 500 mg. All neuraxial blocks were performed in the operating room with the patients awake, in the right lateral decubitus position. Strict aseptic technique was maintained during all procedures. In the DDS technique (Figure 1), an epidural catheter was inserted at the T6–7 or T7–8 interspace *via* a paramedian approach [Perifix (18G Tuohy needle and 20G standard epidural catheter); B. Braun, Melsungen AG, Germany]. Lidocaine 2% combined with epinephrine 1 : 200,000, 3 mL total, were administered *via* the epidural catheter as test dose. In addition, all the patients received a subarachnoid injection of morphine 200 μg, fentanyl 25 μg and bupivacaine 2 mg (0.8 mL of 0.25% solution) at the L2–3 interspace *via* a 25 G spinal needle [Pencan (B. Braun, Melsungen AG, Germany)].

The SST was performed at the L2–3 interspace using an Espocan® needle (B. Braun Medical Inc., Bethlehem, PA, 18 Ga-Espocan Tuohy needle, Perifix epidural catheter 0.85 × 0.45 mm, length 100 mm, 27–Ga Pancan Pencil Point spinal needle) (Figure 2). After epidural space identification, the spinal needle was advanced, and medications (morphine

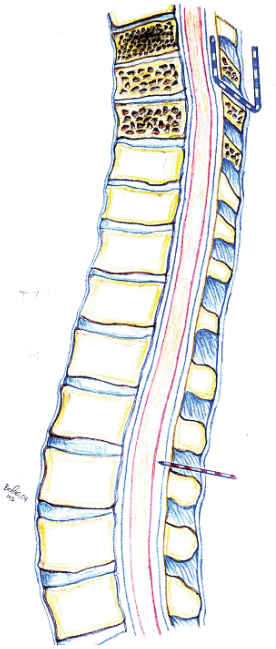

Fig. 1 – Double distant space combined spinal-epidural technique.

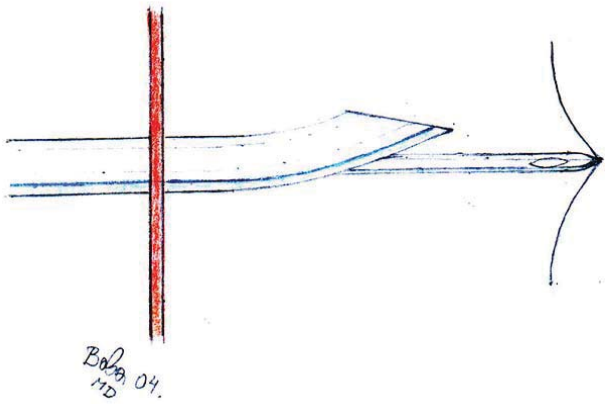

Fig. 2 – Single space technique using the needle-through-needle technique.

200 μg, fentanyl 25 μg and bupivacaine 2 mg (0.8 mL of 0.25% solution) were injected in the subarachnoid space. After the subarachnoid injection was completed, the spinal needle was withdrawn, and the epidural catheter was advanced. Lidocaine 2% with epinephrine 1 : 200,000 3 mL total was given *via* the epidural catheter as test dose to confirm appropriate catheter placement. After the subarachnoid injection, bupivacaine 0.25% 10 mL was administered through the epidural catheter, and sensory blockade level was measured by pinprick at the midclavicular line approximately 20 minutes later. At a minimum, sensory blockade from T6 to L1 was required before inducing general anesthesia. The epidural catheter was used for postoperative pain treatment for 72 hours.

Preoperatively, the patients' body habitus was assessed and classified as: 1 – normal, 2 – slim, 3 – muscular, 4 – obese. Spinal landmarks were classified as: 1 – good (processus spinosus easy to find), 2 – bad (it is difficult to palpate processus spinosus), 3 – extremely bad (impossible to identify processus spinossus). Spinal anatomy was recorded as 1 – normal, 2 – deformity exists. We also recorded the number of epidural and spinal punctures, dura perforation click feeling, time needed for CSE procedure, paresthesias and problems with epidural test dose interpretation. The time needed for the CSE procedure was defined as the time from skin preparation until succesful epidural catheter placement.

Complications during epidural catheter placement were recorded as:1 – none, 2 – dural puncture (cerebrospinal fluid appearance in the hub of needle), 3 – blood vessel puncture (blood appearance in the hub of needle), 4 – epidural catheter placed in the subdural space, 5 – epidural catheter placed in the subarachnoid space, 6 – epidural catheter placed in epidural vein,7 – paresthesias, 8 – impossible epidural catheter placement, 9 – other complications.

Perioperative and postoperative epidural catheter function was recorded as: 1-no problems, 2 – difficult flow, 3 – epidural catheter kinking, 4 – epidural catheter fell out. Time of epidural catheter removal was recorded and reasons for epidural catheter removal were recorded as: 1 – finished treatment, 2 – long duration of therapy, 3 – epidural catheter fell out, 4 – complications, 5 – other reasons.

The patients were assessed daily and complications related to neuraxial anesthesia were recorded as follows: 1 – postdural puncture headache, 2 – catheter migration, 3 – neurologic complications, 4 – epidural hematoma, 5 – infection at skin puncture site, 6 – fistula, 7 – meningitis, 8 – epidural abscess, 9 – other complications. Following catheter removal, all epidural catheter tips were assessed for the presence of bacteria.

Patient's satisfaction regarding the anesthetic procedure was recorded seven days after the surgery using a two-point scale: 1 – good, if necessary I would choose this technique again, or 2 – bad, if necessary I would prefer a different technique [6].

To ensure that sample size for the study is adequate, power analysis was conducted before the study started, using the sample size calculation described in the Norman and Streiner Statistics Book [7], based on the following assumptions [6]: we wanted to detect a 5-minute difference in procedure times between the two groups, with a significance level (alpha) of 0.05 (two-tailed) and power 80%, when the Standard Deviation of observed procedure times is 10 minutes. Sample size calculation based on these assumptions showed that the study would need 64 patients per group, but we decided to increase the number of patients to 80 per group, in order to allow for possible patient attrition or missing data.

Depending on data distribution, data are presented as mean (± standard deviation) or median (range). Parametric and non-parametric statistical tests were applied as appropriate. Data were analyzed using *t*-test or χ^2 test as appropriate. Nominal data were analyzed using χ^2. Correlation was assessed with Spearman's rho. The *p* values of the < 0.05 were considered significant for all tests. Data analysis was performed using the SPSS statistical software package, version 12.0 (SPSS Inc., Chicago, Illinois, USA).

Results

A total of 156 patients were enrolled in the study. Patient characteristics did not differ significantly between the groups, except for body habitus: more patients in the SST group had normal body habitus (Table 1).

Complications during epidural catheter placement were sporadic, and included dural puncture, blood vessel puncture, paresthesia and dural puncture (SST *vs* DDT, $p > 0.05$; Table 4). The epidural catheter functioned well, without problems, in 95% of the patients in each group, and in most cases it was removed after 72 hours, at the completion of the study (Table 4). Overall, the epidural catheter stayed longer than 72 hours in the DDS group, but this was a random, not a planned event, and was not associated with any complication, but correlated with more frequent positive bacteriological cultures ($r = 0.285$; $p < 0.05$) (Table 4). Three months after the procedure, three patients in each group reported lumbar pain (Table 4).

Table 1

Patient characteristics

Patient characteristics	Double space (n = 78)	Single space (n=78)	*p*
Age (years), $\bar{x} \pm SD$	58.55 ± 10.02	61.21 ± 10.03	ns
Weight (kg) , $\bar{x} \pm SD$	69.01 ± 14.20	72.49 ± 14.00	ns
Height (cm) , $\bar{x} \pm SD$	170.15 ± 8.91	171.95 ± 11.38	ns
ASA 1/2/3 (n)	15/54/9	15/54/9	ns
Body habitus, n (%)			
normal	21 (27)	37 (47)	
slim	24 (31)	10 (13)	
muscular	12 (15)	4 (5)	$p < 0.001$
obese	21 (27)	27 (35)	
Spinal signs, n (%)			
good	60 (77)	56 (72)	ns
bad	17 (22)	20 (26)	
extremly bad	1 (1)	2 (2)	
Spinal anatomy, n (%)			
normal	57 (73)	57 (73)	ns
deformity	21 (27)	21 (27)	

ASA – American Society of Anesthesiologists Physical Status Classification (1 – normal healthy patient; 2 – patient with mild systemic disease; 3 – patient with severe systemic disease);
ns – no statistically significant difference.

The epidural and subarachnoid spaces were successfully identified in all the patients. There were no differences between the groups with regards to the duration of the CSE procedure, the number of spinal punctures, dural click feeling and test dose interpretation (Table 2).

The majority of patients clearly understood the explanation regarding the CSE technique, and most of them in both groups stated that the CSE technique would be the preferred procedure for pain management, if they ever need surgery again in the future (Table 3). The CSE technique was uncomfortable for 16% and 20% of the patients when DDS technique and SST technique were used, respectively (Table 3).

In the SST group, a significant correlation was observed between the number of epidural punctures and body habitus ($r = 0.431$, $p < 0.001$), spinal landmarks ($r = 0.431$, $p < 0.001$) and the anatomy ($r = 0.310$, $p < 0.01$). Similarly, there was a significant correlation between the number of spinal punctures and body habitus ($r = 0.243$, $p < 0.05$) and spinal

Table 2

Technical problems related to the combined spinal-epidural anesthesia techniques

Parameters	Double space (n=78)	Single space (n=78)	*p*
Number of epidural punctures, (%)	2.5(1.7)	1.7(1.2)	< 0.01
Number of spinal punctures, (%)	1.2(0.6)	1.1(0.5)	ns
CSE procedure duration (min), $\bar{x} \pm SD$	15.03±6.64	13.14±5.80	< 0.001
Dural click, n (%)	72(92)	64(82)	< 0.001
Difficulties in test dose, n (%)	1(1.3)	3(3.8)	ns

CSE – combined spinal epidural technique; ns –no statistically significant difference.

Table 3

Patients opinion on combined spinal-epidural techniques

Patients opinion	Double space (n = 78)	Single space (n = 78)	*p*
Explanation of CSE technique was clear, n (%)	37 (86)	30 (83)	ns
CSE technique was painfull, n (%)	12 (16)	15 (20)	ns
CSE technique will be procedure of choice for pain management, n (%)	66 (90.4)	64 (87)	ns

ns – no statistically significant difference; CSE – combined spinal-epidural.

Table 4

Epidural catheter complications

Parameters	Double space (n = 78)	Single space (n = 78)	*p*
Epidural catheter placement complications, n (%)			
no complications	68 (87.2)	64 (82.1)	
dural puncture	7 (9)	7 (9)	
blood vessel puncture	2 (2.6)	4 (5.1)	ns
paresthesias	1 (1.3)	0	
dural puncture	0	2 (2.6)	
others	0	1 (1.3)	
Epidural catheter function, n (%)			
functional	74 (94.9)	74 (94.9)	
flow difficulties	3 (3.8)	0	ns
epidural catheter kinking	0	3 (3.8)	
epidural catheter accidenatly removed	1 (1.3)	1 (1.3)	
Epidural catheter removal, n (%)			
treatment completed	70 (89.7)	68 (87.2)	
epidural catheter accidental removal	8 (10.3)	6 (7.7)	ns
complications	0	3 (3.8)	
others	0	1 (1.3)	
Epidural catheter stay (days), n (%)	4.5 (1.29)	3.56 (0.93)	$p < 0.001$
Complications, n (%)			
present	1 (1.3)	2 (2.6)	
absent	77 (98.7)	76 (97.4)	ns
Positive bacteriological culture, n (%)	17/76 (22.4)	19/64 (29.7)	ns
Lumbar pain, n (%)			
preoperative	0	1 (1.3)	ns
3 months after CSE	3(3.8)	3 (3.9)	
6 months after CSE	1 (1.4)	0	

CSE – combined spinal-epidural; ns – no statistically significant difference.

landmarks ($r = 0.268$, $p < 0.05$). In addition, in the SST group there was a significant correlation between the time needed for the CSE procedure and body habitus ($r = 0.338$, $p < 0.01$), spinal landmarks ($r = 0.452$, $p < 0.001$) and anatomy ($r = 0.265$, $p < 0.05$). However, there was no significant correlation between CSE complications and body habitus, spinal signs or spinal anatomy in either group.

In the DDS group, a significant correlation was observed between paresthesias and spinal landmarks ($r = 0.418$, $p < 0.001$), but there was no correlation between the number of epidural punctures and paresthesias. In both groups the number of spinal punctures correlated with the appearance of parethesias (DDS: $r = 0.234$, $p < 0.05$; SST: $r = 0.235$, $p < 0.05$).

There was no correlation between epidural catheter stay and complications or a patient's choice of the CSE technique. In addition, there was no correlation between the number of epidural/spinal punctures and epidural bacteriological findings. Last, there was no correlation between patients' choice of the CSE technique and the number of spinal punctures, procedure time or duration of epidural catheter stay.

Discussion

The study was designed to evaluate the potential benefits of double space *vs* single space (needle-through-needle) CSE technique, and the time needed to perform the CSE procedure was the primary outcome. Both techniques were successful. In the SST group, body habitus, spinal landmarks and the anatomy influenced the number of epidural punctures. However, the time needed for the CSE procedure did not differ between the two techniques. In the SST group, body habitus, spinal signs and anatomy influenced the time needed for the CSE procedure.

The single space "needle-through-needle" technique is the most frequently used CSE technique [2]. After identification of the epidural space, the spinal needle is passed through the epidural needle and beyond its tip until it punctures the dura. Then, after the subarachnoid injection is completed, the epidural catheter is inserted. The CSE kit used in this study includes an epidural needle with a small hole in the greater curvature of the tip, the so called "back-eye", which provides a straight route for the spinal needle. In the SST group, body habitus, spinal landmarks and anatomy influenced the time needed to perform the CSE procedure. Compared to the DDS group, the time needed to perform the CSE procedure was shorter in the SST group, but the difference was not statistically significant. This observed difference can be explained by the need for only one site puncture, and the greater number of patients with normal body anatomy in this group. Similarly, an earlier study comparing three different techniques (CSE set with an interlocking device between the spinal and epidural needle *vs* CSE set with a "back eye" at the epidural needle curve *vs* a double-segment technique) found no difference in the time needed to perform the block [8]. Moreover, one study found greater success with the double space technique [9]. Time to "readiness for surgery" is not as important when CSE is used in combination with general anesthesia, but becomes very important when CSE is used as the sole anesthetic method for surgical anesthesia.

The higher number of epidural punctures observed with the DDS technique can be explained by technically more challenging thoracic approach. However, in the DDS group, the number of epidural punctures, the number of spinal punc-

tures and the mean time to perform DDS was not affected by body habitus, spinal landmarks or the anatomy. We opted for thoracic epidural catheter placement because the thoracic epidural space is the most appropriate space for placing an epidural catheter when the surgery involves a longitudinal abdominal incision. To our knowledge, this is the first study to directly compare the SST and DDT CSE techniques.

In both patient groups, complications were rare and independent on body habitus, spinal landmarks or the anatomy, and we did not observe any serious complications from use of the CSE technique. This finding is in accordance with the current literature which states that "severe complications of central neuraxial blocks are rare" [8, 10].

In agreement with previous studies [6, 11] paresthesias during epidural and spinal puncture were rare in our study, and there was no difference between the two CSE techniques. Based on literature data, the incidence of paresthesia is 0.9–11% [11].

Although we would expect that patients would prefer the SST method because it involves only one puncture site, this was not the case. The patients in both groups were asked what their choice would be, if they would undergo another surgical procedure in future, and their choice was independent of the number of spinal or epidural punctures, duration of CSE procedure or epidural catheter stay. In contrast, patients preferred the SST over the DDT in the Casati study [6].

Because back pain is a serious public health problem, we recorded the incidence of back pain in our patients. Six months after the procedure, only one patient in the DDS group had back pain, and this is in agreement with published data: Persistent back pain after spinal anesthesia in non-obstetric patients has been reported to be 0.8% three months after spinal puncture [12].

The epidural catheter stayed longer in DDS group, but this was a random, not a planned event, and was associated with higher incidence of positive bacteriological cultures (Table 4). We could not find any relevant literature regarding the incidence of epidural catheter colonization and infection after CSE technique in non-obstetric patients. Positive cultures have been reported in 28–28.8% of patients with epidural catheters [13, 14]. However, the significance of these positive cultures is questionable. Results of the study underwent by Simpson et al. [14] suggested that a significant proportion of epidural catheter tips may be culture positive, but this finding represents colonization of the skin at the puncture site with subsequent contamination of the catheter tip on catheter removal, rather than infection, as well as that in most cases routine culture of epidural catheter tips is clinically irrelevant. In our study there was no correlation between the number of epidural or spinal punctures and epidural tip positive bacteriological findings. This is in agreement with an earlier study on bacterial contamination of epidural needles with multiple (two or more) skin passes [15].

