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ORIGINALNI ČLANCI / ORIGINAL ARTICLES

Dana 18. aprila ove godine održana je svečanost povodom nekoliko jubileja Instituta za naučne informacije Vojnomedicinske akademije (VMA) u Beogradu: 51 godine od osnivanja, 50 godina od početka rada i 20 godina od njegovog formalnog priključenja VMA. Ovi jubileji su, na neki način, i jubileji "Vojnosanitetskog pregleda" jer je odmah po osnivanju Instituta 15. aprila 1961. godine, redakcija časopisa postala njegov sastavni deo.

On April 18 current year a celebration was arranged to honor a few anniversaries of the Institute for Scientific Information, Military Medical Academy (MMA): 51 years of establishment, 50 years of starting to work, and 20 years of its formal joining to MMA. These anniversaries are in a certain way anniversaries of *Vojnosanitetski pregled* since right after the establishment of the Institute the editorial staff was included into it on April 15, 1961.

ORIGINALNI ČLANCI

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Razvoj hirurgije katarakte: manji rez – manje komplikacija

Evolution of cataract surgery: smaller incision – less complications

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Apstrakt

Uvod/Cilj. Operacija katarakte sa razvojem tehnologije i hirurške tehnike postala je jedna od „najbezbednijih" operacija u medicini. Iako svedene gotovo na minimum, komplikacije, ipak, i dalje postoje. Cilj ovog rada bio je da uporedi vidni ishod i učestalost pojedinih komplikacija kod različitih hirurških tehnika hirurgije katarakte, odnosno operacija katarakte sa različitom širinom kornealne incizije. **Metode.** U istraživanje je bilo uključeno 3 457 bolesnika, odnosno 4 670 očiju operisanih od katarakte. Korišćene hirurške tehnike bile su: ekstrakapsularna ekstrakcija katarakte (ECCE), fakoemulzifikacija sa implantacijom intraokularnog sočiva implantacionom pincetom (FAKO/IOL), fakoemulzifikacija sa implantacijom intraokularnog sočiva injektorom i mikroinciziona hirurgija katarakte (MICS). Bolesnici su bili praćeni šest meseci. Pri pregledu određivani su: vidna oštrina, kornealni astigmatizam, celularna reakcija u prednjoj komori, pozicija intraokularnog sočiva. **Rezultati.** U zavisnosti od primenjene hirurške tehnike nekorigovana vidna oštrina 30. postoperativnog dana bila je ≥ 0,5: kod 30% očiju – ECCE; 33,1% očiju – FAKO/IOL PMMA; 54,7% očiju – FAKO/IOL implantacija pincetom; 63,0% očiju – FAKO/IOL implantacija injektorom; 5/8 očiju – MICS. Endoftalmitis je registrovan kod 0,15% očiju – ECCE; 0,3% očiju – FAKO/IOL PMMA; 0,1% očiju – FAKO/IOL implantacija pincetom. Kod očiju operisanih tehnikama FAKO/IOL implantacija injektorom i MICS nije bilo zabeleženih slučajeva endoftalmitisa. Intraokularno sočivo nakon šest meseci bilo je dislocirano kod 7,2% očiju – ECCE i 0,6% očiju – FAKO/PMMA. Kod drugih hirurških metoda nije bilo dislokacije IOL-a. **Zaključak.** Manja kornealna incizija daje manju operativnu traumu, manje komplikacija, kraću vidnu rehabilitaciju i bolji vidni ishod.

Ključne reči:
hirurgija, oftalmološka, procedure; katarakta; postoperativne komplikacije; vid, oštrina; astigmatizam; hirurgija, minimalno invazivne procedure; mikrohirurgija.

Abstract

Background/Aim. Cataract surgery has become one of the safest procedures in medicine thanks to advances in technology and surgical techniques. Although minimal, we still witness different complications. The aim of this study was to compare visual outcome and complication rate in different techniques of cataract surgery, *ie* in cataract surgeries with various corneal incision width. **Methods.** The study included 3,457 consecutive patients, *ie* 4,670 eyes that had undergone cataract surgery. The used surgical techniques were: extracapsular cataract extraction, phacoemulsification/forceps IOL implantation, phacoemulsification/injector IOL implantation, microincision cataract surgery (MICS). Patient follow up was 6 months. Patients were evaluated for: visual aquity, corneal astigmatism, cellular reaction in the anterior chamber, IOL position. **Results.** Uncorrected visual aquity 30 days postoperatively was ≥ 0.5 in 30% of the eyes – ECCE; 54.7% of the eyes – phacoemulsification/forceps IOL implantation; 63.0% of the eyes – phacoemulsification/injector IOL implantation; 5/8 of the eyes – MICS. Endophthalmitis was detected in 0.15% of the eyes – ECCE and 0.1% of the eyes – phacoemulsification/forceps IOL implantation. In eyes with phacoemulsification/injector IOL implantation or microincision cataract surgery (MICS) there were no cases of endophthalmitis. After a 6-month period intraocular lens were dislocated in 7.2% of the eyes – ECCE, and 0.6% of the eyes – phacoemulsification/PMMA IOL. There was no IOL dislocation in other surgical techniques. **Conclusion.** Shorter corneal incision implies less complications, less operative trauma, faster visual rehabilitation and better visual outcome.

Key words:
ophthalmologic surgical procedures; cataract; postoperative complications; visual acuity; astigmatism; surgical procedures, minimally invasive; microsurgery.

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Uvod

Operacija katarakte je najčešće izvođena hirurška intervencija ne samo u oftalmologiji, već u medicini uopšte [1]. Napredak tehnologije i hirurške tehnike je, naravno, obrnuto srazmeran broju komplikacija, tako da je fakoemulzifikacija danas ne samo najčešće izvođena, već i jedna od najbezbednijih operacija. Sa sve boljim razumevanjem dinamike fluida, uz razvoj tehnologije, moguće je sa sve većom sigurnošću operisati čak i najkomplikovanije slučajeve i takođe prevenirati i rešiti neke od najtežih komplikacija koje mogu nastati u toku hirurgije.

Iako svedene gotovo na minimum, komplikacije ipak i dalje postoje. Komplikacije su za hirurge sa velikim brojem operacija jednostavno neminovnost i dešavaju se svima. Pažljivim i adekvatnim odabirom hirurške tehnike, materijala, preoperativnom pripremom bolesnika moguće je stepen komplikacija „držati" na teorijskom minimumu [2]. Raspon intraoperativnih komplikacija u smislu ozbiljnosti i mogućih posledica po dalji tok i krajnji ishod operacije nije mali. One obuhvataju gotovo beznačajne, kao što je lezija pigmentnog sloja irisa ultrazvukom, pa sve do onih koje mogu biti katastrofalne po vidni ishod, kao što je ekspulzivna hemoragija.

Nakon što je ekstrakapsularna ekstrakcija katarakte kao hirurška metoda zamenjena fakoemulzifikacijom činilo se da nema mnogo mesta za dalje promene u hirurgiji katarakte. Međutim, kao i u hirurgiji uopšte, i u fakohirurgiji se javila težnja za smanjenjem hirurškog reza, sa idejom da se smanji hirurška trauma uopšte [3]. Tako je započeta implantacija fleksibilnih intraokularnih sočiva injektorom, a razvijena je tehnološki i metoda mikroincizione hirurgije katarakte (*Microincision cataract surgery* – MICS) sa daljim smanjenjem kornealnog reza [4].

Cilj ovog rada bio je da se uporedi vidni ishod i učestalost pojedinih komplikacija [5] kod različitih tehnika hirurgije katarakte, odnosno operacija katarakte sa različitom širinom kornealne incizije.

Metode

Retrospektvno istraživanje obuhvatilo je 3 457 bolesnika, odnosno 4 670 očiju operisanih od katarakte. Od toga je operisano 930 očiju ekstrakapsularnom ekstrakcijom katarakte (ECCE), 2 454 oka fakoemulzifikacijom sa implantacijom intraokularnog sočiva implantacionom pincetom (FAKO/IOL) – od toga 320 očiju sa širenjem reza na 6 mm za implantaciju PMMA intraokularnog sočiva, 1 278 fakoemulzifikacijom sa implantacijom intraokularnog sočiva injektorom, i kod 8 očiju uklonjeno je nezamućeno sočivo zbog visoke miopije bimanuelnom irigacijom/aspiracijom na dve bočne paracenteze od 1 mm i implantiran je kapsularni tenzioni prsten zbog stabilizacije lentalne barijere, što spada u mikroincizionu hirurgiju katarakte (MICS).

Kod ekstrakapsularne hirurgije katarakte širina kornealne incizije iznosila je 11 mm, kod fakoemulzifikacije sa implantacijom intraokularnog sočiva implantacionom pincetom – 3,2 mm, kod fakoemulzifikacije sa implantacijom intraokularnog sočiva injektorom – 2,7 mm, i kod mikroincizione hirurgije katarakte – 2,2 mm, odnosno 1 mm.

Bolesnici su pregledani na biomikroskopu 1. dana postoperativno, nakon 30 dana i nakon šest meseci. Pri pregledu su određivani: nativna vidna oštrina i vidna oštrina sa odgovarajućom korekcijom, kornealni astigmatizam, celularna reakcija u prednjoj komori, pozicija intraokularnog sočiva.

Rezultati

Nativna oštrina vida prvog postoperativnog dana pokazivala je izuzetno velike razlike između grupa bolesnika operisanih različitim hirurškim tehnikama. Prvog postoperativnog dana na vidnu oštrinu značajno utiče i edem rožnjače, tako da su poređeni rezultati vidne oštrine nakon 30 dana. U grupi bolesnika operisanih ekstrakapsularnom ekstrakcijom katarakte nativna vidna oštrina nakon 30 dana kretala se u rasponu 0,05–0,9 (optotip po Snellen-u); u grupi bolesnika operisanih metodom fakoemulzifikacije sa širenjem reza na 6 mm u rasponu od 0,2 do 0,7; u grupi bolesnika operisanih metodom fakoemulzifikacije sa implantacijom fleksibilnog intraokularnog sočiva – od 0,3 do 1,0; u grupi bolesnika operisanih metodom fakoemulzifikacije sa implantacijom intraokularnog sočiva injektorom – od 0,5 do 1,0 i u grupi bolesnika operisanih mikroincizionom tehnikom – od 0,05 do 1,0 (tabela 1). Ne samo da su razlike u rasponu vidne oštrine bile izražene, već se i distribucija bolesnika po različitim vidnim oštrinama značajno razlikovala.

Tabela 1

Raspodela ispitanika prema primenjenoj hirurškoj tehnici i vidnoj oštrini merenoj 30. postoperativnog dana

Vidna oštrina	FAKO/IOL									
	ECCE		PMMA		Pinceta		Injektor		MICS	
	n	%	n	%	n	%	n	%	n	%
0,05–0,1	158	16,9	56	17,5	250	11,7	132	10,3	2	25
0,2–0,4	492	53,1	158	49,4	717	33,6	341	26,7	1	12,5
0,5–0,7	205	22,0	69	21,6	772	36,2	509	39,8	3	37,5
0,8–1,0	75	8,0	37	11,5	395	18,5	296	23,2	2	25
Ukupno	930	100,0	320	100,0	2134	100,0	1278	100,0	8	100,0

ECCE – ekstrakapsularna ekstrakcija katarakte; FAKO/IOL/PMMA – fakoemulzifikacija očnog sočiva sa implantacijom PMMA intraokularnog sočiva; FAKO/IOL/Pinceta – fakoemulzifikacija očnog sočiva sa implantacijom intraokularnog sočiva pincetom; FAKO/IOL/Injektor – fakoemulzifikacija očnog sočiva sa implantacijom intraokularnog sočiva injektorom; MICS – mikroinciziona hirurgija katarakte

Vidna oštrina sa odgovarajućom korekcijom (najbolja korigovana vidna oštrina – *best corrected visual aquity* – BCVA) pokazivala je manja odstupanja među gore navede-

nim grupama, kao što je i očekivano, a najmanja razlika je bila između grupa bolesnika operisanih metodom fakoemulzifikacije sa implantacijom intraokularnog sočiva implantacionom pincetom i implantacijom intraokularnog sočiva injektorom (tabela 2).

no (u različitoj meri – od minimalne dislokacije sa vidljivošću ruba optika u zeničnom predelu bez midrijaze, do potonuća kompletnog IOL-a) kod 37 od 930 očiju (3,9%), a nakon fakoemulzifikacije sa širenjem reza na 6 mm radi implantacije PMMA sočiva kod dva od 320 očiju (0,6%). Kod očiju