Conclusion

Our results suggest that there is no significant difference between the DDS and SST regarding the time needed to perform the CSE procedure. In the SST group, body habitus, spinal landmarks and the anatomy influenced the number of epidural punctures.

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REFERENCES

1. *Eldor J.* Combined spinal-epidural-general anesthesia. Med Hypotheses 1995; 45(1): 86−90.
2. *Cook TM.* Combined spinal-epidural techniques. Anaesthesia 2000; 55(1): 42−64.
3. *Felsby S, Juelsgaard P.* Combined spinal and epidural anesthesia. Anesth Analg 1995; 80(4): 821−6.
4. *Scott NB, James K, Murphy M, Kehlet H.* Continuous thoracic epidural analgesia versus combined spinal/thoracic epidural analgesia on pain, pulmonary function and the metabolic response following colonic resection. Acta Anaesthesiol Scand 1996; 40(6): 691−6.
5. *Stamenkovic DM, Geric V, Slavkovic Z, Raskovic J, Djordjevic M.* Combined spinal-epidural analgesia vs. intermittent bolus epidural analgesia for pain relief after major abdominal surgery. A prospective, randomised, double-blind clinical trial. Int J Clin Pract 2008; 62(2): 255−62.
6. *Casati A, D'Ambrosio A, De NP, Fanelli G, Tagariello V, Tarantino F.* A clinical comparison between needle-through-needle and double-segment techniques for combined spinal and epidural anesthesia. Reg Anesth Pain Med 1998; 23(4): 390−4.
7. *Norman GR, Streiner DL.* Biostatistics: the bare essentials. 2nd ed. Hamilton: B.C. Decker; 2000.
8. *Puolakka R, Pitkanen MT, Rosenberg PH.* Comparison of technical and block characteristics of different combined spinal and epidural anesthesia techniques. Reg Anesth Pain Med 2001; 26(1): 17-23.
9. *Backe SK, Sheikh Z, Wilson R, Lyons GR.* Combined epidural/spinal anaesthesia: needle-through-needle or separate spaces? Eur J Anaesthesiol 2004; 21(11): 854−7.
10. *De TO, Caporuscio A, Tagariello V.* Neurological complications following central neuraxial blocks: are there predictive factors? Eur J Anaesthesiol 2002; 19(10): 705−16.
11. *Hoffmann VL, Vercauteren MP, Buczkowski PW, Vanspringel GL.* A new combined spinal-epidural apparatus: measurement of the distance to the epidural and subarachnoid spaces. Anaesthesia 1997; 52(3): 350−5.
12. *Schwabe K, Hopf HB.* Persistent back pain after spinal anaesthesia in the non-obstetric setting: incidence and predisposing factors. Br J Anaesth 2001; 86(4): 535−9.
13. *Kostopanagiotou G, Kyroudi S, Panidis D, Relia P, Danalatos A, Smyrniotis V,* et al. Epidural catheter colonization is not associated with infection. Surg Infect (Larchmt) 2002; 3(4): 359−65.
14. *Simpson RS, Macintyre PE, Shaw D, Norton A, McCann JR, Tham EJ.* Epidural catheter tip cultures: results of a 4-year audit and implications for clinical practice. Reg Anesth Pain Med 2000; 25(4): 360−7.
15. *Orlikowski C, Majedi PM, Keil AD.* Bacterial contamination of epidural needles after multiple skin passes. Br J Anaesth 2002; 89(6): 922−4.

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PRACTICAL ADVICE FOR PHYSICIANS

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Risk factors and preventive measures for occupational diseases in dental technicians

Faktori rizika i mere sprečavanja profesionalnih bolesti kod zubnih tehničara

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Ključne reči:
zubotehničari; zubna proteza; profesionalne bolesti; faktori rizika; medicina, preventivna.

Introduction

The construction procedure of fixed and mobile dentures is based on principles of dental doctrine and in the way widely used worldwide. The process of constructing prosthetic restorations and mobile orthodontic appliances is the result of team cooperation between dentists and dental technicians. The work of dental technicians is highly specific and implies construction of mobile and fixed dentures and mobile orthodontic appliances on plaster models obtained by casting individual dental impressions and patients' jaws. According to the data of the Serbian Institute of Occupational Medicine and Radiological Prevention there are about 3,800 dental technicians, of whom 70% are women [1]. The working time in state sector is 40 hours per week, while it is much longer in private sector.

The work in dental laboratory requires ultimate precision and manual dexterity, good vision and ability of recognizing slight differences among variety of hues. All dental restorations are the result of correctly established indication and personal creative expression of dental technician, whereby the final piece placed in a patient's oral cavity can be considered a tiny work of art.

On the other hand, the work of dental technicians represents a great risk of occurrence of occupational diseases not only due to numerous harmful substances used and released during the process of constructing dentures and orthodontic appliances but also due to inadequate working conditions in dental laboratories and improper protection of the staff. Dental technicians are constantly exposed to harmful effect of different solvents, non-organic acids, evaporations and gases obtained during material exploitation, dust during finishing and grinding, metal alloys, ceramic and acrylates. The group of potentially toxic substances includes methacrrylates, silicium dioxide, butylene glycol, hexane solutions, ethyl acetate, nitrocellulose, glutaraldehyde, benzoyl peroxide, hydroquinone, bisphenol A, kaolin and oxides of different metals [2, 3]. Concentration values of these substances in the air are very often considerably higher than values of maximum allowable concentrations (MAC), particularly if dental laboratory is without automatic device for measuring air pollution. Particular attention should be focused on methacrylic monomer that is known to have a wide spectrum of detrimental effects such as irritation of skin, eyes and submucose, allergic dermatitis, asthma, and simptoms of central and peripheral nervous system (headache, back pain, nausea, loss of appetite, reduction of gastric motoric activity, tiredness, sleep disturbance, neuropathy, loss of memory) [1, 4, 5]. The toxicity of methyl methacrylate was demonstrated *in vitro* [6–8].

Metal alloys such as vitalium, visil, duralium and vironite are used in construction of crowns, bridges and skeletal partial dentures. Major ingredients of these alloys include cobalt (35–65%), chrome (20–30%) and nickel (0–30%) and small amounts of molybden, silicium dioxide, beryllium, boron and tantalum, the harmful effects of which have already been laboratory and clinically well documented [1, 9]. Gold and palladium alloys are rarely used nowadays. Although considered to be relatively bioinert, conjoined allergic reactions to palladium and nickel have been reported [10].

Contact dermatitis

Dermatological occupational diseases occur as a result of irritation or immunological reaction of skin, most often fingers and hands, and rarely face and eyelids (Table 1). Contact dermatitis is mostly occupational disease in industrially developed countries [11, 12]. The results of the study conducted by Ruste-

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Table 1

Characteristics and classification of occupation-related dermatitis in dentistry

Characteristics of reaction	Type of occupation-related contact dermatitis		
	Type I reaction of hypersensitivity	Type IV reaction of hypersensitivity	Irritant contact dermatitis
Reaction of immune system	Systemic IgE-mediated immune reactions	Localized T-cell mediated reaction	Localized inflammation without immune system involvement
Potential allergens or irritans	Proteins in latex gloves manufacturing, methyl methacrylat	Methacrylates, metal alloys dust, some small proteins	Detergents, acids, alkalies, solvents, continual work in abrasive or wet environments
Potential risk factors	Allergy to different type of food, allergy to latex balloons, condoms and natural rubber products, continual using of latex gloves , history of allergies (atopy) and eczema	Atopy, skin reactions (eczema and dermatitis)	Atopy, skin reactions (eczema and dermatitis), female sex, age
Initiation of symptoms	Within minutes or hours of contact	Within hours or days of contact	Within minutes or hours of contact
Cessation of symptoms	After a few hours of contact	After a few weeks of contact	After irritant removing
Symptoms	Local symptoms (skin redness and itching, urticaria) often related with systemic symptoms (asthma, bronchospasm, angioedema, coughing, rhinitis, nausea, vomiting, diarrhea, hypotension, tachycardia, anaphylactic shock)	Skin reactions: soreness, redness, cracking, scabbing, crusting, papuling, swelling, itching and pain	Skin reactions: redness, burning, swelling and pain

meyer and Frosch show that 16% of dental technicians in Germany have symptoms of contact dermatitis [13]. The prevalence of contact dermatitis is 22% and 43% in Australian and Danish dental staff, respectively [14, 15]. In the last few the years increase of affected persons has been observed [13, 16]. Contact dermatitis of hands is clinically manifested by skin dryness of fingers and hands, redness, broken and peeling skin, itching and pain [12, 17, 18] (Figure 1). The disease improves at weekends and holidays. Mechanical friction (abrasion, attrition), work with plaster, constant changes of temperature and hand washing further contribute to the development of skin changes. When symptoms of dermatitis are present among dental staff the standard Patch test is used for detecting hypersensitivity to a specific group of allergens: methyl methacrylate, potassium dichromate, cobalt nitrate, nickel-sulfate, formaldehyde, hexamethylenetetramine, epoxy resin, phthalic anhydride, mercury precipitate, colophonium, benzoyl peroxide, benzocaine, hydroquinone [2, 11].

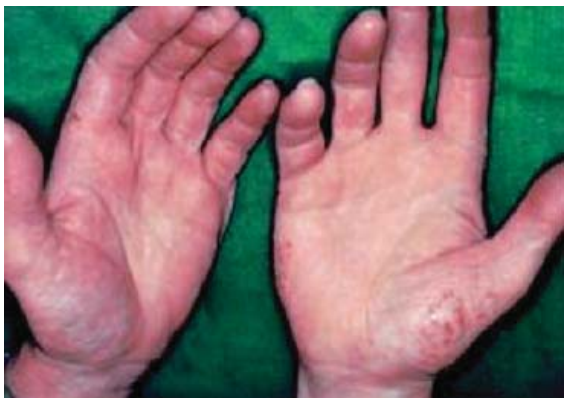

Fig. 1 – Allergic contact dermatitis on the hands of a dental technician caused by methyl methacrylate.

Dental staff is at increased risk of developing contact dermatitis caused by methacrylates molecules which pass through thin latex gloves. Methacrylates represent ingredients of acrylic resins used in construction of plate and skeletal dentures [11]. According to the laboratory investigations carried out by Marks et al. [19] and Werrer et al. [20] immunological reaction to methyl metacrylates was present in 1% of examined subjects. In addition, local contact reactions to butyl methacrylate, urethane dimethacrylate and cross-linking agents (dimethacrylate, ethylene glycol dimethacrylate, 2-hydroxylethyl methacrylate, etc.) were clinically described [21]. Cockayne et al. [22] lave described the case of a dental technician allergic to colophonium, the ingredient of numerous waxes used in dentures construction.

Dental technicians intentionally avoid using protective latex gloves because of reduced precision in work. On the other hand, various studies report very frequent allergic reactions to some components and plasticizers used for manufacturing these gloves among medical staff [2, 17, 23]. On the basis of literature data it is evident that reactions to wearing latex gloves ars present in 5–10% of health care workers in Europe and 17% in the United States and Canada [23].

Allergic diseases

Systemic allergic reactions to chemical substances that dental technicians come in contact with during their everyday work are, fortunately, very rare. They include type I hypersensitivity reactions manifested as generalized urticaria, bronchial asthma, and very rarely as anaphylactic shock or edema of larynx [24, 25]. Jaakkola et al. [26] in their epidemiological study indicate that medical staff is more often affected by

bronchial asthma if exposed to chemical toxic substances for a long period of time.

Literature data point to link between systemic autoimmune diseases including rheumatoid arthritis, systemic sclerosis and systemic lupus erythematosus and extra work with potentially toxic substances in dental laboratory [27]. Asudillo et al. [28] reported the case of a dental technician affected by Sjögren's syndrome after long-lasting exposure to silicium dioxide.

Neurological diseases

During their work dental technicians are in contact with chemical solvents containing hexane and metals (mercury, iron, chrome, cobalt and nickel) that were proven to have detrimental effect on central nervous system [3]. According to findings of Fabrizio et al. [3] 14 out of 27 dental technicians who underwent neurological examination showed some disorders including postural tremor, and Parkinson's disease was diagnosed in one dental technician. The results of a clinical study conducted by Gorell et al. [29] indicate that long-lasting work with metal alloys increases the risk of developing Parkinson's disease. Sadoh et al. [5] reported the case of dental technician with generalized neuropathy as the consequence of inhalation with evaporation of methyl methacrylate.

A meticulous finishing of dentures implies extra strain of the eye muscles, which along with increased probability of olfactory infections and mechanical injuries represents risk for damaging sight among staff in dental laboratories [4]. Benzoyl peroxide, the initiator of polymerization of methacrylates under *in vitro* conditions damages fibroblasts of the eye [1].

Respiratory diseases

Vaporization of methyl methacrylates and dust which is the result of finishing dentures and metal alloys may lead to damage of nasal cells with subsequent higher susceptibility to respiratory infections [30]. Clinical manifestations of respiratory diseases of dental technicians are cough, enhanced mucous secretion, and decreased respiratory capacity [31].

Investigations carried out by the Serbian Institute of Occupational Medicine and Radiological Protection indicates that the values of MAC of silicium dioxide in dental laboratories are twofold or threefold higher in relation to prescribed ones. Measured concentrations of methyl methacrylates were 2.4 times higher in relation to allowed values (MAC = 410 mg/m^3) [1].

Exposure of respiratory organs to high concentrations of silicium dioxide and dust as a consequence of finishing cobalt-chrome-molybdenum alloy represents great risk of developing pneumoconiosis, the occupational restrictive lung disease [32]. Selden et al. [33] conducted a clinical study in which they found higher incidence of lung fibrosis and pneumoconiosis in Swedish dental technicians who were engaged in finishing cobalt-chrome-molybdenum alloys in relation to a control group. Froudarakis et al. [34] found that the incidence of pneumoconiosis was 9.8% among examined dental technicians in Crete. Pneumoconiosis is particularly common among smokers [25]. Complications of bronchial asthma and rheumatoid syndrome include interstitial inflammation and fibrosis of lung tissue.

Noise and injuries

Noise in dental laboratory is caused by finishing, grinding, cutting, polishing, as well as ventilation. This type of noise is discontinuous, of wide spectrum with dominant high frequencies [35]. According to the Serbian Institute of Occupational Medicine and Radiological Protection noise in dental laboratory is on the average 92 dB [1].

Hands of dental technicians are constantly exposed to vibrations of different intensity. "White finger syndrome", damage of conductivity of *nervus medianus* is considered to be severe occupational disease of dental technicians [36].

Regarding the nature of work (ceramics baking, handling spirituous lamp, polymerization of dentures in water bath), there is the risk of skin burn as the result of awkward handling and wearing no protective uniform. While finishing metal and porcelain crowns, dental technicians are exposed to heat and infrared radiation.

Other risks for health damage

Finishing minor dentures requires high precision and extra strength, so that cramps and painful tension of muscular and skeletal system are possible. Although slight, loading of back and neck should not be neglected taking into account time duration of fixed body position. Work with material taken from patient's oral cavity is accompanied by risk of developing infection if adequate disinfection is not carried out.

Clinical study on increased risk of developing carcinogenic diseases among dental technicians has not been conducted yet, but there is some evidence suggesting mutagenic effect of particular components of metal alloys such as chrome, cobalt, nickel and beryllium, as well as crystals of silicium dioxide [30, 37]. Choudat [25] suggests link between bronchial cancer, mesotheliomas and dental technicians' work.

Preventive measures for dental technicians in workplace

In order to improve life and work efficacy of dental technicians it is necessary to provide them with standardized and optimal working conditions. Dental laboratories, both state and private, should be spacious, clean and well lit. Air pollution is prevented by adequate local and general ventilation system. Dental technician's workplace should have adequate ventilation system. It should also have separate worktable equipped with kit for grinding, cutting and polishing of dentures, spirituous lamp and hand instruments. In order to avoid damages of musculoskeletal system brought about by strain, adequate adjustable chair should be chosen. Eating,

drinking and smoking are forbidden at workplace. In addition, it is preferable to have regular shorter breaks spent in a clear air area.

Dental staff should adopt standard procedures for handling with different substances and objects. Manufacture of dentures and orthodontic appliances implies utilization of wide spectrum of different materials that could damage health of the employees. Whenever it is possible, all substances and chemical agents that could be potentially harmful should be replaced with those that are more efficient and less toxic, irritable and sensible. This particularly refers to the use of hypoallergic acrylates and alloys without nickel and beryllium.