Tabela 2

Raspodela ispitanika prema primenjenoj hirurškoj tehnici i korigovanoj vidnoj oštrini merenoj 30. postoperativnog dana

Vidna oštrina	ECCE		FAKO/IOL						MICS	
			PMMA		Pinceta		Injektor			
	n	%	n	%	n	%	n	%	n	%
0,05–0,1	73	7,9	20	6,3	143	6,7	132	6,3	2	25
0,2–0,4	216	23,1	46	14,3	280	13,1	341	15,2	0	0
0,5–0,7	355	38,2	76	23,7	465	21,8	509	19,8	1	12,5
0,8–1,0	286	30,8	178	55,7	1246	58,4	296	58,7	5	62,5
Ukupno	930	100,0	320	100,0	2134	100,0	1278	100,0	8	100

ECCE – ekstrakapsularna ekstrakcija katarakte; FAKO/IOL/PMMA – fakoemulzifikacija očnog sočiva sa implantacijom PMMA intraokularnog sočiva; FAKO/IOL/Pinceta – fakoemulzifikacija očnog sočiva sa implantacijom intraokularnog sočiva pincetom; FAKO/IOL/Injektor – fakoemulzifikacija očnog sočiva sa implantacijom intraokularnog sočiva injektorom; MICS – mikroinciziona hirurgija katarakte

Kornealni astigmatizam evaluiran je i prvog postoperativnog dana, ali su zbog zarastanja reza, njegove vrednosti upoređivane nakon 30 dana. Razlike u kornealnom astigmatizmu među grupama bolesnika operisanih različitim hirurškim metodama bile su izrazito povezane sa širinom kornealne incizije (tabela 3).

operisanih drugim tehnikama nije bilo dislokacije IOL-a. Nakon šest meseci broj očiju sa dislociranim IOL-om u grupi bolesnika operisanih ekstrakapsularnom ekstrakcijom katarakte iznosio je 67 (7,2%). U drugim grupama bolesnika pozicija IOL-a nije se menjala.

Tabela 3

Promena kornealnog astigmatizma 30. postoperativnog dana u odnosu na preoperativni nalaz u zavisnosti od primenjene hirurške tehnike/širine reza

Hirurška tehnika	Širina incizije (mm)	Promena kornealnog astigmatizma (dpt)
ECCE	11,0	1,00–6,00
FAKO/IOL/PMMA	6,0	0,50–3,00
FAKO/IOL/Pinceta	3,2	0,25–2,00
FAKO/IOL/Injektor	2,7	0,00–1,00
MICS	2,2 (1,0)	0,00–0,25

ECCE – ekstrakapsularna ekstrakcija katarakte; FAKO/IOL/PMMA – fakoemulzifikacija očnog sočiva sa implantacijom PMMA intraokularnog sočiva; FAKO/IOL/Pinceta – fakoemulzifikacija očnog sočiva sa implantacijom intraokularnog sočiva pincetom; FAKO/IOL/Injektor – fakoemulzifikacija očnog sočiva sa implantacijom intraokularnog sočiva injektorom; MICS – mikroinciziona hirurgija katarakte

Celularna reakcija u prednjoj očnoj komori prvog postoperativnog dana kod ekstrakapsularne ekstrakcije katarakte kretala se od + do ++++, u grupi bolesnika operisanih metodom fakoemulzifikacije sa širenjem reza na 6 mm od + do +++, u ostalim grupama od ± do ++.

Endoftalmitis u grupi bolesnika operisanih ekstrakapsularnom ekstrakcijom katarakte registrovan je kod dva oka (0,15%); u grupi bolesnika operisanih metodom fakoemulzifikacije sa širenjem reza na 6 mm kod jednog oka (0,3%); u grupi bolesnika operisanih metodom fakoemulzifikacije sa implantacijom fleksibilnog intraokularnog sočiva pincetom kod dva od 2 134 oka (0,1%); u grupi bolesnika operisanih metodom fakoemulzifikacije sa implantacijom intraokularnog sočiva injektorom i u grupi bolesnika operisanih mikroincizionom tehnikom nije bilo nijednog slučaja endoftalmitisa.

Intraokularno sočivo nakon ekstrakapsularne ekstrakcije katarakte 1. i 30. postoperativnog dana bilo je dislocira-

Diskusija

Hirurgija katarakte od davnina predstavlja jednu od najčešće izvođenih intervencija, a u moderno vreme ubedljivo najčešću operaciju i u oftalmologiji i u hirurgiji uopšte. Stoga, nije začuđujuće da je njeno menjanje bilo relativno često jer je iskustvo u hirurgiji katarakte veliko zbog broja bolesnika (odnosno očiju) koji se godišnje svuda u svetu operišu [6]. U svetskim razmerama, operacija katarakte još uvek je intervencija sa vrlo velikim rasponom hirurških tehnika koje se koriste, a u vezi sa socioekonomskim stanjem podneblja na kojem se operacija izvodi. I u našoj sredini prelazak na modernu hirurgiju katarakte nije ni blizu potpunog sprovođenja. U Klinici za očne bolesti VMA imali smo sreće da prvi u našoj zemlji započnemo eru savremene hirurgije katarakte, i da je iza nas već zavidan broj operacija katarakte metodom fakoemulzifikacije. Zato je i materijal predstavljen ovde dobar presek i sadašnjeg stanja i razvoja hirurgije katarakte.

Iz iznetog materijala jasno se uočava da se razvoj hirurgije katarakte direktno očitava u poboljšanju vidnog ishoda, što je i primarni cilj intervencije. Smanjenje incizije u intraoperativnom toku povoljno utiče na dinamiku fluida, i smanjenje intraoperativnih komplikacija [7–9]. Sa druge strane evidentno je da se korišćenjem manjeg reza postiže ne samo bolji finalni vizus, već se vrlo rano postiže odlična vidna oštrina bez korekcije [10, 11]. U grupi bolesnika kod kojih je korišćena bimanuelna irigacija / aspiracija vrlo loša vidna oštrina kod dva bolesnika (0,05–0,10) bila je rezultat opsežnih miopnih degenerativnih promena na očnom dnu, uključujući miopnu makulopatiju.

Različita udružena oboljenja na očnom dnu, pre svega dijabetesna makulopatija i senilna degeneracija žute mrlje, objašnjavaju prilično sličan procenat vizusa – između 0,05 i 0,4 u različitim grupama hirurških tehnika. Sa druge strane, najbolja nekorigovana vidna oštrina postignuta već prvog postoperativnog dana koja iznosi 0,8–1,0 u najvećem procentu postignuta je hirurškim tehnikama sa malim kornealnim rezom, i kod ove kategorije vidne oštrine razlike su najuočljivije.

Hirurška trauma, takođe, je evidentno manja sa smanjenjem kornealne incizije, što se ogleda u postoperativnoj reakciji u prednjoj komori i u broju registrovanih endoftalmitisa.

Zaključak

Hirurgija katarakte pokazuje tendenciju smanjenja kornealne incizije poslednje dve decenije. Manja operativna trauma, manje komplikacija, kraća vidna rehabilitacija, bolji vidni ishod očigledni su razlozi za ovakav pristup hirurgiji katarakte danas. Nije zanemarljiv ni pristup bolesnika koji u eri refraktivne hirurgije imaju veća očekivanja nego ranije, tako da moderna tehnologija prati i medicinske i sociološke razloge za promenu tehnike operacije. Međutim, moderna hirurgija katarakte zahteva i celokupnu socioekonomsku osnovu visokog stepena, zbog čega u našoj sredini još uvek preovlađuju mnoge prevaziđene hirurške tehnike. U Klinici za očne bolesti VMA, na zadovoljstvo i bolesnika i lekara, hirurgija katarakte sa minimalnim zaostatkom prati vodeće svetske tendencije, pa se nadamo da će vrlo brzo kod nas preovlađujuća tehnika biti mikroinciziona hirurgija katarakte.

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Toxicokinetics and correlation of carbamazepine salivary and serum concentrations in acute poisonings

Toksikokinetika i korelacija koncentracija karbamazepina u salivi i serumu kod akutnog trovanja

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Abstract

Background/Aim. Saliva is a body fluid which, like serum, can be used for determination of concentrations of certain drugs, both in pharmacotherapy as well as in acute poisonings. The aim of this study was to determine carbamazepine concentrations in both saliva and serum in acute poisoning in order to show if there is a correlation between the obtained values, as well as to monitor toxicokinetics of carbamazepine in body fluides. **Methods.** Saliva and serum samples were obtained from 26 patients treated with carbamazepine and 20 patients acutely poisoned by the drug immediately after their admission in the Emergency Toxicology Unit. Determination of salivary and serum carbamazepine concentrations was performed by the validated high pressure liquid chromatography-ultraviolet (HPLC-UV) method. **Results.** A significant correlation of salivary and serum carbamazepine concentrations in both therapeutic application and acute poisoning (r = 0.9481 and 0.9117, respectively) was confirmed. In acute poisonings the mean ratio between salivary and serum concentrations of carbamazepine (0.43) was similar to the mean ratio after its administration in therapeutic doses (0.39), but there were high inter-individual variations in carbamazepine concentrations in the acutely poisoned patients, as a consequence of different ingested doses of the drug. In acute poisoning the halftime of carbamazepine in saliva and serum was 12.57 h and 6.76 h, respectively. **Conclusion.** Our results suggest a possible use of saliva as an alternative biological material for determination of carbamazepine concentrations in therapeutic application and acute poisoning as well, and a possible extrapolation of the results obtained in saliva to serum concentrations of carbamazepine.

Key words:
carbamazepine; pharmacokinetics; poisoning; serum; saliva; chromatography; sensitivity and specificity.

Apstrakt

Uvod/Cilj. Slično serumu, saliva je biološki materijal koji se može primeniti za određivanje koncentracije lekova kako nakon terapijske primene, tako i u akutnom trovanju. Cilj ovog rada bio je da se odrede koncentracije karbamazepina u salivi i serumu u akutnom trovanju da bi se pokazalo da li postoji korelacija između dobijenih vrednosti, kao i da se isprati toksikokinetika karbamazepina u salivi i serumu. **Metode.** Uzorci salive i seruma uzeti su od 26 bolesnika na terapiji karbamazepinom i 20 bolesnika akutno otrovanih ovim lekom nakon prijema u toksikološku ambulantu. Određivanje koncentracije karbamazepina vršeno je validovanom metodom visokoefikasne tečne hromatografije sa ultravioletnom detekcijom (HPLC-UV). **Rezultati.** Potvrđena je značajna korelacija koncentracija karbamazepina u salivi i serumu nakon terapijske primene (r = 0,9481), kao i u akutnom trovanju ovim lekom (r = 0,9117). Prosečni odnos koncentracija karbamazepina u salivi i serumu u akutnim trovanjima (0,43) bio je sličan odgovarajućem parametru nakon terapijske primene leka (0,39), ali je bilo većih interindividualnih razlika u koncentracijama leka u akutnim trovanjima, zbog, najverovatnije, razlika u ingestiranim dozama karbamazepina. U akutnim trovanjima poluvreme eliminacije karbamazepina u serumu bilo je 12,57 h, a u salivi 6,76 h. **Zaključak.** Dobijeni rezultati govore o mogućoj primeni salive kao biološkog materijala za određivanje koncentracije karbamazepina tokom terapijske primene i u akutnom trovanju, kao i o mogućoj ekstrapolaciji vrednosti koncentracija karbamazepina u salivi na serumske koncentracije ovog leka.

Ključne reči:
karbamazepin; farmakokinetika; trovanje; serum; pljuvačka; hromatografija; osetljivost i specifičnost.

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Introduction

Traditional biological materials for qualitative and quantitative measurements of most drugs are serum and urine. Many substances and their metabolites are present in different concentrations in these samples. A number of data shows that saliva is a suitable alternative for determining plasma levels of many drugs. It has the advantage of noninvasive and easy sampling, so detection of drugs in saliva can be very useful [1–5].

Under standardized and well-controlled sampling conditions, therapeutic drug monitoring of anticonvulsant drugs in saliva can be useful for determining compliance with medication, especially in pediatric patients [6].

Correlation of different drugs concentrations given in therapeutic doses in saliva and blood are known. But, there is relatively insufficient data about drugs determination, and correlation of their concentrations in blood and saliva in cases of acute poisonings by them.

Since carbamazepine is the most used drug for treating seizures, it is understandable why it is also the most frequently used antiepileptic in self poisoning [7].

The aim of this investigation was to show if there is a correlation between carbamazepine salivary and serum concentrations and dynamic of their changes in the time.