It is imperative that dental technicians use adequate personal protection. Protective uniform includes work uniform, protective gloves, glasses and masks. Nitrile and rubber gloves made of synthetic materials are recommended regarding the fact that latex and vinyl gloves do not provide adequate protection from penetrating molecules of methacrylate monomer and other potentially toxic substances and that allergic reaction to their ingredients is rather common [12, 38]. However, these gloves reduce precision and efficacy of work, so that some additional effort is needed for carrying out any delicate work on dentures. In order to protect periphery nervous system from deleterious effect of vibrations, the use of specialized anti-vibration gloves is recommended. Asbestos gloves are used for handling hot molds. Protective glasses should have lateral shield so as to avoid eye injuries. Wearing protective masks represents the first line of defense against damage of respiratory organs and nervous system [5]. Protection of hearing is needed while finishing metals of skeletal dentures and caps of fixed dentures and is imperative when noise is higher than 80 dB [35, 39]. Disinfection of impressions and corrected dentures is necessary for protection of dental laboratory from microbial contamination.

While manipulating acrylates a direct contact with non-polymerized mass (no-touch technique) should be avoided. Personal hygiene is important factor in prevention from contact dermatitis. The use of low base soap and lotions is recommended. It is contraindicated to use creams and lotions under latex gloves because they could deteriorate stimulating effect [18].

In order to reduce harmful effect of vibrations of handpiece in the process of finishing dentures as well as to avoid continuous exposure of one and the same person to toxic substances and noise, dental technicians should change their tasks, which turned out to be efficient measure. If a person is hypersensitive to a particular substance or working procedure, change of workplace or even change of qualification is indicated within dental laboratory.

Dental technicians should regularly undergo specific medical examinations with primary emphasis on lung function, skin diseases, diseases of ear, throat and nose, disorder of hearing and periphery circulation. Preventive measures also imply health-education work so that the staff could get acquainted with potential risks of their work, early symptoms of diseases, as well as using adequate protection.

Conclusion

Dental technicians run the risk of developing local and systemic occupational diseases. Therefore, preventive measures should include adequate workplace, proper equipment handling, selection of biocompatible materials, wearing protective uniform, health-education work and early detection of disease symptoms. The goal of prevention is optimization of working conditions with individual physical and mental capabilities in order to preserve health of dental technicians and thus maintain appropriate level of their working and life skills.

REFERENCES

1. *Torbica N, Krstev S*. World at work: dental laboratory technicians. Occup Environ Med 2006; 63(2): 145−8.
2. *Rubel DM, Watchorn RB*. Allergic contact dermatitis in dentistry. Austral J Dermatol 2000; 41(2): 63−, quiz 70−1.
3. *Fabrizio E, Vanacore N, Valente M, Rubino A, Meco G*. High prevalence of extrapyramidal signs and symptoms in a group of Italian dental technicians. BMC Neurol 2007; 7: 24.
4. *Hensten-Pettersen A, Jacobsen N*. The role of biomaterials as occupational hazards in dentistry. Int Dent J. 1990; 40(3): 159−66.
5. *Sadoh DR, Sharief MK, Howard RS*. Occupational exposure to methyl methacrylate monomer induces generalized neuropathy in a dental technician. Br Dent J 1999; 186(8): 380−81.
6. *Kostić M, Najman S, Kocić J, Krunić N, Ajduković Z, Petrović D,* et al. Effect of denture base resin extrats on hela cells growth in vitro. Hemijska industrija 2008; 62(3): 217−22. (Serbian)
7. *Kostić M, Krunić N, Najman S, Kocić J, Veselinović M*. Changes on hela cell culture in presence on acrilic resins. Acta Stomatol Naissi 2008; 24(58): 793−800. (Serbian)
8. *Krunić N, Nikolić Lj, Kostić M, Najman S, Nikolić V, Najdanović J*. *In vitro* examination of oral tissue conditioners potential toxicity. Chem Ind. 2011; In press. DOI: 10.2298/HEMIND 110627056K.
9. *Leghissa P, Ferrari MT, Piazzola S, Caironi M, Parigi PC, Lebbolo E*. Cobalt exposure evaluation in dental prostheses production. Sci Total Environ 1994; 150(1): 253−7.
10. *Kielhron J, Melber C, Keller D, Mangelsdorf I*. Palladium- A review of exposure and effects to human health. Int J Hyg Environ Health 2002; 205(6): 417−32.
11. *Mikov I, Turkalj I, Jovanović M*. Occupational contact allergic dermatitis in dentistry. Vojnosanit Pregl 2011; 68(6): 523−25.
12. *Koch P*. Occupational contact dermatitis. Recognition and management. Am J Clin Dermatol 2001; 2(6): 353−65.
13. *Rustemeyer T, Frosch PJ*. Occupational skin diseases in dental laboratory technicians. Contact Dermatitis 1996; 34(2): 125−31.
14. *Katelaris CH, Widmer RP, Lazarus RM*. Prevalence of latex allergy in a dental school. Med J Aust 1996; 164(12): 711−4.
15. *Jacobsen N, Hensten-Pettersen A*. Occupational health problems and adverse patient reactions in orthodontics. Eur J Orthod 1989; 11(3): 254−64.
16. *Estander T, Rajaniemi R, Jolanki R*. Hand dermatitis in dental technicians. Contact Derm. 1984; 10(4): 201−5.
17. *Miri S, Purpak Z, Zarinara A, Heidarzade M, Kazemnejad A, Kardar G,* et al. Prevalence of type I allergy to natural rubber

latex and type IV allergy to latex and rubber additives in operating room staff with glove-related symptoms. Allergy Asthma Proc 2007; 28(5): 557−63.
18. *Hamann CP, Depaola LG, Rodrigez PA.* Occupation-related allergies in dentistry. J Am Dent Assoc 2005; 136(4): 500−10.
19. *Marks JG Jr, Besito DV, DeLeo VA, Fower JF, Franswaz AF, Maibach HI*, et al. North American contact dermatitis group patch-test results, 1998 to 2000. Am J Contact Dermat 2003; 14(2): 59−62.
20. *Werrer DA, Davis MD, Yiannis JA, Cheng JF, Connoly SM, el-Azbary RA*, et al. Patch test results from Mayo clinic contact dermatitis group, 1998-2000. J Am Acad Dermatol 2005; 53(3): 416−21.
21. *Aalto Karte K, Alanko K, Kuuliala O, Jolanki* R. Methacrylate and acrylate allergy in dental personnel. Contact Derm. 2007; 57(5): 324−30.
22. *Cockayne SE, Murphy R, Gawkrodger DJ.* Occupational contact dermatitis from colophonium in a dental technician. Contact Dermatitis 2001; 44(1): 42−3.
23. *Gawkrodger D*J. Investigation of reactions to dental materials. Br J Dematol 2005; 153(39: 479−85.
24. *Doutre MS.* Occupational contact urticaria and protein contact dermatitis. Eur J Dermatol. 2005; 15(6): 419−24.
25. *Choudat D.* Occupational lung diseases among dental technicians. Tuber Lung Dis. 1994: 75(2): 99−104.
26. *Jaakkola JJK, Piipari R, Jaakkola MS.* Occupation and asthma: a population-based incident case-control study. Am J Epidemiol 2003; 158(10): 981−7.
27. *Ianello S, Camuto M, Cantarella S, Cavaler A, Ferriero P, Leanza A,* et al. Rheumatoid syndrome associated with lung interstitial disorder in a dental technician exposed to ceramic silica dust. A case report and critical literature review. Clin Rheumatol. 2002; 21(1): 76−81.
28. *Astudillo L, Sailler L, Ecoiffier M, Girin J, Couret B, Arlet-Suau E.* Expositure to silica and primary Sjögren s syndrome in a dental technician. Rheumatology (Oxford) 2003; 42(10): 1268−9.
29. *Gorell JM, Johnson CC, Rybicki BA, Peterson EL, Kortsha GX, Brown GG,* et al. Occupational exposures to metals as risk factors for Parkinson's disease. Neurology 1997; 48(3): 650−8.
30. *Burgaz s, Demircigil GC, Yilmazer M, Ertas N, Kemaloglu Y, Burgaz Y.* Assessment of cytogenetic damage in lymphocytes and in exfoliated nasal cells of dental laboratory technicians exposed to chromium, cobalt, and nickel. Mutat Res 2002; 521(1−2): 47−56.
31. *Cirmin A, Komus N, Karaman C, Tertemiz KC.* Pneumoconiosis and work-related health complains in Tukish dental laboratory workers. Tuberk Toraks 2009; 57(3): 282−8.
32. *Ozdemir Dogan D, Ozdemir AK, Polat NT, Dal U, Akkurt I.* Prevalence of respiratory abnormalities and pneumoconiosis in dental laboratory technicians. Tuberk Toraks. 2010; 58(2): 135−41.
33. *Selden AI, Presson B, Bornberger-Dankvardt SI, Winstrom LE, Bodin LS.* Exposure to cobalt chromium dust and lung disorders in dental technicians. Thorax 1995; 50(7): 769−72.
34. *Froudarakis ME, Voloudaki A, Bouros D, Drakonakis G, Hatzakis K, Siafakis NM.* Pneumoconiosis among Cretan dental technicians. Respiration 1999; 66(4): 338−42.
35. *Setcos JC, Mahyuddin* A. Noise levels encountered in dental clinical and laboratory practice. Int J Prosthodont 1998; 11(2): 150−7.
36. *Nakladalova M, Fialova J, Korycanova H, Nakladal Z.* State of health in dental technicians with regard to vibration exposiure and overload of upper extremities. Cent Eur J Public Health 1995; 3 (Suppl): 129−31.
37. *Gennart JP, Baleux C, Verellen-Dumoulin C, Buchet JP, Lauwerys* R. Increased sister chromatid exchanges and tumor markers in workers exposed to elemental chromium-, cobalt- and nickel-containing dusts. Mutat Res 1993; 299(1): 55−61.
38. *Meding B, Wrangsio K, Hosseiny S, Andersson E, Hagberg S, Toren K,* et al.. Occupational skin exposiure and hand eczema among dental technicians-need for improved prevention. Scand J Work Environ Health. 2006; 32(3): 219−24.
39. *Bahaman S, el-Hamid AA, Bahnassy A.* Noise level of dental headpieces and laboratory engines. J Prosthet Dent 1993; 70(4): 356−69.

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Adhesive capsulitis: How to treat your patient?

Adhezivni kapsulitis – kako lečiti bolesnika

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Key words:
bursitis; shoulder joint; diagnosis; drug therapy; physical therapy modalities; rehabilitation; treatment outcome.

Ključne reči:
burzitis; rameni zglob; dijagnoza; lečenje lekovima; fizikalna terapija, metodi; rehabilitacija; lečenje, ishod.

Introduction

Adhesive capsulitis is a condition characterized by scapulohumeral pain and loss of shoulder mobility. The condition was first described by Dupley in 1896. who named it "peri-arthritis scapulohumerale" [1]. Codmann [2] introduced the term "frozen shoulder" in 1934 to describe the condition characterized by pain and limitation of range of motion in the affected shoulder. Neviaser [3] was the first to use the term "adhesive capsulitis" to describe the condition characterized by chronic shoulder inflammation. The present definition of the American Shoulder and Elbow Surgeons is "a condition of uncertain etiology characterized by significant restriction of both active and passive shoulder motion that occurs in the absence of a known intrinsic shoulder disorder" [4]. The pravelance of shoulder pain is high, and ranges from 7% to 36% of the population [5]. In order to provide adequate therapy accurate diagnosis of different conditions causing shoulder pain must be made. The aim of the study was to review the pathogenesis, diagnosis, and natural course of adhesive capsulitis, and provide evidence-based clinical practice guidelines on selected rehabilitation interventions.

Pathogenesis, diagnosis and course of the disease

Adhesive capsulitis is a condition that occurs in 2–5% of the general population. It most commonly occurs in women aged 40–60 years [6]. Men rarely suffer from adhesive capsulitis, but are at greater risk for longer recovery and greater functional loss [7]. The condition occurs often bilaterally, and the contralateral side is frequently affected 6 months to 7 years after onset of symptoms in the first shoulder [6]. However, the same shoulder is never affected twice [8]. The condition is also more common in people with sedentary vocations [9], with the non-dominant hand being more often affected [10]. Adhesive capsulitis can often be seen in patients with diabetes mellitus. The incidence of adhesive capsulitis is also higher in patients with various cardiac, endocrine, and neurologic comorbid diseases [11–13].

Adhesive capsulitis can be classified as primary or secondary. The diagnosis of primary or idiopathic adhesive capsulitis is made when there are no data from adequate medical history or findings during the examination that account for the beginning of the disease. Abnormal response of the immune system may be the underlying cause of the idiopathic form of the disease. In recent years several studies showed an increase in the production of cytokines such as transforming growth factor β (TGF-β) and platelet-derived growth factor (PDGF) causing abnormal regulation of expression of collagen type I and type III and proliferation of fibroblasts, leading to adhesion formation in the joint [14–16].

Secondary adhesive capsulitis is a result of known causes of shoulder stiffness or immobilization, such as previous injuries, surgical interventions, etc [8]. The etiology and pathophysiology of adhesive capsulitis are still poorly understood. The condition is considered to be basically a combination of synovial inflammation and capsular fibrosis [8]. The natural course of adhesive capsulitis involves a continuum of three phases [9]. The disease begins with the painful, or "freezing" phase. This phase is mostly characterized by the presence of pain usually without any known precipitating factors. Pain is first felt with activities, and is common at

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night. Patients often report that they cannot sleep on the affected shoulder. Typically, pain precedes the limitation of movement, but in some cases, loss of mobility can be the first symptom. Because of the non-specific symptoms patients rarely seek medical attention at this stage of the disease. In the early phase, arthroscopy shows a fibrinous synovial inflammatory reaction without adhesions and capsular contracture, while later in the phase a thickened, hypervascular synovitis can be seen [9]. In the beginning of the freezing phase biopsy of the joint capsule reveals rare inflammatory cells, hypervascular, hypertrophic synovitis and normal capsular tissue, while later hypervascular synovitis with perivascular, and subsynovial scar formation can be seen [17]. The "freezing" phase lasts between 10 and 36 weeks, and is followed by a "frozen" phase, in which pain gradually diminishes, but a progressive decrease in shoulder range of motion takes place. The "frozen" phase can last between 4 and 12 months. Arthroscopic examination shows loss of the axillary recess, while capsular biopsy reveals features characteristic for fibrosing conditions [17]. Most patients visit doctor at this stage of disease. Finally, the recovery, or "thawing" phase shows a gradual spontaneous recovery of shoulder mobility and function over 5 to 26 months. Arthroscopic findings indicate mature adhesions [9]. The average disease duration is 30 months (from 1 to 3.5 years.).

Although most patients with adhesive capsulitis have a complete recovery, some authors reported long-term pain and residual restrictions of motion [6, 18]. External rotation is the plane of motion that predominantly remains restricted, but this deficit may not interfere with activities of daily living [8]. Incomplete resolution of symptoms in some cases is in contrast to Codman's statement that "recovery is always sure and may be confidently expected" [2]. Diagnosis of adhesive capsulitis is primarily made by history and physical examination. Criteria that must be taken into account when making the diagnosis include a gradual onset, night pain, pain provoked by isolated passive motion in the scapulohumeral joint, painful limitation of passive elevation (less than 100°) and external rotation (up to half of the full range of motion), and radiographs excluding other pathological processes in the shoulder [8]. In the physical examination the most important part is the evaluation of passive range of motion in the shoulder joint. Real mechanical restriction that occurs in capsular contracture is characterized by a fixed ending point which must be distinguished from resistance arising due to pain. When making differential diagnosis of adhesive capsulitis the clinician should not forget that in addition to adhesive capsulitis, only osteoarthritis and neglected posterior shoulder luxation may present with passive restriction of scapulohumeral motion. Plain magnetic resonance imaging (MRI), MR arthrography, and ultrasound can be useful in diagnosing adhesive capsulitis [19, 20].

Pharmacological treatment and rehabilitation

Conservative treatment of adhesive capsulitis includes pharmacological treatment (analgesics, corticosteroids) and physical therapy interventions (modalities, manual techniques, and therapeutic exercises). Although there is no scientific evidence that supports the use of non-steroidal anti-inflammatory medications, they are often prescribed in the early, inflammatory stage of the disease in order to attain adequate analgesia [8]. Oral corticosteroids are, on the other hand, a well established therapy in the acute phase of adhesive capsulitis. A number of studies demonstrated their efficacy in pain reduction, especially night pain [21], and short-term improvement of scapulohumeral range of motion [21–23]. It is important to critically select patients for this treatment option because of its known side-effects [24]. Intraarticular, subacromial or glenohumeral administration of corticosteroids is often performed, and its efficacy in reducing pain for several weeks has been proven [25]. It has been advised to perform this procedure under ultrasound or fluoroscopic guidance, because exclusive use of anatomical landmarks is unprecise [26].

Physical therapy interventions are widely recommended in the treatment of adhesive capsulitis, although evidence that clearly confirms their effectiveness is still deficient. According to the Cochrane database review of physiotherapy for painful shoulder conditions due to deficiencies in the literature, there is little evidence to guide treatment and no evidence that physiotherapy alone is of benefit in adhesive capsulitis [5]. A recent study confirmed insufficient evidence regarding the most commonly applied therapies, such as physical therapy and analgesics [25]. Regardless of this, physical therapy interventions remain the mainstay of adhesive capsulitis treatment. Different modalities should always be used in accordance with the underlying pathophysiological changes of the concurrent phase of the disease.