Methods

Saliva and serum samples were collected from 20 patients acutely poisoned by carbamazepine after their admission in the Emergency Toxicological Unit. Every acutely poisoned patient had previously used carbamazepine for therapy.

Twenty six saliva and serum samples were also collected from the epileptic patients treated by carbamazepine at least 6 months. Sampling of saliva and blood were done 4 h after taking the drug.

Samples were stored at -20°C until preparation and analyzing. They were prepared and analyzed by the validated high pressure liquid chromatography-ultraviolet (HPLC-UV) method previously described by Djordjevic et al. [8].

Calculation of a saliva/serum ratio and linear regression dependence of carbamazepine concentrations in saliva and serum were done by the computer software Microsoft Excel 2003.

A correlation of carbamazepine concentrations in saliva and serum was determined by Pearson's regression analysis, and calculating its halftime in saliva and serum in acute poisonings was determined using the computer software WinNonlin.

Results

In the patients on a long-term therapy with carbamazepine, salivary and serum concentrations are shown in Table 1.

Salivary and serum carbamazepine concentrations in the acutely poisoned patients and their ratios are shown in Table 2. Carbamazepine salivary and serum concentrations during the followed time period are shown in Table 3. Carbamazepine saliva levels correlated well with blood concentrations. The salivary and serum concentrations ratio for different patients also correlated well.

In both cases of treated and acutely poisoned patients, carbamazepine concentrations in saliva had a lower value compared with those in serum when the samples were collected at the same time. The mean concentrations of carbamazepine in serum and saliva samples of treated patients were 4.40 mg/L (from 1.51 to 7.52 mg/L) and 1.71 mg/L (from 0.58 to 2.82 mg/L), respectively.

Table 1

Carbamazepine serum and saliva concentrations (c) and their ratios during therapeutic use of the drug

Patient N°	Serum (c) (mg/L)	Saliva (c) (mg/L)	Saliva/serum ratio	Patient N°	Serum (c) (mg/L)	Saliva (c) (mg/L)	Saliva/serum ratio
1	4.71	1.65	0.351	14	7.52	2.54	0.338
2	1.80	0.70	0.389	15	3.87	1.69	0.438
3	2.10	1.10	0.524	16	5.84	1.98	0.338
4	5.20	1.99	0.383	17	2.99	0.86	0.288
5	4.98	1.90	0.382	18	5.45	2.37	0.435
6	2.89	1.40	0.484	19	2.85	1.00	0.353
7	6.89	2.82	0.409	20	6.01	2.33	0.387
8	5.65	2.10	0.371	21	1.51	0.61	0.406
9	4.58	1.69	0.369	22	2.47	1.13	0.460
10	6.92	2.74	0.396	23	2.42	0.58	0.240
11	4.50	2.12	0.471	24	2.78	1.16	0.417
12	4.44	1.58	0.356	25	3.57	1.30	0.363
13	5.74	2.54	0.442	26	3.83	1.50	0.391
	Serum (c) (mg/L),		$\bar{x} \pm SD$: 4.29 ± 1.68				
	Saliva (c) (mg/L),		$\bar{x} \pm SD$: 1.67 ± 0.66				
	Saliva/serum ratio,		$\bar{x} \pm SD$: 0.391 ± 0.060				

For monitoring carbamazepine toxicokinetics, serum and saliva samples were taken in the subgroup of 6 patients immediately after their admission in the Emergency Toxicological Unit, as well as after 2.5 h and 4.5 h. Saliva samples were taken with a buffer impregnated by 3% citric acid.

In the acutely poisoned patients the mean serum and saliva concentrations were 9.54 mg/L (ranged from 1.24

Table 2
Carbamazepine serum and saliva concentrations (c) and their ratios in acute poisonings by the drug

Patient N°	Serum (c) (mg/L)	Saliva (c) (mg/L)	Saliva/serum ratio
1	4.61	0.31	0.067
2	2.41	0.87	0.361
3	6.02	3.84	0.638
4	25.03	7.14	0.285
5	30.30	7.26	0.239
6	1.24	0.16	0.129
7	5.55	3.47	0.625
8	5.02	2.37	0.472
9	12.86	4.72	0.367
10	7.34	2.46	0.335
11	16.78	5.81	0.346
12	3.28	2.35	0.716
13	9.76	3.66	0.375
14	3.34	2.50	0.748
15	23.70	12.48	0.527
16	29.30	14.71	0.502
17	12.71	7.10	0.559
18	35.77	19.49	0.545
19	28.35	12.56	0.443
20	10.36	4.52	0.436
Serum (c) (mg/L),	$\bar{x}$ ± SD: 14.28 ± 10.99		
Saliva (c) (mg/L),	$\bar{x}$ ± SD: 5.89 ± 5.19		
Saliva/serum ratio,	$\bar{x}$ ± SD: 0.436 ± 0.180		

Table 3
Changes in carbamazepine serum and saliva concentrations (c) in patients acutely poisonet by the drug within 6 h after hospital admission

Patient N°	Time after admission (h)	Serum (c) (mg/L)	Saliva (c) (mg/L)	Saliva/serum ratio
	0	23.70	12.48	0.526
1	2.5	19.45	7.96	0.410
	4.5	16.07	6.39	0.397
	0	29.30	14.71	0.502
2	2.5	27.30	11.33	0.415
	4.5	21.91	9.82	0.448
	0	12.71	7.81	0.614
3	2.5	11.12	6.06	0.545
	4.5	9.89	5.70	0.576
	0	35.77	19.49	0.545
4	2.5	27.60	11.97	0.434
	4.5	26.22	9.96	0.380
	0	28.35	12.56	0.443
5	2.5	25.68	10.61	0.413
	4.5	21.83	8.40	0.385
	0	10.36	4.52	0.436
6	2.5	9.43	3.43	0.364
	4.5	8.01	2.62	0.327
Serum (c) (mg/L),		$\bar{x}$ ± SD: 20.26 ± 8.42		
Saliva (c) (mg/L),		$\bar{x}$ ± SD: 9.21 ± 4.24		
Saliva/serum ratio,		$\bar{x}$ ± SD: 0.453 ± 0.080		

mg/L to 30.30 mg/L) and 3.35 mg/L (ranged from 0.16 mg/L to 7.26 mg/L), respectively.

The carbamazepine saliva/serum ratio after therapeutic application was 0.39, and in acute poisonings 0.43. In both cases, *ie.* in therapeutic use and acute poisonings, there was a strong correlation between carbamazepine salivary and serum concentrations. The coefficients of correlation were 0.9481 and 0.9117 ($p < 0.005$), respectively.

The serum and saliva halftimes of carbamazepine in acute poisonings were 12.57 h and 6.7 h, respectively. On the other hand, when the drug was used in therapeutic doses, its serum and saliva halftime was in a wide range from 10 to 35 h, and 4.1 to 33.1 h, respectively.

The correlation between carbamazepine serum and saliva concentrations was calculated by using Pearson's regression analysis ($y = 1.03*x - 0.897$; $r = 0.9427$, $p < 0.01$).

Discussion

It is known that saliva can be suitable medium for monitoring free concentrations of carbamazepine providing a noninvasive method of sampling biological material for drug determination. Monitoring of carbamazepine in saliva is of particular interest in the management of children with epilepsy, and in geriatric patients in whom trombosed peripheral veins might limit blood sampling [9].

For determination of salivary carbamazepine concentrations when the drug is given in therapeutic doses stimulated or non-stimulated saliva can be used [10]. Age, gender and time of sampling have no influence on carbamazepine proteins binding and its saliva serum ratio [11].

Findings of Rosenthal et al. [10] have shown that stimulation of salivary excretion has no influence on carbamazepine concentration.

Salivary carbamazepine concentrations were independent of volume of fluid produced, pH of saliva, and degree of stimulation [12].

Gorodisher et al. [13] used stimulated saliva for monitoring carbamazepine concentration in children. Their results showed that correlations between saliva and free plasma anticonvulsant concentrations were equal or only slightly better than between saliva and plasma total concentrations.

Significant linear relationships between saliva and total plasma concentrations and between saliva and free plasma concentrations were observed for carbamazepine. However, salivary concentrations of carbamazepine were significantly more reliable as predictors of their respective free plasma concentrations than of their respective total plasma concentrations. It is considered that measurement of carbamazepine in saliva of chronically medicated epileptic patients provides a more reliable estimate of pharmacodynamically active, free concentrations of this compound in plasma [11].

We also used stimulated saliva for carbamazepine monitoring. For salivary stimulation we used, like many other authors, citric acid. There is a strong correlations between salivary and serum concentrations of carbamazepine ($r = 0.9481$) in accordance with literature data. For example in the study of Vasudev et al. [5] the coefficient of correlation was $r = 0.659$, in that of Rozenthal et al. [10] $r = 0.89$, al Za`abi et al. [14] $r = 0.99$ and Knot and Reynolds [15] $r = 0.94$.

Ratios between carbamazepine saliva and total blood concentrations presented by different authors, were in the range from 0.27 to 0.386 [10, 15, 16]. The described ratios show a level of carbamazepine protein binding, because the salivary drug concentration is equal to serum free concentration. This is proved by the results presented by al Za`abi et al. [14], where the mean ratio of carbamazepine saliva/free serum concentration was 1.02 +/- 0.11.

Our results are similar to those of other authors. The carbamazepine saliva/serum ratio was 0.39, which means that concentration of carbamazepine in saliva was about 39% of the total blood concentration.

We also studied a saliva/serum ratio in acute poisonings by carbamazepine. Data about correlation of salivary and serum concentration in poisoning by antiepileptic drugs do not exist.

As in patients on therapy with carbamazepine, in those overdosed with the drug, we also used stimulated saliva. Stimulating of salivation enables sampling in patients who are in coma, dehydrated or have insufficient vein pathway.

We found that as in carbamazepine treatment, there was a strong correlation between saliva and serum concentrations of carbamazepine in cases of drug poisoning ($r = 0.9117$, $p < 0.05$). The salivary and serum ratio of carbamazepine concentrations was slightly higher (0.43) than in a long-term use of therapeutic doses carbamazepine (0.39). A higher saliva/serum ratio in acute poisoning could be explained by increasing of free serum carbamazepine concentration due to saturation of finding proteins after ingestion of high doses of drug.

There were high inter-individual variations, as a result of poisoning with different doses of carbamazepine, various times from ingestion to admission to the Emergency Toxicological Unit and various time from ingestion to sampling.

The results concerning dynamics of carbamazepine concentrations changes in time showed decreasing of the carbamazepine saliva/serum ratio during the observed period. It could be explained by metabolism of free serum carbamazepine, reflected by decreasing saliva concentration.

We also calculated a value of carbamazepine halftime in acute poisonings. Halftime is a parameter which enables predicting a degree of drug elimination and ingoing to therapeutical range. Our data indicate that in acute poisoning the halftime of carbamazepine in serum and saliva is 12.57 h, and 6.76 h, respectively.

The halftime of carbamazepine in serum after its long-term treatment is in range from 10 h to 35 h [17]. Data about carbamazepine saliva halftime were in wide range from 4.1 h to even 33.1 h [18].

Our results were similar to those in the literature because all of the poisoned patients had carbamazepine in their therapy for long time.

Because there is a strong correlation between salivary and serum concentrations in acute poisonings, the salivary concentrations could be used for calculating carbamazepine serum concentrations by using the formula $y = 1.03*x - 0.897$, where y is a serum concentration of carbamazepine, and x is a salivary one.

Conclusion

The results of this study demonstrate that monitoring of salivary carbamazepine concentrations can be a realistic alternative to blood in routine clinical analysis after therapeutic application or in acute poisoning. Saliva is an attractive alternative biological material, due to its painless collection and noninvasive sampling comparing with blood. Salivary drug levels correlated well with serum drug concentrations in acute poisoning. Moreover, it is possible to extrapolate concentrations of carbamazepine obtained from saliva to their serum concentrations on basis of given correlation curves in patients acutely poisoned with this drug.