In the first phase of the disease, the goal of rehabilitation is primarily to reduce inflammation and eliminate pain. In addition to analgesics and corticosteroids, implementation of certain physical therapy procedures is indicated because of their known analgesic, anti-inflammatory and scar tissue modifying effects. There is strong evidence that low-power laser [27–29], transcutaneous electrical nerve stimulation (TENS) [30], and acupuncture [31] provide short-term pain relief. Efficacy of other modalities, such as ultrasound, massage, iontophoresis and sonophoresis has not been proven in the treatment of patients with adhesive capsulitis [32, 33]. At this stage of the disease, patient education and activity modification is necessary. In addition, light range of motion exercises are introduced. Patients are given a home exercise programm consisting of self-assisted stretching, as well as pendulum exercises in the pain free range of motion, and advised to perform it daily [34, 35]. Since pain can change glenohumeral kinematics, performance of adequate exercises aimed at restoring the scapulohumeral rhythm is necessary. In the first place, hyperactivation of the upper trapezius, as a results of restricted capsular extensibility must be assessed. Static contractions and closed-chain exercises aimed at strengthening scapular stabilizing muscles are advocated in this phase of the disease [17].

In addition to reducing pain, and inflammation, the goal of treatment in the second phase of the disease is to decrease capsular adhesions. Thus, the focus of therapy is treatment of

loss of motion and abnormal scapulohumeral rhythm. Regarding the optional range of motion exercise program, Diercks and Stevens [36] found that physical therapy consisting of pain-free active exercises leads to better functional outcome in a shorter time when compared to physical therapy based on strenuous active and passive exercises, and stretching beyond what was painful. Similarly, Griggs et al. [7] showed good results in patients in the second phase of adhesive capsulitis treated with a specific exercise program where motion was limited to the range of tolerable discomfort. There is also evidence that that prolonged, low-load stretching is more effective than brief, high-load stretching [30]. At this stage, different joint mobilization techniques are advocated in order to improve range of motion [17]. Systematic literature reviews demonstrated moderately strong evidence for short- and long-term positive effects of this kind of therapy approach [25]. In addition, there is evidence that high-grade mobilization techniques are more effective than low-grade mobilization techniques [35], and that posterior glide mobilization is more efficient than anterior glide, especially for the improvement of external rotation range of motion [37]. Continuous passive motion is also used in the treatment of these patients, but there are still no recommendations for the duration and intensity of this kind of therapy [38]. Exercise intensity must be such that the patient does not have significant pain. Strengthening of scapular stabilizers continues in this phase in accordance with the functional status. Rotator cuff muscles strengthening should also be introduced as soon as adequate range of motion is obtained [17].

At the end of the second and the beginning of third phase of the disease, the mainstay of therapy is stretching of contracted structures that can be done more vigorously once the pain has subsided. Heat therapy is suggested before stretching, as well as active warm-up that promotes soft tissue circulation, relaxation of surrounding structures, and facilitates easier stretching.

A conservative rehabilitation approach will lead to a positive outcome in the majority of patients with adhesive capsulitis. Most studies documented that only 10% of patients do not achieve satisfactory therapy results [6]. Generally, it is advised to treat patients with adhesive capsulitis for 6 months conservatively, before taking into a consideration any other, more invasive treatment procedures. Indications for more invasive procedures are not clearly defined, and have to be set out individually for every patient. Manipulation under anesthesia, hydrodilatation, suprascapular nerve block, arthroscopic or open capsular release are treatment options in the case of failed conservative treatment.

Conclusion

Although adhesive capsulitis is commonly seen in everyday clinical practice, lack of strong scientific evidence enables setting of clear guidelines for its treatment. Knowing the natural history of disease, the key point of treatment is the patience of both the doctor and his patient.

Treatment must be tailored according to the phase of the disease. Recommendations based on current literature suggest the use of nonsteroidal anti-inflammatory drugs and corticosteroids in the first phase of the disease for the reduction of inflammation and pain. The use of physical therapy modalities, especially low-power laser and TENS is also recommended. In addition, a low intensity exercise program within the pain-free range of motion should be introduced along with modification of daily activities. In the second phase, as pain diminishes, the exercise program should specifically target shoulder contracture and the distorted scapulohumeral rhythm. The keystone of the third phase of the disease is stretching the shortened shoulder structures, and strengthening the rotator cuff muscles. Bearing in mind the long-lasting nature of the disease, and the fact that patients can easily become unmotivated a continuous follow-up is mandatory.

The results of our paper highlight the necessity of updating conventional rehabilitation approaches for the treatment of adhesive capsulitis in our hospitals in order to promote optimal painless functional recovery. Future prospective studies are expected to identify the causes of adhesive capsulitis, define specific causal treatment, determine the influence of different treatment modalities on the natural history of the disease, and precisely distinguish therapeutic options that provide the best treatment outcome.

REFERENCES

1. *Duplay S.* De la periarthrite scapulohumerale. Rev Frat D Trav De Med 1896; 53: 226.
2. *Codmann EA.* The shoulder: rupture of the suprpraspinatus and other lesions in or about the subacromial bursa. Boston, MA: Thomas Todd Co; 1934.
3. *Neviaser JS.*Adhesive capsulitis of the shoulder: a study of the pathologcal findings in periarthritis of the shoulder. J Bone Joint Surg Am 1945; 27: 211−22.
4. *Zuckerman J, Cuomo F, Rokito S.* Definition and classification of frozen shoulder: a consensus approach. J Shoulder Elbow Surg 1994; 3(1): S72.
5. *Green S, Buchbinder R, Hetric S.* Physiotherapy interventions for shoulder pain. Cochrane database Syst Rev 2003; (2): CD004258
6. *Hand C, Clipsham K, Rees JL, Carr AJ.* Long-term outcome of frozen shoulder. J Shoulder Elbow Surg 2008; 17(2): 231−6.
7. *Griggs SM, Ahn A, Green A.* Idiopathic adhesive capsulitis. A prospective functional outcome study of nonoperative treatment. J Bone Joint Surg Am 2000; 82-A(10): 1398−407.
8. *Hsu JE, Anakwenze OA, Warrender WJ, Abboud JA.*Current review of adhesive capsulitis. J Shoulder Elbow Surg 2010; 20(3): 502−14.
9. *Neviaser RJ, Neviaser TJ.* The frozen shoulder: diagnosis and management. Clin Orthop Relat Res 1987; 223: 59−64.
10. *Lewin WN, Kashyap CP, Bask SF, Ahmad CS, Blaine TA, Bigliani LU.* Nonoperative management of of idiopathic adhesive capsulitis. J Shoulder Elbow Surg 2007; 16(5): 569−73.
11. *Wolf JM, Green A.* Influence of Comorbidity on Self-Assessment Instrument Scores of Patients with Idiopathic Adhesive Capsulitis. J Bone Joint Surg Am 2002; 84-A(7): 1167−73.

12. *Bunker TD, Esler CN*. Frozen shoulder and lipids. J Bone Join Surg Br 1995; 77(5): 684−6.
13. *Cakir M, Samanci N, Balci N, Balci MK*. Musculoskeletal manifestations in patients with thyroid disease. Clin Endocrinol (Oxf) 2003; 59(2): 162−7.
14. *Rodeo SA, Hannafin JA, Tom J, Warren RF, Wickiewicz TL*. Immunolocalization of cytokines and their receptors in adhesive capsulitis of the shoulder. J Orthop Res 1997; 15(3): 427−36.
15. *Bunker TD, Reilly J, Baird KS, Hamblen DL*. Expression of growth factors, cytokines and matrix metalloproteinases in frozen shoulder. J Bone Joint Surg Br 2000; 82(5): 768−73.
16. *Kabbabe B, Ramkumar S, Richardson M*. Cytogenic analysis of the pathology of frozen shoulder. Int J Shoulder Surg 2010; 4(3): 75−8.
17. *Neviaser AS, Hannafin JA*. Adhesive capsulitis: a review of current treatment. Am J Sports Med 2010; 38(11): 2346−56.
18. *Shaffer B, Tibone JE, Kerlan RK*. Frozen shoulder. A long term follow-up. J Bone Joint Surg Am 1992; 74(5): 738−46.
19. *Connel D, Padmanabhan R, Buchbinder R*. Adhesive capsulitis;role of MR imaging in differential diagnosis. Eur Radiol 2002; 12(6): 2100−6.
20. *Homsi C, Bordalo-Rodrigues M, da Silva JJ, Stump XM*. Ultrasound in adhesive capsulitis of the shoulder: is assessment of the coracohumeral ligament a valuable diagnostic tool? Skeletal Radiol 2006; 35(9): 673−8.
21. *Binder A, Hazleman BL, Parr G, Roberts S*. A controlled study of oral prednisolone in frozen shoulder. Br J Rheumatol 1986; 25(3): 288–92.
22. *Buchbinder R, Green S, Youd JM, Johnston RV*. Oral steroids for adhesive capsulitis. Cochrane Database Syst Rev 2006; (4): CD006189.
23. *Buchbinder R, Hoving JL, Green S, Hall S, Forbes A, Nash P*. Short course prednisolone for adhesive capsulitis (frozen shoulder or stiff painful shoulder): a randomised, double blind, placebo controlled trial. Ann Rheum Dis 2004; 63(11): 1460−9.
24. *Rookmoneea M, Dennis L, Brealey S, Rangan A, White B, McDaid C*, et al. The effectivness of interventions in the management of patients with primary frozen shoulder. J Bone Join Surg Br 2010; 92(9): 1267−72.
25. *Favejee MM, Huisstede BM, Koes BW*. Frozen shoulder: the effectivness of conservative and surgical interventions-systemativ review. Br J Sports Med 2011; 45(1): 49−56.
26. *Lee HJ, Lim KB, Kim DY, Lee KT*. Randomized controlled trial for efficasy of intraarticular injection for adhesive capsulitis: ultrasonography-guided versus blind technique. Arch Phys Med Rehabil 2009; 90(12): 1997−2002.
27. *Taverna E, Parrini M, Cabitza P*. Laser therapy versus placebo in the treatment of some bone and joint pathology. Minerva Ortop Traumatol 1990; 41: 631−6. (Italian)
28. *Sunders L*. The efficacyof low laser therapy in supraspinatus tendinitis. Clin Rehabil 1995; 9: 126−34.
29. Stergioulas A. Low-power laser treatment in patients with frozen shoulder: preliminary results. Photomed Laser Surg 2008; 26(2): 99−105.
30. *Rizk TE, Christopher RP, Pinals RS, Higgins AC, Frix R*. Adhesive capsulitis (frozen shoulder): a new approach to its menagement. Arch Phys Med Rehabil 1983; 64(1): 29−33.
31. *Sun KO, Chan KC, Lo SL*. Acupuncture for frozen shoulder. Hong Kong Med J 2001; 7(4): 381−91.
32. *Dorgu H, Basaran S, Sarpel T*. Effectivness of therapeutic ulrasound in adhesive capsulitis. Joint Bone Spine 2008; 75(4): 445−50.
33. *Jewell DV, Riddle DL, Thacker LR*. Interventions associated with increased or dicreased likelihood of pain reduction and improved function in patients with adhesive capsulitis:a retrospective cochort study. Phys Ther 2009; 89(5): 419−29.
34. *Vermeulen HM, Obermann WR, Burger BJ, Kok GJ, Rozing PM, van Den Ende CH*. End-range mobilization techniques in adhesive capsulitis of the shoulder joint: A multiple-subject case report. Phys Ther 2000; 80(12): 1204−13.
35. *Vermeulen HM, Rozing PM, Obermann WR, le Cessie S, Vliet Vlieland TP*. Comparison of high-grade and low-grade mobilization techniques in the management of adhesive capsulitis of the shoulder: randomized controlled trial. Phys Ther 2006; 86(3): 355−68.
36. *Diercks RL, Stevens M*. Gentle thawing of the frozen shoulder: a prospective study of supervised neglect versus intensive physical therapy in seventy-seven patients with frozen shoulder syndrome followed up for two years. J Shoulder Elbow Surg 2004; 13(5): 499−502.
37. *Johnson AJ, Godges JJ, Zimmerman GJ, Ounanian LL*. The effect of anterior versus posterior glide joint mobiliyation on external rotation range of motion in patients with shoulder adhesive capsulitis. J Orthop Sports Phys Ther 2007; 37(3): 88−9.
38. *Page P, Labbe A*. Adhesive capsulitis:use the evidence to integrate your interventions. N Am J Sports Phys Ther 2010; 5(4): 266−73.

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CASE REPORT

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Brain metastases of choriocarcinoma – A report on two cases

Moždane metastaze horiokarcinoma

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Abstract

Introduction. Gestational trophoblastic diseases (GTD) are a spectrum of tumors with a various of biological behavior and potential for metastases. It consists of hydatiform mole, invasive mole, choriocarcinoma and placental site trophoblastic tumor. Choriocarcinoma presents a very aggressive tumor with high malignant potential. **Case report.** We presented the two cases of choriocarcinoma with brain metastases. The first one was manifested by neurological deterioration as the first sign of metastasis, while the second patient had firstly metrorrhagia and in the further couse neurological disturbances that suggested the presence of brain tumor. In both cases we applied a combined treatment of surgery, chemotherapy and radiation therapy. Both patient survived with high quality of life. **Conclusion.** A successful outcome of brain metastases of choriocarcinoma was obtained by the use of a combined treatment of surgery, chemotherapy and radiation therapy. In cases of young women with brain metastases, gynecological malignancy should be always considered.

Key words:
choriocarcinoma; neoplasm metastasis; brain neoplasms; diagnosis; drug therapy; radiotherapy; neurosurgical procedures; treatment outcome.

Apstrakt

Uvod. Gestacijske trofoblastne bolesti predstavljaju spektar tumora sa različitim biološkim ispoljavanjem i metastatskim potencijalom. Obuhvataju hidatiformnu molu, invazivnu molu, horiokarcinom i tumor placentnog ležišta. Horiokarcinom predstavlja agresivni tumor sa visokim malignim potencijalom. **Prikaz bolesnika.** U radu su prikazana dva bolesnika sa horiokarcinomom i metastatskim promenama u mozgu. Kod prvog bolesnika bolest se manifestovala neurološkom simptomatologijom kao prvim znakom horiokarcinoma, dok je kod druge bolesnice najpre bilo prisutno krvarenje iz materice, a u daljoj fazi javili su se neurološki poremećaji koji su ukazivali na prisustvo tumora u mozgu. Kod obe bolesnice primenjeno je kombinovano lečenje (hirurško odstranjenje tumora, hemio- i radioterapija) koje je dovelo do izlečenja. **Zaključak.** Uspešno lečenje metastaza na mozgu poreklom od horiokarcinoma postignuto je primenom hirurškog zbrinjavanja, hemioterapije i radioterapije. Kod mlađih bolesnika sa metastatskim promenama na mozgu, uvek bi trebalo razmišljati diferencijalno-dijagnostički i o ginekološkom malignitetu.

Ključne reči:
horiokarcinom; neoplazme, metastaze; mozak, neoplazme; dijagnoza; lečenje lekovima; radioterapija; neurohirurške procedure; lečenje, ishod.

Introduction

Gestational trophoblastic diseases (GTD) consist of neoplasms of trophoblasts and conditions predisposing the neoplasm. These diseases include hydatidiform mole, invasive mole, choriocarcinoma and placental-site trophoblastic tumor [1]. Choriocarcinoma is a malignant form of GTD. Clinically, it is most frequently presented as abnormal uterine hemorrhage after abortion or hydatidiform mole. Considering high malignancy potential, the metastases are frequent, and mostly found in the lungs, vagina, brain, kidneys and ovaria [2]. Sometimes, the initial manifestations of this disease are just the symptoms related to metastatic focus [3]. Cerebral metastases are found in 10–20% of choriocarcinoma cases, and usually manifested as intracerebral or subdural hematoma, vascular occlusion, arterial aneurysm or spinal epidural hematoma [4].

We reported two cases of metastatic brain choriocarcinoma. In the first case brain metastasis gave first sign of the disease, which led to prompt treatment with fertility sparing at the end. In the second case brain metastasis was discovered a year after the first signs of choriocarcinoma which led

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to a higher number of chemotherapeutical cures with no fertility sparing. This emphasizes the necessity of complete body screening, including computed tomography (CT) of the brain when the diagnosis of choriocarcinoma is made.

Case report

Case 1

A 19-year-old female patient was admitted to the Institute of Neurosurgery, Clinical Center of Serbia, as an emergency due to spontaneous right parietal intracerebral hematoma whose presence was verified by computerized CT of the brain (Figure 1).