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Korelacija između dužine dugih kostiju podlaktice i potkolenice sa telesnom visinom u našoj populaciji

Correlation between the lenghts of the long bones of the forearm and the fibula with body height in our population

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Apstrakt

Uvod/Cilj. Prilikom ekshumiranja skeletnih ostataka zadatak forenzičara je i da izračuna zaživotnu visinu osobe čiji su skeletni ostaci pronađeni. Antropološka istraživanja koja su dala formule za izračunavanje zaživotne visine su iz XIX ili prve polovine XX veka. Najčešće se koriste formule Trotter-Gleser do kojih se došlo istraživanjem skeletnih ostataka iz II svetskog rata. Navedena istraživanja obavljena su na skeletnim ostacima različite starosti i stepena očuvanosti. Naša iskustva pri ekshumacijama pokazala su da postojeće formule ne daju pouzdane vrednosti zaživotne visine. Cilj rada bio je da se ustanovi da li postoji korelacija dužine dugih kostiju potkolenice i podlaktice sa telesnom visinom u našoj populaciji i da se na osnovu dobijenih vrednosti ustanovi formula za izračunavanje zaživotne visine u okviru naše populacije. **Metode.** Merenjem dužine kostiju živih osoba, korišćenjem digitalnog rendgen aparata, precizno su utvrđene dužine lakatne kosti, žbice, lišnjače i golenjače. Antropometrom je izmerena visina osoba kojima su merene dužine kostiju. **Rezultati.** Najveću korelaciju dužine kosti i telesne visine pokazuje golenjača kod muškog pola ($r = 0{,}859$, $p < 0{,}005$) i lakatna kost kod ženskog pola ($r = 0{,}679$, $p < 0{,}05$). Ustanovili smo regresione formule za izračunavanje zaživotne visine, koje se razlikuju od postojećih formula za izračunavanje visine. **Zaključak.** Dužine dugih kostiju podlaktice i potkolenice pokazuju različit stepen korelacije sa telesnom visinom u okviru naše populacije. Formule koje smo ustanovili daju manju razliku između izmerene visine i izračunate visine u odnosu na formule Trotter-Gleser, pa se nadamo da će njihova primena olakšati identifikacije skeletnih ostataka u okviru naše populacije.

Ključne reči:
medicina, sudska; antropologija; telesna visina; radijus; ulna; tibija; fibula.

Abstract

Background/Aim. The task of a forensic examiner during exhumation of skeletal remains is to calculate *ante-mortem* height of a person whose skeletal remains were found. Anthropological investigations which provided formulae for calculating ante-mortem body height date back from XIX or from the first half of XX centuries. The most commonly used formulae are those of Trotter-Gleser, which were used to investigate skeletal remains from the World War II. Those investigations were conducted on skeletal remains of various ages and degrees of decay. Our experience with exhumation have shown that the present formulae do not deliver reliable values of *ante-mortem* height. The aim of this study was to investigate if there is a correlation of the length of long bones of leg and forearm with body height within our population and to establish the formulae for calculating *ante-mortem* body height within our population based on the obtained values. **Methods.** The lengths of ulna, radius, fibula and tibia were determined precisely by measuring bones on living individuals using a digital X-ray system. The height of individuals whose bones were measured was determined using an anthropometer. **Results.** The highest degree of correlation between bone length and body height was found for tibia in males ($r = 0.859$, $p < 0.005$) and ulna in females ($r = 0.679$, $p < 0.05$). We calculated the regression formulae for determination of *ante-mortem* body height that differ from the current body height formulae. **Conclusion.** In our population the length of long bones of the forearm and the leg are characterized by various degree of correlation with body height. The formulae that we set, make less distinction between the measured and the calculated body height as compared with the Trotter-Gleser formulae. We do hope that their implementation will facilitate identification of sceletal remains in our population.

Key words:
forensic medicine; antropology; body height; radius; ulna; tibia; fibula.

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Uvod

Kod ekshumiranja skeletnih ostataka ljudi za izračunavanje zaživotne visine najčešće se koriste duge kosti ekstremiteta. Trotter i Gleser [1, 2], čije su formule do sada najčešće korišćene, ne preporučuju korišćenje lišnjače za izračunavanje zaživotne visine, a formule u kojima se koristi dužina golenjače ne daju validne rezultate zbog različitog merenja maksimalne dužine kosti [3, 4]. Novija istraživanja na posmrtnim ostacima ljudi u Bosni i Hercegovini ukazuju na to da lišnjača ima najveću korelaciju sa visinom osobe [5].

Cilj ovog rada bio je da se ustanovi da li postoji korelacija između dužine lakatne kosti, žbice, golenjače i lišnjače sa telesnom visinom kod našeg stanovništva, kao i da se na osnovu dobijenih vrednosti kreiraju formule za izračunavanje zaživotne visine u našoj populaciji.

Metode

Obrađeno je ukupno 150 osoba, 80 muškog i 70 ženskog pola, starosti od 21 do 60 godina. Istraživanjem su bile obuhvaćene osobe koje su dolazile na dijagnostički rendgenski pregled podlaktice i potkolenice, osim onih koji imaju prelome kostiju. Kod 71 osobe muškog pola i 59 osoba ženskog pola merene su obe kosti podlaktice i potkolenice. Kod 9 osoba muškog pola i 11 osoba ženskog pola merene su ili kosti podlaktice ili kosti potkolenice. Na pojedinim rendgenskim snimcima nije bilo moguće videti ceo okrajak određene kosti, pa je tada merena samo jedna kost podlaktice ili potkolenice. Korišćenjem digitalnog rendgen aparata Shimadzu, sa distance od 2 m merena je maksimalna dužina žbice kao rastojanje od najviše tačke glave žbice do vrha stiloidnog precesusa; maksimalna dužina lakatne kosti kao rastojanje od najviše tačke olekranona do najniže tačke stiloidnog procesusa; maksimalna dužina golenjače od vrha interkondilarne eminencije do donjeg kraja maleolusa i maksimalna dužina lišnjače od vrha glave do donjeg okrajka maleolusa [6]. Svakoj od osoba obuhvaćenih istraživanjem antropometrom je izmerena visina tela, uz primenu standardizovanih pravila antropometrijskih merenja [7, 8].

Dužina 50 golenjača, lišnjača, žbica i lakatnih kostiju kontrolne grupe, iz kolekcije Instituta za anatomiju Medicinskog fakulteta u Beogradu, izmerena je digitalnim rendgen aparatom, Ustanovljene vrednosti su upoređene sa vrednostima koje su dobijene merenjem antropometrom. Srednja vrednost dužine dugih kostiju merena antropometrom bila je 376 mm, a merena digitalnim rendgen aparatom 377,65 mm. Razlika dobijena merenjem digitalnim rendgen aparatom sa distance od 2 m i merenjem izolovanih kostiju bila je 1,65 cm i nije bila statistički značajna, $p > 0,05$. Na distanci od 1,1 m rendgenski se dobijaju veće vrednosti koje zahtevaju korekcione faktore.