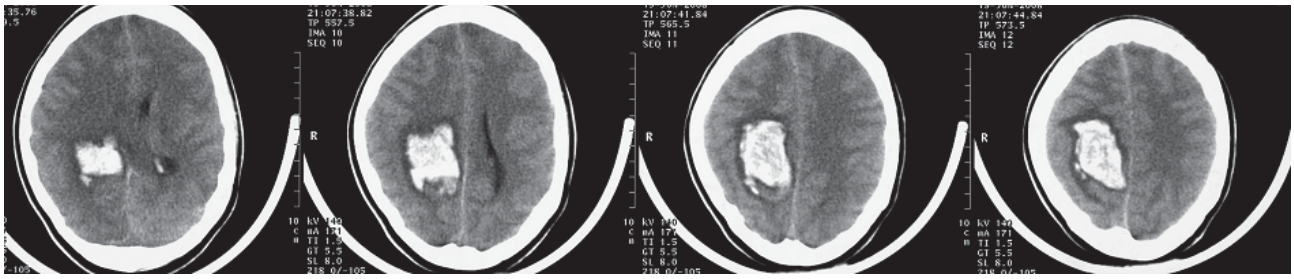

Fig. 1 – Computed tomography (CT) on admission showed a right intracerebral hematoma.

A week before admission the patient had a headache associated with vision impairment. On the admission day, the patient suddenly lost consciousness. Neurological examination revealed uncommunicative patient with circular pupil responding to light, as well as dextral paresis of the lower level. Her medical history recorded one vaginal birth. After 3 days of admission, her condition was abruptly aggravated with respiratory arrest, and appropriate cardiopulmonary resuscitation (CPR) measures were applied. Control brain CT showed the enlargement of hematoma mass and cerebral edema, due to which the patient immediately operated on and hematoma evacuated. Control brain CT revealed hypodense changes in the remaining hematoma, i.e. tumor or malformations of cerebral blood vessels, requiring digital subtraction pan-angiography which ruled out the presence of vascular malformation as the cause of hemorrhage. Eight days later, the patient was reoperated, and the right paraventricular tumor of about 2 cm in size removed (Figure 2). After operation, the patient was aware with the passing dexter hemiparesis and psychoorganic syndrome of the mid degree.

Given that preliminary histopathological examination aroused suspicion about the choriocarcinoma, CT of the chest, abdomen and small pelvis was carried out immediately, which demonstrated multiple circular soft-tissue changes scattered in both lungs. Other findings were regular. Subsequently, blood tests for alpha-fetoprotein and beta hCG were carried out, revealing the serum beta hCG concentration over 225000.0 IU/L (less than 5 is normal), and alpha-fetoprotein of 0.5 μg/L (13.4 μg/L is normal). Immunohistochemical examination of the tumor confirmed the choriocarcinoma.

The Medical Board decided to introduce 20 cGy radiation therapy. The patient tolerated radiotherapy well, with no antiedematous therapy, and consciously but slightly slow from psychic aspect. After completed radiotherapy, the patient was transported to the Clinic of Gynecology and Obstetrics because of metastatic pulmonary changes, further diagnostics and treatment of choriocarcinoma. Upon Trophoblastic Diseases Board consideration, it was concluded that the patient had brain choriocarcinoma and metastases to lungs without any evidence of underlying uterine disease. Considering that it was the patient with FIGO stage IV, WHO 17, with beta hCG value of 470,235 IU/L, it was decided to employ chemotherapy (etoposide, methotrexate, actinomycin D, cyclophosphamide and Oncovin – EMACO). Until a complete remission (41 days), the patient was administered two therapies according to this protocol. The patient was discharged recovered with preserved fertility. Neurological status on discharge and two months later was completely normal.

Case 2

A 35-year-old female patient was admitted to the Clinic of Gynecology and Obstetrics, Clinical Center of Serbia, in December 2010 due to previous histopathologically verified uterine choriocarcinoma upon exploration curettage which had been performed for abundant uterine bleeding. Her personal anamnesis reads that she had two deliveries by Cesarian section in 2002 and 2008. Between two births, the pa-

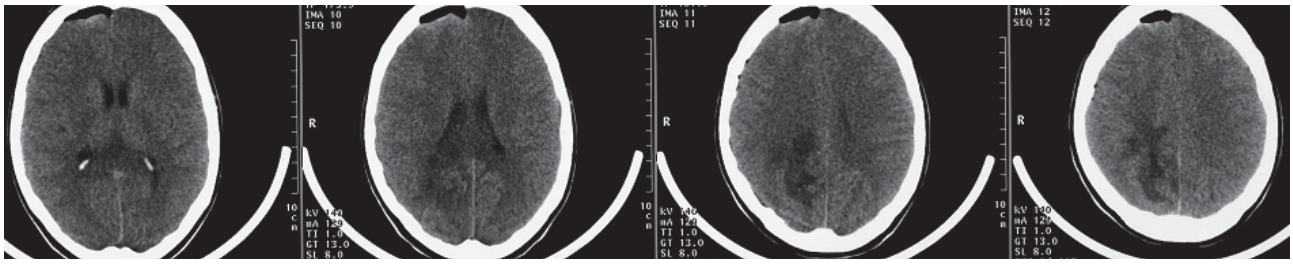

Fig. 2 – Upon tumor evacuation computed tomography (CT) verified the complete regression of changes.

tient had one complete molar pregnancy (complete hydatid mole) which, because of being refractory, was treated by methotrexate. On admission, ultrasonography verified the isthmic-cervical uterine tumor and magnetic resonance imaging (MRI) of the abdomen and small pelvis corroborated the presence of 96 × 77 × 66 mm tumor with bilateral parailiac and inguinal lymphadenopathy. The chest X-ray was normal. The patient was staged by Trophoblastic Diseases Board as WHO 9, FIGO I, and urgent hysterectomy with bilateral ovarian conservation was indicated. Immediately prior to surgery, beta hCG was 188,871 IU/L. In postoperative course, the patient received one course of chemotherapy by EMACO Protocol. Control MRI of the abdomen and chest detected metastatic changes to lungs, on what account the patient was restaged by the Board as FIGO 3, WHO 10, and accordingly, two courses of EMACO chemotherapy were added; this new administration resulted in 90-day remission of the disease and complete normalization of beta subunits. The patient was rehospitalized in May 2010 due to vertigo and occasional vision field incidents, what aroused the suspicion to metastatic changes in the brain. Neurological status revealed discrete dexter hemiparesis. Endocranial CT verified the presence of the right parietooccipital tumor (Figure 3).

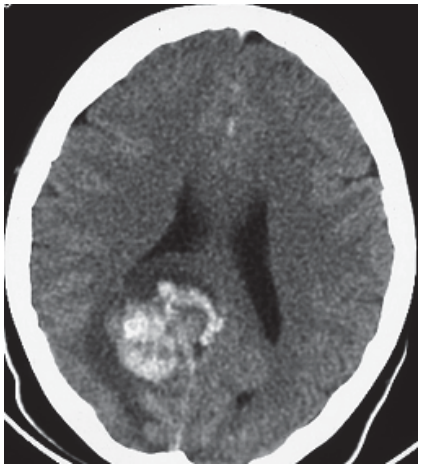

Fig. 3 – Computed tomography (CT) finding indicated a right parietooccipital tumor change.

Repeated rise of beta hCG was 2,284 IU/L and the patient received IV, V and VI course of chemotherapy, and neurosurgical examination (MRI, liquor puncture) found congenital cavernous angioma. Chemotherapy resulted in regression of brain tumor and normalization of beta subunits. The patient was discharged recovered in July 2010, and advised by the neurosurgeon to have her control done in 3 months. At the beginning of October, the patient manifested again the same symptoms as in earlier hospitalization. Based on endocranial CT scanning and symptoms (vertigo, dizziness and crural hemiparesis to the left), the neurosurgeon decided to operate on her. In addition, the increase of blood beta hGC level was increased again. Upon tumor extirpation, the patient was again transferred to the Clinic of Obstetrics and Gynecology to receive VII and VIII course of EMACO chemotherapy. A histopathological finding indicated the metastatic brain choriocarcinoma which was hemorrhagically and necrotically modified. According to the decision made by Neurosurgery Board, palliative 20 cGy radiotherapy was applied. After radiation therapy, the patient went well, but her fertility was not preserved. Neurological status on discharge was normal.

Discussion

The risk of choriocarcinoma is rare before the age of 20 years, and it is significantly increased in individuals over 40 years [5]. Both presented cases are beyond typical etiology of choriocarcinoma.

GTDs are most frequent in Asian countries with the annual incidence of 1/2000 of all pregnancies (births and miscarriages). Recent literature has described only 150 choriocarcinomas metastasized to the lungs and brain [6]. In diagnosis of choriocarcinoma, metastatic changes are detected in about 30% of patients [7]. Due to hematogenic spread of trophoblastic tissue, the metastases are manifested very early, and their symptoms are usually related to bleeding from metastatic focus. Staging of patients based on WHO and FIGO criteria allows for rapid orientation and prompt treatment. The WHO criteria suggest that any patient with WHO score over 8 is considered at high risk and the initiation of treatment is suggested as soon as possible without additional therapy such as surgery or radiation therapy. Both presented cases had high WHO score (17 and 9, respectively).

Treatment of choriocarcinoma consists of polychemotherapy. Initiation of EMACO radiotherapy is the first treatment choice. Surgical treatment is used in cases of local, chemoresistant metastatic focus and recurring disease. Nevertheless, some studies show that surgical treatment of metastatic changes shortens the time of cure [8].

Application of radiotherapy in cases of metastatic brain choriocarcinoma is controversial. Certain authors suggest 30 to 40 Gy radiotherapy along with chemotherapy. Study on 78 subjects affected by choriocarcinoma with brain metastases demonstrated survival of 50% in patients treated both by chemo- and radiotherapy *vs* 24% survival rate in those treated with chemotherapy only [7, 8].

Our experience in both cases show that the synergism of chemotherapy, surgical evacuation of tumorous changes, and, finally, radiotherapy is a pathway to preservation of reproductive ability and healing of patients.

Conclusion

Treatment of GTD with metastatic changes in the brain is a great challenge. Nevertheless, the incidence of cure is high. The first treatment choice is chemotherapy and surgery, and in cases where it is required, radiotherapy, as well. Given high metastatic potential, choriocarcinoma should be considered in cases of intracranial hemorrhage with the unusual location in reproductive women. Histopathological findings and measurements of beta hCG are necessary for making the diagnosis of choriocarcinoma.

REFERENCES

1. *Milenković V, Lazović B.* Gestational trophoblastic disease--literature review. Med Pregl 2011; 64(3−4):188−93. (Serbian)
2. *James FV, Lijeesh AL, Koshy SM, Kumar A.* Choriocarcinoma with brain involvement. J Cancer Res Ther 2011; 7(3): 383−4.
3. *Chien JC, Hsiao YL, Lin SE, Chan WP.* Off-midline retroperitoneal choriocarcinoma presenting as neurologic symptoms. Eur J Gynaecol Oncol. 2011; 32(3): 343−6.
4. *Dadlani R, Furtado SV, Ghosal N, Prasanna KV, Hegde AS.* Unusual clinical and radiological presentation of metastatic choriocarcinoma to the brain and long-term remission following emergency craniotomy and adjuvant EMA-CO chemotherapy. J Cancer Res Ther 2010; 6(4): 552−6.
5. *Kyriakou F, Vaslamatzis MM, Bastani S, Lianou MA, Vourlakou C, Koutsoukou A.* Primary choriocarcinoma of the renal pelvis presenting as intracerebral hemorrhage: a case report and review of the literature. J Med Case Reports 2011; 5(1): 501.
6. *Soares PD, Maestá I, Costa OL, Charry RC, Dias A, Rudge MV.* Geographical distribution and demographic characteristics of gestational trophoblastic disease. J Reprod Med 2010; 55(7−8): 305−10.
7. *Lurain JR.* Gestational trophoblastic disease I: epidemiology, pathology, clinical presentation and diagnosis of gestational trophoblastic disease, and management of hydatidiform mole. Am J Obstet Gynecol 2010; 203(6): 531−9.
8. *Dadlani R, Furtado SV, Ghosal N, Prasanna KV, Hegde AS.* Unusual clinical and radiological presentation of metastatic choriocarcinoma to the brain and long-term remission following emergency craniotomy and adjuvant EMA-CO chemotherapy. J Cancer Res Ther 2010; 6(4): 552−6.

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CASE REPORT

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Extramedullary plasmacytoma of the tongue base: A rare presentation of head and neck plasmacytoma

Ekstramedularni plazmocitom baze jezika: retka prezentacija plazmocitoma glave i vrata

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Abstract

Introduction. Special entities like solitary bone plasmocytoma (SBP) or extramedullary plasmacytoma (EMP) can be found in a less than 5% of patients with plasma cell disorders. EMP of the tongue represents very rare localization of the head and neck plasmacytoma. **Case report.** We report a case of 78-years-old woman who developed EMP of the tongue base detected by the magnetic resonance imaging (MRI) of the head and neck region. Immunohistochemical profile of the tumor tissue biopsy (CD38, IgG, kappa positivity) indicated diagnosis of EMP. The diagnosis was established with additional staging which confirmed the absence of other manifestation of the disease. The patient was treated with 40 Gy of radiotherapy in 20 doses resulting in the achievement of the complete remission of the disease. This case was discussed with the reference to the literature. **Conclusion.** EMP of the tongue base is a very rare entity of plasma cell dyscrasias. Appropriate irradiation results in the achievement of a long-term remission and a potential cure of the disease.

Key words:
plasmacytoma; diagnosis; tongue; radiotherapy; treatment outcome.

Apstrakt

Uvod. Posebni entiteti kao što su solitarni plazmocitom kostiju ili ekstramedularni plazmocitom (EMP) mogu se naći kod manje od 5% bolesnika sa plazmaćelijskim oboljenjima. Ekstramodularni plazmocitom baze jezika je veoma retka lokalizacija plazmocitoma glave i vrata. **Prikaz bolesnika.** U radu je prikazana bolesnica, stara 78 godina, sa EMP baze jezika, čije postojanje je ustanovljeno magnetnom rezonancom (MR) glave i vrata. Imunohistohemijskim profilom bioptata tumorskog tkiva (CD38, IgG, kappa pozitivnost) potvrđena je dijagnoza EMP. Dopunskim ispitivanjima ustanovljeno je odsustvo drugih manifestacija bolesti. Bolesnica je lečena lokalnom zračnom terapijom sa 40 Gy u 20 seansi, čime je postignuta kompletna remisija bolesti. **Zaključak.** Ekstramodularni plazmocitom baze jezika je veoma redak vid ispoljavanja plazmaćelijskih oboljenja. Odgovarajućom zračnom terapijom postižu se dugotrajne remisije bolesti uz postojanje potencijalne mogućnosti izlečenja.

Ključne reči:
plazmocitom; dijagnoza; jezik; radioterapija; lečenje, ishod.

Introduction

Plasmacytomas are localized tumors consisting of monoclonal plasma cells that may develop in either bones or soft tissue [1]. Less than 5% of patients with plasma cell dyscrasia present with a single bone or extramedullary lesion due to a malignant plasma cell infiltrate, without apparent evidence of systemic myeloma. Solitary extramedullary plasmacytoma (EMP) is less common than solitary bone plasmacytoma (SBP) and occurs when there is soft tissue infiltration of clonal plasma cells. EMP is approximately three times more often in men than in women, usually in the age group of 50–70 years. The diagnosis requires biopsy confirmation of monoclonal plasma cells from single site. There should be no evidence of bone destruction, clonal marrow plasmacytosis or occult disease elsewhere [2]. Approximately 85% of lesions occur in the head and neck mucosa probably related to long-term stimulation by inhaled irritants or viral infection. An underlying bone involvement, particularly in the sinuses, may be noted. They account for fewer than 1% of all head and neck tumors [3]. Gastrointestinal involvement, although significantly less common, is the next most frequent site, and other areas of involvement, reported infrequently, include: lung, bladder, thyroid, testis, ovary, and

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tonsil among other. Solitary plasmacytomas of the tongue base are rare tumors that occurre in 1.7% of all EMPs in the upper aerodigestive tract [4, 5]. Similar to the SBP, EMPs are highly radiosensitive with nearly all patients successfully achieving local control and approximately 50–65% of patients remaining free of disease longer than 10 years. Due to small patient numbers and historical retrospective analyses over many decades, no firmly established treatment criteria exist [6, 7].

Its rare occurance and variety of clinical manifestations may cause clinical uncertainty prior to the receipt a histologic and hematologic diagnosis. With an idea to highlight diagnosis and treatment modalities, in this presentation we report a case of extramedullary plasmacytoma of the tongue base.

Case report

In July 2010, a 78-year-old woman was admitted with complaints as tongue swelling without any other symptoms. The patient past medical history revealed durable five years of complete remission after surgical removal of the colorectal carcinoma.

Physical exam showed an elastic, irregular tumor mass at the ventral left side of the tongue base without significant lymphadenopathy. The magnetic resonance imaging (MRI) exam of the head and neck region confirmed tumor mass of 3.5 × 2.5 × 1.0 cm size at the ventral left side of the tongue (Figure 1).

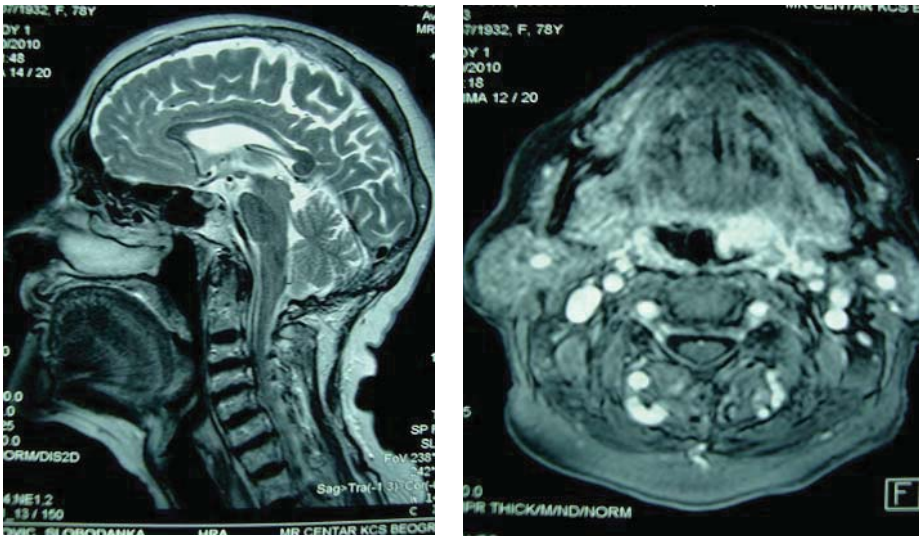

Fig. 1 – Magnetic resonance imaging (MRI) findings of the head and neck region showing tumor mass on the ventral left side of the tongue base.

Tumor biopsy showed massive diffuse infiltrate of abnormal plasma cells (70%) with the following immunohistochemical profile (Figure 2): CD38+++ (70% cells); *kappa* ++ (30% cells); lambda- (< 10% cells); IgG++ (60% cells); p53+ (20% cells); FGFR3- (< 10% cells). Blood count was normal (Hb 123 g/L, WBC 6.0 × 10^9/L, PLT 170 × 10^9/L).

Results of the other laboratory tests were unremarkable with normal levels of the erythrocyte sedimentation rate (14), total proteins (80 g/L), without renal impairment and proteinuria (0.08g/24h), and without suppression of the uninvolved immunoglobulins. Protein electrophoresis with immunofixation did not confirm the existence of monoclonal (M) protein accompanied with the absence of Bence Jones proteinuria. Bone marrow (BM) trephine biopsy with immunohistochemical staining did not show plasma cell infiltration accompanied with positive expression of osteoprotegerin (OPG, 25% cells) and the absence of receptor activator of nuclear factor κB ligand (RANKL, < 10% cells). An x-ray skeletal survey found no osteolytic or neoplastic processes followed with normal MRI of the axial skeleton. Computed tomography (CT) scan of the chest and abdomen did not reveal any pathological findings. The patient was negative for the tumor (CEA, CA19.9, CA125) and viral (HBsAg, HCV, HIV, HHV8) markers.

Following above mentioned exams, the diagnosis of solitary EMP of the tongue base was established. The patient was treated with 40 Gy of a local radiotherapy in 20 doses achieving complete remission confirmed at the last control check-up in December 2010.

Discussion

In comparison to SBP, solitary EMP is less common than SBP. Solitary plasmacytoma of the tongue is extremely rare, with only a few cases having been reported in the English literature [8–14]. This entity requires distinction from reactive plasmacytosis, plasma cell granuloma and lymphoproliferative disorders like mucosa-associated lymphoid tissue (MALT), marginal zone, and immunoblastic lymphoma [3, 15, 16]. It is suspected that in pathogenesis of EMP, both of clonal event (chromosomal abnormalities, i.e. losses at 13q) and IL-6 are required [1]. In accordance with literature data, our patient is the senior female who developed EMP of the tongue base in the age of 78 years [2]. The immunohistochemical profile of the tumor in our patient indicated massive diffuse infiltration

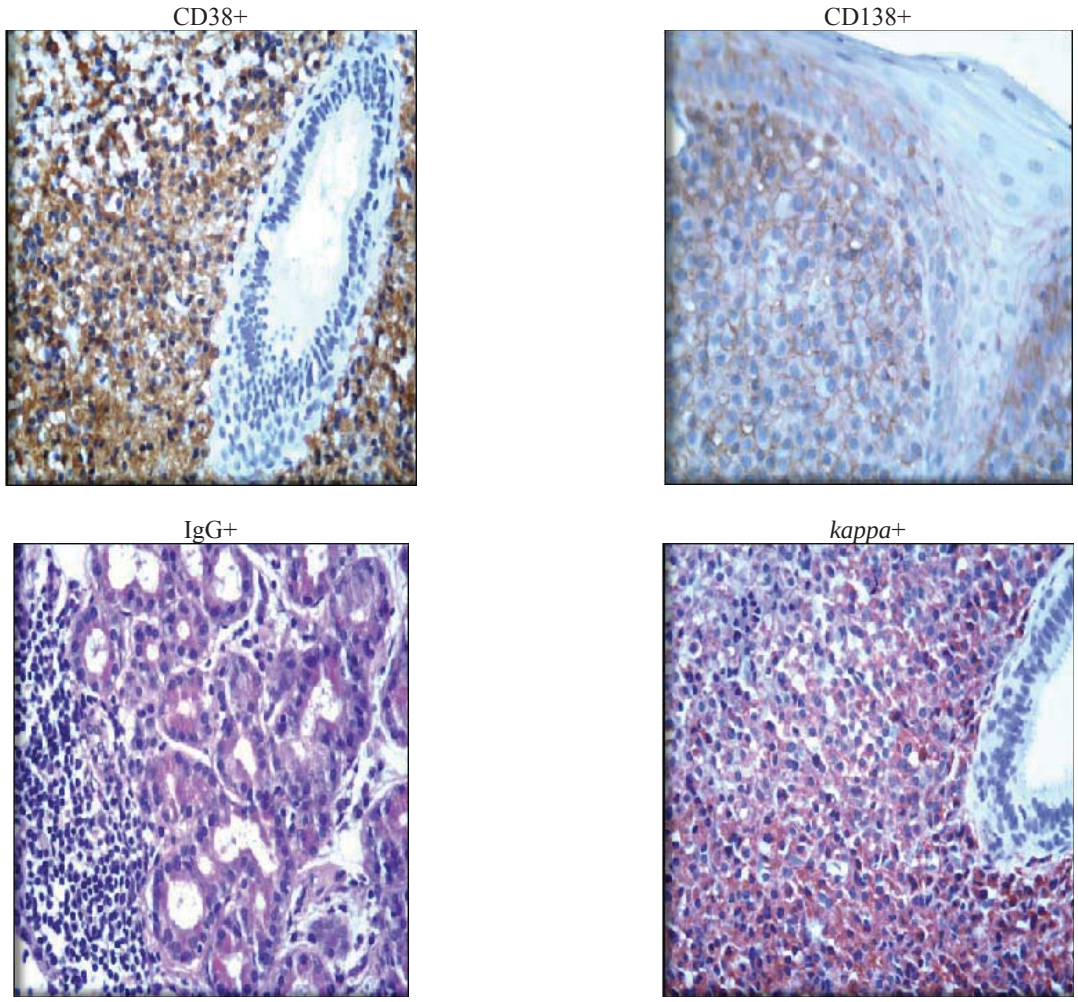

Fig. 2 – Immunohistochemical profile of the tumor tissue biopsy (CD38+, CD138+, IgG+, *kappa* +).

with monoclonal CD38 and IgG *kappa* positive plasma cells. Phenotypic studies for CD38 and monoclonal cytoplasmic light chain expression of malignant plasma cells obtained by biopsy or fine needle aspiration of the solitary lesion are necessary for the accomplishment of the EMP diagnosis [2, 15, 16]. Aberrant expression of fibroblast growth receptor 3 oncogene (FGFR 3) as a product of *t* (4,14) is present in approximately 15% of myeloma patients and contribute to myeloma progression. Lack of FGFR 3 expression in our patient could explain the indolent course of disease [17]. The absence of bone disease in the patient concurs with the findings of both low expression of RANKL in the bone marrow as a marker of octeoclastic activity and pronounced expression of its naturally occurring decoy receptor, OPG [18]. Additionally, according to the literature data [1], the lack of CD56 expression could indicate the lack of bone disease in EMP. Confirmation of the diagnosis requires as well the absence of bone marrow infiltration, skeletal events or any signs of symptomatic disease elsewhere [1–3, 15, 16].

In order to verify the extent of the solitary lesion, CT or MRI is required. Similarly to SBP and 1A clinical stage of myeloma, spinal MRI was performed in the patient for the accurate staging of EMP indicating the absence of the bone disease. Although there was no detectable M-protein in the serum and urine of our patient, by electrophoresis and immunofixation its low levels can be detected in less than 25% of patients with EMP or SBP [2, 3, 15, 16]. Additionally, normal level of uninvolved immunoglobulin in the patient confirmed the absence of occult disease elsewhere. Serum-free light chain assays could be useful in staging EMP and SBP patients, accompanied with the absence of underlying myeloma by bone survey and abnormalities of biochemistry attached to plasma cell disorders [19].

Due to a small number of patients, there are no established criteria for the treatment. Both entities, SBP and EMP, are highly radiosensitive. The achievement of local control is expected in nearly all patients. About half of these will remain free of the disease longer than 10 years. In accordance with the literature, elective radiotherapy with 40 Gy of mean irradiation dosage was applied in the described patient [4, 7] resulting in the achievement of a complete remission after irradiation at the last three months of follow-up. The United Kingdom Myeloma Forum recommended radiotherapy dose of 40 Gy in 20 fractions for tumors < 5 cm and up to 50 Gy in 25 fractions for tumors a 5 cm with at least a 2 cm margin encompassing the primary tumor. Involvement of cervical nodes or Waldeyer's ring tumors requires inclusion in the radiotherapy field [16]. Radical surgery of the head and neck is a generally mutilating procedure that is not indicated as the tumours are generally highly radiosensitive and the majority

of patients are cured with radiotherapy. Nevertheless, surgery may be considered for other sites of disease, such as the gastrointestinal tract [20]. Comparing patients with sites other than the head and neck, who received either surgery, radiation, or a combined-modality treatment, there was no difference among these 3 arms, suggesting that either surgery or radiotherapy is reasonable for such patients. At the present time, adjuvant chemotherapy is not indicated because it has not been shown to reduce relapse or improve survival rates. However, it can be used at the time of recurrence or dissemination of the disease [2, 16, 19–21].

Less than 10% of patients have local reccurence of the disease, with achievement of 50–80% of the 10-year disease free and overall survival in 30–50% of patients who develop disease progression to myeloma. The progression to myeloma might occur after the median of 1.5–2.5 years. The clinical course at progression of these patients is similar to patients with newly diagnosed symptomatic myeloma. Possible risk factors for EMP evolution to myeloma may be bulky disease > 5 cm, elderly age, suppression of uninvolved immunoglobulins and persisting M protein for more than one year after radiotherapy indicating age as the only one positive risk factor in our patient [2, 7, 16].

Conclusion

EMP of the tongue base is a very rare entity of plasma cell dyscrasias accounting less than 1% of all head and neck tumors. Appropriate irradiation results in a log-term stability and potential cure in more than half of the patients. Spinal MRI and new modalities of the disease monitoring like serum free-light chain assay might be of significance for staging and risk stratification. More detailed individual patient data analyses of the hitherto published cases are needed to identify different prognostic subgroups of patients and optimal treatment approach.

REFERENCES

1. *Lust J.* Solitary plasmacytoma of bone and extramedullary plasmacytoma. In: *Gertz M, Greipp P*, editors. Hematologic malignancies: Multiple myeloma and related plasmacell disorders. New York: Springer-Verlag; 2004. p. 111−8.
2. *Weber DM.* Solitary bone and extramedullary plasmacytoma. Hematology Am Soc Hematol Educ Program 2005: 373−6.
3. *Dimopoulos M, Hamilos G.* Solitary bone plasmacytoma and extramedullary plasmacytoma. Curr Treat Options Oncol 2002; 3(3): 255−9.
4. *Susnerwala S, Shanks J, Banerjee S, Scharffe J, Farrington W, Slevin N.* Extramedullary plasmacytoma of the head and neck region: clinicopathological correlation in 25 cases. Br J Cancer 1997; 75(6): 921−7.
5. *Wax M, Yun K, Omar R.* Extramedullary plasmacytomas of the head and neck. Otolaryngol Head Neck Surg 1993; 109(5): 877−85.
6. *Chao MW, Gibbs P, Wirth A, Quong G, Guiney M, Liew K.* Radiotherapy in the management of solitary extramedullary plasmacytoma. Intern Med J 2005; 35(4): 211−5.
7. *Tsang R, Gospodarowicz K, Pintilie M, Bezjak A, Wells W, Hodgson C,* et al. Solitary plasmacytoma treated with radio therapy: Impact of tumor size on outcome. Int J Radiat Oncol Biol Phys 2001; 50(1): 113−20.
8. *Garas G, Choudhury N, Prasad N, Tatla T.* Extramedullary plasmacytoma of the tongue base. JRSM Short Rep 2010; 6; 1(7): 60.
9. *Alwan H, Moor JW, Wright D, Kanatas AN, Cruickshank HE.* Extramedullary plasmacytoma of the tongue base: a case report and clinical review of head and neck plasmacytoma. Ear Nose Throat J 2010; 89(8): 369−73.
10. *Hama Y, Uematsu M, Kusano S.* Solitary extramedullary plasmacytoma of the tongue. Ulster Med J 2004; 73(2): 132−4.
11. *Webb J, Makura G, Jackson R, Helliwell T.* Primary extramedullary plasmacytoma of the tongue base. Case report and review of the literature. ORL J Otorhinolaryngol Relat Spec 2002; 64(4): 278−80.
12. *Montero C, Alvarez J, Torrico P, Pando-Pinto J, Blasco A.* Primary extramedullary plasmocytoma of the tongue base. Acta Otorrinolaringol Esp 1999; 50(8): 657−9.
13. *Izumiyama K, Murakami M, Hashimura T, Hirota S, Imanaka K, Kono M,* et al. A case of extramedullary plasmacytoma in the radix linguae treated with radiation and chemotherapy. Rinsho Hoshasen 1990; 35(6):741−4.
14. *Layton A, Cook N, Henry A.* Monoclonal plasmacytic ulcerative stomatitis. A plasma cell dyscrasia? Oral Surg Oral Med Oral Pathol 1993; 75(4): 483−7.
15. *Dimopoulos M, Moulopoulos M, Maniatis A, Alexanian R.* Solitary plasmacytoma of bone and asymptomatic multiple myeloma. Blood 2000; 96(6): 2037−44.
16. *Soutar R, Lucraft H, Jackson G, Reece A, Bird J, Low E,* et al. Guidelines Working Group of the UK Myeloma Forum (UKMF). Guidelines on the diagnosis and management of solitary plasmacytoma of bone and solitary extramedullary plasmacytoma. Br J Haematol 2004; 124(6): 717−26.
17. *Chesi M, Brents A, Ely A, Bais C, Robbiani F, Mesri A*, et al. Activated fibroblast growth factor receptor 3 is an oncogene that contributes to tumor progression in multiple myeloma. Blood 2001; 97(3): 729−36.
18. *Standal T, Seidel C, Hjertner O, Plesner T, Sanderson D, Waage A,* et al. Osteoprotegerin is bound, internalized, and degraded by multiple myeloma cells. Blood 2002; 100(8): 3002−7.
19. *Liebross H, Ha S, Cox D, Weber D, Delasalle K, Alexanian K.* Clinical Course of extramedullary plasmacytoma. Radiother Oncol 1999; 52(6): 245−9.
20. *Frassica D, Frassica F, Schray M, Sim F, Kyle R.* Solitary plasmacytoma of bone: Mayo clinic experience. Int J Radiat Oncol Biol Phys 1989; 16(1): 43−8.
21. *Fang Z, Yi X, Zhu T.* Anterior approach to the second thoracic vertebral body for surgical treatment (vertebrectomy, bone grafting and titanium alloy plate fixation). Int J Clin Oncol 2001; 6(4): 205−8.

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CASE REPORT

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Listeria monocytogenes meningitis in an immunocompetent 18-year-old patient as a possible diagnostic and therapeutical problem

Meningitis prouzrokovan bakterijom *Listeria monocytogenes* kod imunokompetentnog 18-godišnjeg bolesnika kao moguć dijagnostički i terapijski problem

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Abstract

Introduction. *Listeria monocytogenes* is the third most frequent cause of bacterial meningitis in adults. It commonly affects persons with defective cell-mediated immunity or advanced age, and only a few patiens with no underlying predisposition have been reported. **Case report.** We presented an previously healthy, 18-year-old man with typical clinical features of meningitis. On the account of earlier treatment with ceftriaxone and cerebrospinal fluid finding, an assumption of partially treated bacterial meningitis was made. The initial treatment with vancomycin and ceftriaxone, substituted on day 4 with meropenem, did not produce any clinical effect. On day 6 *Listeria monocytogenes* was isolated and, even as late as that, the administration of ampicillin was followed by complete recovery of the patient. **Conclusion.** In younger, immunocompetent individuals, in spite of the existent diagnostic and therapeutic problems, the subacute course of *Listeria monocytogenes* meningitis provides enough time for appropriate treatment and favorable disease outcome.

Key words:
meningitis; listeria monocytogenes; diagnosis; therapeutics; anti-bacterial agents.

Apstrakt

Uvod. *Listeria monocytogenes* je treći najčešći uzročnik bakterijskih meningitisa kod odraslih. Obično pogađa osobe sa poremećajem ćelijski posredovanog imuniteta ili u odmaklom životnom dobu. Opisano je samo nekoliko bolesnika bez postojeće predispozicije. **Prikaz bolesnika.** U radu je prikazan osamnaestogodišnji, prethodno zdrav bolesnik, sa tipičnom kliničkom slikom meningitisa. Na osnovu ambulantnog lečenja ceftriaksonom i nalaza u cerebrospinalnoj tečnosti postavljena je pretpostavka o parcijalno lečenom bakterijskom meningitisu. Terapija, započeta vankomicinom i ceftriaksonom, koji je 4. dana zamenjen meropenemom, nije dala kliničko poboljšanje. Šestog dana od prijema iz cerebrospinalne tečnosti izolovana je *Listeria monocytogenes*, a primena ampicilina, mada odložena, dovela je do potpunog oporavka bolesnika. **Zaključak.** Kod mladih, imunokompetentnih osoba, uprkos prisutnim dijagnostičkim i terapijskim problemima, subakutni tok meningitisa prouzrokovanog bakterijom *Listeria monocytogenes* omogućava adekvatano lečenje i povoljan ishod bolesti.

Ključne reči:
meningitis; listeria monocytogenes; dijagnoza; lečenje; antibiotici.

Introduction

Listeria monocytogenes (*L. monocytogenes*) is a Gram-positive intracellular bacterium widespread in the natural environment. Nevertheless, it is not common human pathogen. It commonly causes infections in neonates and patients with defective cell-mediated immunity due to hematologic malignancy, organ transplatation, pregnency, chronic corticosteroid therapy, alcoholism and/or cirrhosis, renal diseases, advanced age, AIDS etc [1].

Listeriosis in adults usually presents as meningitis (in over 30%) or meningoencephalitis (especially as rhombencephalitis) and occasionally as isolated cerebritis [2, 3]. It is the third most common cause of acute bacterial meningitis, after *Streptococcus pneumoniae* and *Neisseria meningitidis*, with the frequency of 4% to 12% in different countries of the Northern hemisphere [1, 4–6]. However, among the immunocompetent persons below 50 years of age, *L. monocytogenes* meningitis is rare and has been reported only in a few patiens, but never in Serbia and neighboring countries [7, 8].

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Case report

A previously healthy 18-year-old man with a 3-day history of fever, severe headache and vomiting was admitted to the clinic. For two days before, he was treated with ceftriaxone (2 g IV q24 h).

On examination, he was febrile (38.4°C), adynamic, dehydrated, with heart rate of 95/min. There were neck stiffness, and positive signs of Kernig's and Brudzinski's. Other physical findings were normal. Initial laboratory investigations showed an elevated white blood cells (WBC) count of 21,600/mm^3 with 85% neutrophils and elevated C-reactive protein (CRP) content of 126.3 mg/L. Additional blood data were unremarkable.

On the admission day, the analysis of slightly turbid cerebrospinal fluid (CSF) showed pleocytosis (WBC 134/mm^3; 54% neutrophils and 46% lymphocytes), raised concentrations of proteins (1.61 g/L) and decreased glucose concentration (2.1 mmol/L; simultaneous serum glucose 5.3 mmol/L). Gram-staining of the CSF smear did not demonstrate any microorganism. Latex agglutination antigen test (Pastorex^{Tm}, Bio-Rad, France) was negative for *Neisseria meningitidis* serogroups A, C, Y/W135, *Neisseria meningitidis* serogroup B/E. coli K1, *Streptococcus pneumoniae*, and *Haemophilus influenzae* b.

The patient was initially treated with ceftriaxone (2 g IV, q12 h) and vancomycin (1 g IV, q12 h). On day 4 after admission the patients was still febrile. Marked meningeal syndrome was present, and computed tomography (CT) scan showed diffuse cerebral edema, in spite of already administered dexamethasone and mannitol. Ceftriaxone was replaced with meropenem (2 g IV, q8 h), without any significant clinical improvement in the next two days.

At the same time, the initial CSF was inoculated onto Columbia agar, chocolate agar and MacConkey agar plates and tube of thioglycolate broth. After incubation, only thioglycolate broth culture was positive. Broth was subcultured to Columbia and chocolate agar plates and bacterial growth was seen on both media. Gram stain of the isolate demonstrated Gram-positive rods with coryneform appearance. The microorganism was identified as *L. monocytogenes* by Vitek 2 System (BioMerieux, France). It was sensitive to ampicillin minimum inhibitory concentration (MIC ≤ 0.125 μg/mL), cotrimoxazole (MIC ≤ 0.125 μg/mL), meropenem (MIC ≤ 0.064 μg/mL), chloramphenicol (MIC ≤ 0.125 μg/mL), gentamicin (MIC ≤ 0.064 μg/mL), and vancomycin (MIC ≤ 0.73 μg/mL).

After *L. monocytogenes* isolation on day 6, the treatment with ampicillin was initiated (2 g IV, q4 h). The day after, the patient was afebrile and the signs of meningeal syndrome started to resolve. A week after the treatment with ampicillin started, CSF analysis revealed 40 WBC per mm^3 (12.5% neutrophils and 87.5% lymphocytes), proteins of 0.34 g/L and glucose of 3.2 mmol/L (glycemia 5.7 mmol/L). Control CT scan was normal. After three weeks of the treatment with ampicillin, the patient was fully recovered and discharged from the clinic.

In addition, the result of the serum human immunodeficiency virus test was negative. CD4 lymphocyte count was 685 per mm^3 with CD4/CD8 ratio of 1.35. Further laboratory investigations failed to confirm any immunological abnormalities in the course of hospitalization and subsequent 6-month follow-up.

Discussion

Bacterial meningitis is one of the most dramatic conditions in medicine, with the mortality rate of up to 30% [6]. The precondition of favorable outcome of the disease is early administration of adequate antimicrobial therapy, which usually implies an empirical treatment [9]. Recommended primary regimens for community-acquired bacterial meningitis in adults consists of ceftriaxone or cefotaxime plus vancomycin, with the addition of ampicillin 2 g IV, q4 h in the circumstances suggesting possible *L. monocytogenes* origin of the infection, e.g. age > 50 years or alcoholism or other debilitating associated diseases or impaired cellular immunity [10, 11].

Immune suppression or advanced age were present in all 30 patients described by the first prospective study of community-acquired *L. monocytogenes* meningitis in adults. Otherwise, the patients presented with signs and symptoms that were not different from those found in the general population with bacterial meningitis, and the majority (77%) had at least 1 individual CSF finding indicative of acute bacterial meningitis [12].

Furthermore, Gram-staining of CSF specimens is negative in over two-thirds of *L. monocytogenes* meningitis episodes, and can be misleading in many of the remaining cases (resembling pneumococci or diphtheroids). Besides, *L. monocytogenes* may be difficult to culture in initial isolation during the time-consuming process of its microbiologic identification [13].

Again, in a large literature review including all case series and case reports, young previously healthy adults constitute only 6% of patients with *L. monocytogenes* meningitis [14]. Without any apparent underlying predisposition to infection, this group of patients represents a real diagnostic problem, especially in terms of an appropriate empiric therapy.

The presented patient was a student, with nonsignificant medical history, with excluded HIV infection or any other apparent reason for immune suppression. As usual, there were no epidemiologic clues suggesting *L. monocytogenes* infection, which was mostly sporadic and food-borne by numerous types of food [15, 16].

In these circumstances, the derived CSF finding (fewer WBC, lower percentage of polymorphonuclear leukocytes, lower protein concentrations and less hypoglycorrhachia), although suggestive of *L. monocytogenes* meningitis, was interpreted as the result of bacterial meningitis previously partially treated with ceftriaxone. Such a miscalculation in patient management could have been expected, in view of a longer prodromal phase and subacute disease course [3, 14, 17].

The treatment was initiated with cephalosporin (to which *L. monocytogenes* was innately resistant) and vancomycin (with proven ineffectivity *in vivo* against listeriosis) [17, 18]. Favorable results were not obtained either after the replacement (though for a short period of time) of

cephalosporin with meropenem, as a possible therapeutical alternative for *L. monocytogenes* meningitis, though with a variable clinical experience [19, 20]. Moreover, cerebral edema has been reported as a possible serious complication, and an important cause of death in bacterial meningitis.

Even with appropriate antibiotic therapy, as a predominant infection of older and immunocompromised patients, mortality due to *L. monocytogenes* meningitis is among the highest (28%) of all causes of acute bacterial meningitis [21]. However, in the case here reported, previously healthy, immunocompetent 18-year-old patient was successfully cured with ampicillin (the medicament of choice in the treatment of *L. monocytogenes* meningitis), although its administration was significantly delayed to the moment of microbiologic identification of the causal pathogen.

Conclusion

L. monocytogenes is one of the most common causes of bacterial meningitis in immunocompromised or elderly patients. In younger, previously healthy individuals, the infection is extremely rare, and presents a diagnostic and therapeutic challenge. However, in these circumstances (as in the presented case), the subacute course of *L. monocytogenes* meningitis provides enough time for the initial treatment correction and favorable disease outcome.

REFERENCES

1. *Hussein AS, Shafran SD*. Acute bacterial meningitis in adults: a 12-year review. Medicine (Baltimore) 2000; 79(6): 360−8.
2. *Clauss HE, Lorber B*. Central nervous system infection with Listeria monocytogenes. Curr Infect Dis Rep 2008; 10(4): 300–6.
3. *Bortolussi R, Kennedy W*. Aerobic Gram-Positive Bacilli. In: *Armstrong D, Cohen J*, editors. Infectious Diseases. London: Mosby; 1999. p. 13−8.
4. *Sigurdardottir B, Bjornsson OM, Jonsdottir KE, Erlendsdottir H, Gudmundsson S*. Acute bacterial meningitis in adults: a 20-year overview. Arch Inter Med. 1997; 157(4): 426−30.
5. *McMillan DA, Lin CY, Aronin SI, Quagliarello VJ*. Community-acquired bacterial meningitis in adults: categorization of causes and timing of death. Clin Infect Dis 2001; 33(7): 969−75.
6. *van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M*. Clinical features and prognostic factors in adults with bacterial meningitis. N Engl J Med 2004; 351(18): 1849–59.
7. *Zuniga M, Aquado JM, Vada J*. Listeria monocytogenes menigitis in previously haelthy adults: ling-term follow-up. Q J Med 1992; 85(307−308): 911−5.
8. *Jamal WY, Al-Shomari S, Boland F, Rotimi VO*. Listeria monocytogenes in an immunocompetent adult patient. Med Princ Pract 2005; 14(1): 55−7.
9. *Aronin SI, Peduzzi P, Quagliarello VJ*. Community-acquired bacterial meningitis: risk stratification for adverse clinical outcome and effect of antibiotic timing. Ann Intern Med 1998; 129(11): 862−9.
10. *Gilbert DN, Moellering RC Jr, Eliopoulos GM, Chambers HF, Saag MS*. The Sanford Guide to Antimicrobial Therapy 2011. 41th ed. Sperryville, VA: Antimicrobial Therapy, Inc; 2010.
11. *Brouwer MC, Tunkel AR, van de Beek D*. Epidemiology, Diagnosis, and Antimicrobial Treatment of Acute Bacterial Meningitis. Clin Microbiol Rev 2010; 23(3): 467–92.
12. *Brouwer MC, van de Beek D, Heckenberg SG, Spanjaard L, de Gans J*. Community-acquired Listeria monocytogenes meningitis in adults. Clin Infect Dis 2006; 43(10): 1233–8.
13. *Ross KL, Tunkel AR, Scheld WM*. Aute bacterial meningitis. In: *Scheld WM, Whitley RJ, Marra CM,* editors. Infections of the central nervous system. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2004. p. 347−422.
14. *Mylonakis E, Hohmann EL, Calderwood SB*. Central nervous system infection with *Listeria monocytogenes:* 33 years of experience at a general hospital and review of 776 episodes from the literature. Medicine (Baltimore) 1998; 77(5): 313–36.
15. *Pinner RW, Schuchat A, Swaminathan B, Hayes PS, Deaver KA, Weaver RE*, et al. Role of foods in sporadic listeriosis. II: Microbiologic and epidemiologic investigation. JAMA. 1992; 267(15): 2046−50.
16. *Ramaswamy V, Cresence VM, Rejitha JS, Lekshmi MU, Dharsana KS, S. Prasad SP*, et al. Listeria – review of epidemioloy and pathogenesis. J Microbiol Immunol Infect. 2007; 40(1): 4–13.
17. *Lorber B*. Listeriosis. Clin Infect Dis 1997; 24(1): 1−9, quiz 10−1.
18. *Hohmann EL, Portnoy DA*. Infections caused by Listeria monocytogenes. In: *Kasper DL, Fauci AS, Longo DL, Braunwald E, Hauser SL, Jameson JL*, editors. Harrison's principles of internal medicine. 17 th ed. USA, New York: The McGraw-Hill; 2008. p. 895−7.
19. *Quagliarello VJ, Scheld WM*. Treatment of Bacterial Meningitis. N Engl J Med 1997; 336(10): 708−16.
20. *Stepanovic S, Lazarevic G, Jesic M, Kos R*. Meropenem therapy failure in Listeria monocytogens infection. Eur J Clin Microbiol Infect Dis 2004; 23(6): 484−6.
21. *Amaya-Villar R, García-Cabrera E, Sulleiro-Igual E, Fernández-Viladrich P, Fontanals-Aymerich D, Catalán-Alonso P*, et al. Three-year multicenter surveillance of community-acquired Listeria monocytogenes meningitis in adults. BMC Infect Dis 2010; 10: 324.

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ERRATA

Žorić L. Pseudoexfoliation syndrome [Pseudoeksfolijativni sindrom]. Vojnosanit Pregl 2013; 70(8):762–767.

1. On the page 762, a title listed as:
   Pseudoexfoliation syndrome [Pseudoeksfolijativni sindrom]

   Should read as:
   Pseudoexfoliation syndrome [Pseudoeksfolijacioni sindrom]

2. On the page 762, Key words listed as:
   Key words: exfoliation syndrome; glaucoma; diagnosis; comorbidity; biochemistry.
   [Ključne reči: eksfolijativni sindrom; glaukom; dijagnoza; komorbiditet; biohemija].

   Should read as:
   Key words: exfoliation syndrome; glaucoma; diagnosis; comorbidity; risk factors; biological markers.
   [Ključne reči: eksfilijativni sindrom; glaukom; dijagnoza; komorbiditet; faktori rizika; biološki pokazatelji].

3. On the page 763, the right column, the last sentence in the 4th paragraph listed as:
   Both OCT and HRT have shown a high correlation between the retinal nerve fiber layer thickness and the visual field mean defect during achromatic perimetry.

   Should read as:
   Both OCT and HRT have shown a high correlation between the retinal nerve fiber layer thickness and the visual field defect during achromatic perimetry.

4. On the page 764, the right column, the 2nd sentence in the 2nd paragraph listed as:
   However, it has not been confirmed by authors [12, 13] from Iceland and Greece.

   Should read as:
   However, it has not been confirmed by authors from Iceland and Greece [12, 13].

5. On the page 764, right column, the first sentence in the last paragraph of the part entitled “Extraocular localization of pseudoexfoliations and syndrome comorbidity”, listed as:
   PEX syndrome is rare in patients with diabetic retinopathy [50] yet initiated a series of new tests.

   Should read as:
   The finding of rare occurence of PEX syndrome in patients with diabetic retinopathy [50] has initiated a series of new tests.

I N M E M O R I A M

prof. dr sc. med. VLADIMIR TADIĆ pukovnik u penziji (1947–2013)

Trećeg septembra ove godine u Beogradu je preminuo pukovnik u penziji, prof. dr Vladimir Tadić, bivši načelnik Instituta za naučne informacije Vojnomedicinske akademije (VMA) i bivši glavni i odgovorni urednik časopisa „Vojnosanitetski pregled“ (VSP).

Prof. dr Vladimir Tadić rođen je 1947. godine u Beogradu, u porodici lekara, što je, svakako, uticalo na njegovo kasnije opredeljenje za lekarski poziv. Medicinski fakultet Univerziteta u Beogradu završio je 1974. godine i iste godine stupio u aktivnu vojnu službu kao sanitetski poručnik. Posle završetka obaveznog lekarskog staža, koji je obavio u VMA, raspoređen je na radno mesto sanitetskog referenta u Vazduhoplovnoj bazi u Batajnici, odakle 1979. godine prelazi u Medicinsko odeljenje Vojnotehničkog instituta (VTI) u Beogradu, na mesto istraživača u oblasti vojne toksikologije. Iz okvira tih istraživanja su njegova magistarska („Uticaj organofosfornih inhibitora holinesteraze i njihovih antagonista na utrošak kiseonika u mozgu pacova“) i doktorska teza („Značaj citohromoksidaze i uloga endogenih opioida i histaminergičkog sistema u akutnoj toksičnosti i terapiji trovanja cijanidima“), obe odbranjene na VMA, prva 1982, a druga 1990. godine. Godine 1994. prelazi u Institut za naučne informacije VMA na mesto načelnika Odseka za informisanje i dokumentaciju, a 2000. godine preuzima funkciju načelnika Instituta na kojoj ostaje do penzionisanja 2005. Dolaskom u Institut za naučne informacije postaje urednik sekundarne publikacije „Informativni bilten“ i uključuje se u rad uređivačkog odbora časopisa VSP, čiji glavni i odgovorni urednik postaje 2000. godine. Pod njegovim rukovodstvom proširen je sastav uređivačkog odbora VSP-a sa stručnjacima iz civilnih akademskih i naučnih institucija i uvedene su dvostruke „slepe“ recenzije, čime je značajno unapređen kvalitet radova objavljenih na stranicama časopisa. Zahvaljujući tome, VSP je postao vodeći nacionalni biomedicinski časopis što se odrazilo i na sve veći priliv radova autora van vojnog saniteta, pa čak i iz inostranstva, što je, između ostalog, bio jedan od značajnih preduslova za ulazak časopisa u sistem praćenja čuvene baze naučne publicistike *Science Citation Index* (SCI) 2008. godine i dobijanje impakt faktora.

Od dolaska u Institut za naučne informacije VMA prof. dr Vladimir Tadić posebno se angažovao u organizaciji nastave iz medicinske naučne informatike na poslediplomskim studijama na VMA i Stomatološkom fakultetu Univerziteta u Beogradu. Kao vrsni znalac ove oblasti, ali i osoba izvanredno širokog obrazovanja, bio je naučni redaktor kapitalnog udžbenika iz dermatologije na našem jeziku (Đ. Karadaglić, urednik) koji je objavljen 2000. godine.

Godine 1992. izabran je u zvanje docenta, 1997. u zvanje vanrednog profesora, a 2002. u zvanje redovnog profesora za užu naučnu oblast farmakologija i toksikologija. Kao nastavnik iz ove oblasti držao je predavanja polaznicima poslediplomskih studija na VMA i Škole rezervnih oficira Sanitetske službe, kao i kadetima Vojne akademije u Beogradu. Takođe, jedno vreme bio je gostujući profesor farmakologije na Medicinskom fakultetu u Foči (Univerzitet Istočno Sarajevo, Republika Srpska, BiH). Pod njegovim mentorstvom urađene su i uspešno odbranjene dve doktorske disertacije.

Prof. dr Vladimir Tadić bio je istaknuti član Nastavno-naučnog veća VMA i posebno se angažovao u organizaciji poslediplomskih studija, kao i proceduri prijave, izrade i odbrane magistarskih i doktorskih teza, a značajan je i njegov

doprinos uspostavljanju kriterijuma za izbor u nastavna i naučna zvanja u VMA u skladu sa postojećima u naučnoj i akademskoj zajednici Srbije.

Prof. dr Vladimir Tadić objavio je preko 90 radova iz oblasti farmakologije, toksikologije i naučne informatike, od čega je njih 30 objavljeno u časopisima indeksiranim u SCI i MEDLINE bazi naučne publicistike. Bio je aktivan član Srpskog farmakološkog društva, Toksikološke sekcije Srpskog lekarskog društva i Udruženja toksikologa Srbije i u radu ovih tela ostavio je dubok trag

Pamtićemo ga kao velikog eruditu sa, gotovo, enciklopedijskim znanjem iz različitih oblasti, ne samo medicine. Nama, njegovim kolegama i saradnicima iz Instituta za naučne informacije, uvek će biti na umu njegovo insistiranje na lepoti jezika i stila u pisanju naučnih radova, na etici u publikovanju, a sve u cilju unapređenja renomea VSP-a, tog „našeg čeda“, kako je znao govoriti.

Za sve što je učinio na uspostavljanju najviših standarda u medicinskoj naučnoj informatici, a posebno u naučnom izdavaštvu, neka mu je večna slava i hvala!

prof. dr Silva Dobrić,
načelnik Instituta za naučne informacije VMA i
glavni i odgovorni urednik „Vojnosanitetskog pregleda“

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Poziv za reklamiranje u 2013. godini

U prilici smo da vam ponudimo mogućnost oglašavanja i reklamiranja proizvoda i usluga u časopisu „**Vojnosanitetski pregled**“ (VSP). To je sigurno najbolji vid i najzastupljeniji način upoznavanja eventualnih korisnika sa vašim uslugama i proizvodima.

Časopis „**Vojnosanitetski pregled**“, zvanični organ lekara i farmaceuta Vojske Srbije, naučno-stručnog je karaktera i objavljuje radove iz svih oblasti medicine, stomatologije i farmacije. Radove ravnopravno objavljuju stručnjaci iz vojnih i civilnih ustanova i iz inostranstva. Štampa se na srpskom i engleskom jeziku. Časopis izlazi neprekidno od 1944. godine do sada. Jedini je časopis u zemlji koji izlazi mesečno (12 brojeva), na oko 100 strana A4 formata, a povremeno se objavljuju i tematski dodaci (suplementi). Putem razmene ili pretplate VSP se šalje u 23 zemlje sveta. Radove objavljene u VSP-u indeksiraju: *Science Citation Index Expanded (SCIE)*, *Journal Citation Reports/Science Edition*, *Index Medicus (Medline)*, *Excerpta Medica (EMBASE), EBSCO* (preko ove baze VSP je *on line* dostupan od 2002. godine u *pdf* formatu) i *Biomedicina Serbica*.

Cene reklama i oglasa u časopisu „Vojnosanitetski pregled“ u 2012. godini su:

1.	Oglas u crno-beloj tehnici A4 formata za jedan broj	20 000,00 dinara
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Od 1. januara 2012. godine Vojnosanitetski pregled prešao je na e-Ur: Elektronsko uređivanje časopisa.

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Rukopis se piše sa proredom 1,5 sa levom marginom od **4 cm**. Koristiti font veličine 12, a načelno izbegavati upotrebu **bold** i *italic* slova, koja su rezervisana za podnaslove. Originalni članci, opšti pregledi i metaanalize ne smeju prelaziti 16 stranica (sa prilozima); aktuelne teme – osam, kazuistika – šest, prethodna saopštenja – pet, a pisma uredniku, izveštaji sa skupova i prikazi knjiga – dve stranice.

U celom radu obavezno je korišćenje međunarodnog sistema mera (SI) i standardnih međunarodno prihvaćenih termina.

Za obradu teksta koristiti program **Word for Windows** verzije 97, 2000, XP ili 2003. Za izradu grafičkih priloga koristiti standardne grafičke programe za **Windows**, poželjno iz programskog paketa **Microsoft Office** (**Excel, Word Graph**). Kod kompjuterske izrade grafika izbegavati upotrebu boja i senčenja pozadine.

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Priprema rada

Delovi rada su: **naslovna strana, apstrakt sa ključnim rečima, tekst** i **literatura.**

1. ***Naslovna strana***

a) Naslov treba da bude kratak, jasan i informativan i da odgovara sadržaju rada. Podnaslove treba izbegavati.

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c) Navode se puni nazivi ustanove i organizacijske jedinice u kojima je rad obavljen i mesta u kojima se ustanove nalaze, sa jasnim obeležavanjem odakle je autor, koristeći standardne znake za fus-note.

2. ***Apstrakt i ključne reči***

Na drugoj stranici nalazi se strukturisani apstrakt sa naslovom rada. Kratkim rečenicama na srpskom i engleskom jeziku iznosi se **uvod i cilj** rada, osnovne procedure - **metode** (izbor ispitanika ili laboratorijskih životinja; metode posmatranja i analize), glavni nalazi - **rezultati** (konkretni podaci i njihova statistička značajnost) i glavni **zaključak**. Naglasiti nove i značajne aspekte studije ili zapažanja. Strukturisani apstrakt (**250** reči) ima podnaslove: *uvod/cilj, metode, rezultati* i *zaključak*. Za apstrakte na engleskom dozvoljeno je i do **450** reči. Strukturisani apstrakt je obavezan za metaanalize (istog obima kao i za originalne članke) i kazuistiku (do 150 reči, sa podnaslovima *uvod, prikaz slučaja i zaključak*). Ispod apstrakta, pod podnaslovom „Ključne reči“ predložiti 3–10 ključnih reči ili kratkih izraza koji oslikavaju sadržinu članka.

3. ***Tekst članka***

Tekst sadrži sledeća poglavlja: **uvod**, **metode**, **rezultate** i **diskusiju**. **Zaključak** može da bude posebno poglavlje ili se iznosi u poslednjem pasusu diskusije. U **uvodu** ponovo napisati naslov rada, bez navođenja autora. Navesti hipotezu (ukoliko je ima) i ciljeve rada. Ukratko izneti razloge za studiju ili posmatranje. Navesti samo strogo relevantne podatke iz literature i ne iznositi opširna razmatranja o predmetu rada, kao ni podatke ili zaključke iz rada o kome se izveštava.

Metode. Jasno opisati izbor metoda posmatranja ili eksperimentnih metoda (ispitanici ili eksperimentne životinje, uključujući kontrolne). Identifikovati metode, aparaturu (ime i adresa proizvođača u zagradi) i proceduru, dovoljno detaljno da se drugim autorima omogući reprodukcija rezultata. Navesti podatke iz literature za uhodane metode, uključujući i statističke. Tačno identifikovati sve primenjene lekove i hemikalije, uključujući generičko ime, doze i načine davanja. Za ispitivanja na ljudima i životinjama navesti saglasnost etičkog komiteta.

Rezultate prikazati logičkim redosledom u tekstu, tabelama i ilustracijama. U tekstu naglasiti ili sumirati samo značajna zapažanja.

U **diskusiji** naglasiti nove i značajne aspekte studije i izvedene zaključke. Posmatranja dovesti u vezu sa drugim relevantnim studijama, u načelu iz poslednje tri godine, a samo izuzetno i starijim. Povezati zaključke sa ciljevima rada, ali izbegavati nesumnjive tvrdnje i one zaključke koje podaci iz rada ne podržavaju u potpunosti.

Literatura

Literatura se u radu citira kao superskript, a popisuje rednim brojevima pod kojima se citat pojavljuje u tekstu. Navode se svi autori, ali ako broj prelazi šest, navodi se prvih šest i dodaje et al. Svi podaci o citiranoj literaturi moraju biti tačni. Literatura se u celini citira na engleskom jeziku, a iza naslova se navodi jezik članka u zagradi. Ne prihvata se citiranje apstrakata, sekundarnih publikacija, usmenih saopštenja, neobjavljenih radova, službenih i poverljivih dokumenata. Radovi koji su prihvaćeni za štampu, ali još nisu objavljeni, navode se uz dodatak „u štampi“. Rukopisi koji su predati, ali još nisu prihvaćeni za štampu, u tekstu se citiraju kao „neobjavljeni podaci“ (u zagradi). Podaci sa *Interneta* citiraju se uz navođenje datuma.

Primeri referenci:

Đurović BM. Endothelial trauma in the surgery of cataract. Vojnosanit Pregl 2004; 61(5): 491–7. (Serbian)

Balint B. From the haemotherapy to the haemomodulation. Beograd: Zavod za udžbenike i nastavna sredstva; 2001. (Serbian)

Mladenović T, Kandolf L, Mijušković ŽP. Lasers in dermatology. In: *Karadaglić Đ*, editor. Dermatology. Beograd: Vojnoizdavački zavod & Verzal Press; 2000. p. 1437–49. (Serbian)

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: *Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG,* editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [serial on the Internet]. 2002 Jun [cited 2002 Aug 12]; 102(6): [about 3 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

Tabele

Sve tabele pripremaju se sa proredom 1,5 na posebnom listu. Obeležavaju se arapskim brojevima, redosledom pojavljivanja, u desnom uglu (**Tabela 1**), a svakoj se daje kratak naslov. Objašnjenja se daju u fusnoti, ne u zaglavlju. Za fus-notu koristiti sledeće simbole ovim redosledom: ***, †, ‡, §, ||, ¶, **, ††, ...** Svaka tabela mora da se pomene u tekstu. Ako se koriste tuđi podaci, obavezno ih navesti kao i svaki drugi podatak iz literature.

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Detaljno uputstvo može se dobiti u redakciji ili na sajtu:

www.vma.mod.gov.rs/vsp/download/uputstvo_za_autore.pdf.

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MS Word for Windows (97, 2000, XP, 2003) is recommended for word processing; other programs are to be used only exceptionally. Illustrations should be made using standard **Windows** programs**.** Avoid the use of colors in graphs.

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Parts of the manuscript are: **Title page; Abstract with key words; Text; References**.

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b) Full name of each author;

c) Name and place of department(s) and institution(s) of affiliation, clearly marked by standard footnote signs.

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The second page should carry a structured abstract with the title for original articles, metanalyses and case reports. The abstract should state the purposes of the study or investigation, basic procedures (selection of study subjects or laboratory animals; observational and analytical methods), main findings (giving specific data and their statistical significance, if possible), and the principal conclusions. It should emphasize new and important aspects of the study or observations. S t r u c t u r e d abstract should contain typical subtitles: *background/aim, methods, results* and *conclusion*. The abstract for metaanalyses and obrginal papers should have up to 450 words, and up to 150 words for case reports (with subtitles *background, case report, conclusion*). Below the abstract authors should provide, and identify as such, 3–10 key words or short phrases that will assist indexers in cross-indexing the article and will be published with the abstract.

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The text of original articles is divided into sections with the headings: **Introduction**, **Methods**, **Results**, and **Discussion**. Long articles may need subheadings within some sections to clarify their content.

In the **Introduction** repeat the title of the article, excluding the names of authors. State the purpose of the article and summarize the rationale for the study or observation. Give only strictly pertinent references and do not include data or conclusions from the work being reported.

Methods. Describe your selection of the observational or experimental subjects (patients or experimental animals, including controls) clearly. Identify the methods, apparatus (manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods. Identify precisely all drugs and chemicals used, with generic name(s), dose(s), and route(s) of administration. State the approvement of the Ethnics Committe for the tests in humans and enimals.

Results should be presented in logical sequence in the text, tables and illustrations. Emphasize or summarize only important observations.

Discussion is to emphasize the new and important aspects of the study and the conclusions that result from them. Relate the observations to other relevant studies. Link the conclusions with the goals of the study, but avoid unqualified statements and conclusions not completely supported by your data.

References

References should be superscripted and numbered consecutively in the order in which they are first mentioned in the text. **The references must be verified by the author(s) against the original document.** List all authors, but if the number exceeds 6, give 6 followed by et al. Do not use abstracts, secondary publications, oral communications, unpublished papers, official and classified documents. References to papers accepted but not yet published should be designated as ”in press“. Information from manuscripts not yet accepted should be cited in the text as ”unpublished observations“. References are cited according to the ***International Committee of Medical Journal Editors.*** *Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Ann Intern Med 1997; 126: 36–47. Updated October 2001.*

Examples of references:

Jurhar-Pavlova M, Petlichkovski A, TrajkovD, Efinska-Mladenovska O, Arsov T, Strezova A, et al. Influence of the elevated ambient temperature on immunoglobulin G and immunoglobulin G subclasses in sera of Wistar rats. Vojnosanit Pregl 2003; 60(6): 657–612.

DiMaio VJ. Forensic Pathology. 2nd ed. Boca Raton: CRC Press; 2001.

Blinder MA. Anemia and Transfusion Therapy. In: Ahya NS, Flood K, Paranjothi S, editors. The Washington Manual of Medical Therapeutics, 30th edition. Boston: Lippincot, Williams and Wilkins; 2001. p. 413-28.

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: *Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG,* editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [serial on the Internet]. 2002 Jun [cited 2002 Aug 12]; 102(6): [about 3 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

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Each table should typed double-spaced on a separate sheet, numbered in the order of their first citation in the text in the upper right corner and supplied with a brief title each. Explanatory notes are printed under a table, using the following symbols, in this sequence: ***, †, ‡, §, ||, ¶, **, ††, ...** Each table has to be mentioned in the text. If you use data from another source, acknowledge fully.

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