Za statističku obradu korišćen je Microsoft Office Excel. Prikazane su srednje vrednosti, standardna devijacija i Pearsonov faktor korelacije, sa statističkom značajnošću $p < 0,05$, a linearnom regresijom kreirane su formule za izračunavanje zaživotne visine.

Rezultati

Merenjem dužine lakatne kosti osoba muškog pola utvrđena je minimalna vrednost od 237,9 mm i maksimalna od 306,7 mm. Vrednosti dužine lakatne kosti kod osoba ženskog pola bile su 229,9 – 277,6 mm.

Najmanja vrednost dužine žbice muškaraca iznosila je 225,4 mm, a najveća 287,8 mm. Kod žena minimalne i maksimalne vrednosti dužine žbice bile su 196,2 mm i 258,2 mm.

Golenjača muškaraca imala je najmanju izmerenu dužinu 378 mm, a najveću 464,8 mm, dok su kod žena te vrednosti bile 302,9 mm i 392,4 mm.

Dužina lišnjače muškaraca bila je u rasponu od 361,7 mm do 463,8 mm, a žena od 318,9 mm do 385,8 mm.

Ustanovljene su razlike dužina dugih kostiju podlaktice i potkolenice kod osoba muškog i ženskog pola (tabela 1).

Tabela 1

Srednje vrednosti dužine dugih kostiju podlaktice i potkolenice muškaraca i žena

Vrsta kosti	Dužina kosti (mm)	
	muškarci $\bar{x} \pm SD$	žene $\bar{x} \pm SD$
Lakatna	277,60 ± 15,73	251,19 ± 13,69
Žbica	257,40 ±16,58	232,09 ± 13,10
Golenjača	415,13 ± 21,77	372,88 ±14,54
Lišnjača	405,69 ± 24,22	364,91 ± 12,77

Razlika srednje vrednosti dužina kostiju muškog i ženskog pola iznosila je za lakatnu kost 26,41 mm, žbicu 25,31 mm, golenjaču 42,25 mm, a lišnjaču 40,78 mm.

U našem istraživanju srednja visina muškaraca iznosila je 177,42 cm, a žena 162,53 cm. Koeficijent koji pokazuje odnos dužine kostiju potkolenice i telesne visine pokazala je manju polnu različitost, pa je za golenjaču razlika odnosa kod muškog i ženskog pola 0,6, a za lišnjaču 0,5. Kada su u pitanju kosti podlaktice taj koeficijent je kod ženskog pola i za lakatnu kost i za žbicu bio veći za 1,1.

Faktor korelacije dužine kosti i telesne visine bio je najveći za golenjaču muškog pola, a najmanji za lišnjaču ženskog pola. Sve vrednosti faktora korelacije dužine kosti sa telesnom visinom manje su kod osoba ženskog pola (tabela 2).

Regresione formule za izračunavanje zaživotne visine muškaraca i žena naše populacije ustanovljene u ovom istraživanju, prikazane su u tabeli 3.

Tabela 2

Odnos telesne visine i dužine kosti u zavisnosti od polne pripadnosti

Vrsta kosti	Muški pol		Ženski pol	
	$\bar{x}$ (min-max)	r (*p*)	$\bar{x}$ (min-max)	r (*p*)
Lakatna	6,34 (6,04 – 7,02)	0,822 (< 0, 005)	6,45 (5,84 – 6,91)	0,679 (< 0,05)
Žbica	6,84 (6,36 – 7,24)	0,819 (< 0,05)	6,95 (6,41 – 7,84)	0,630 (< 0,005)
Golenjača	4,28 (4,13 – 4,60)	0,859 (< 0,005)	4,34 (4,08 – 5,15)	0,485 (< 0,05)
Lišnjača	4,39 (4,16 – 4,75)	0,759 (< 0,005)	4,44 (4,14 – 4,89)	0,33 (< 0,005)

r – faktor korelacije; $p < 0,05$ – statistički značajno

Tabela 3

Regresione formule za izračunavanje zaživotne visine muškaraca i žena naše populacije dobijene u ovom istraživanju

Vrsta kosti	Muški pol	Ženski pol
Žbica	y = 90,179 + 3,36 x ± 3,95	y = 85,772 + 3,30 x ± 5,43
Lakatna	y = 78,013 + 3,55 x ± 3,93	y = 77,145 + 0,34 x ± 5,13
Lišnjača	y = 84,538 + 2,31 x ± 4,85	y = 99,974 + 1,72 x ± 5,48
Golenjača	y = 57,376 + 2,91 x ± 3,81	y = 88,854 + 1,97 x ± 5,24

x – dužina kosti; y – izračunata telesna visina

U tabeli 4 prikazane su izračunate vrednosti visina prema formuli Trotter-Gleser, formuli do koje se došlo u našem istraživanju i stvarne izmerene visine.

Najmanja razlika između visine izračunate prema Trotter-Gleser formuli i izmerene visine dobija se kada se koristi dužina žbice kod osoba muškog pola (0,22 mm), a najveća kada se koristi dužina lakatne kosti ženskog pola (9,66 mm).

Tabela 4

Izračunate vrednosti visina prema formuli Trotter-Gleser, prema formuli u ovom istraživanja i stvarne izmerene visine

Kost	Pol	Trotter-Gleser (cm)	Formula u našem istraživanju (cm)	Izmerena visina (cm)
Lakatna	M	179,92 ± 4,72	176,65 ± 3,93	176,51 ± 6,78
Lakatna	Ž	152,96 ± 4,30	162,55 ± 5,13	162,62 ± 6,8
Žbica	M	176,97 ± 4,66	176,66 ± 3,95	176,75 ± 6,8
Žbica	Ž	164,94 ± 4,24	162,36 ±5,43	162,47 ± 6,84
Golenjača	M	182,39 ± 4,00	178,18 ± 3,81	178,23 ± 7,37
Golenjača	Ž	169,66 ± 3,66	162,31 ± 5,24	162,41 ± 5,91
Lišnjača	M	180,97 ± 3,86	178, 25 ± 4,85	178,2 ± 7,41
Lišnjača	Ž	166,52 ± 3,57	163,46 ± 5,48	162,62 ± 6,8

Diskusija

Na osnovu našeg istraživanja može se zaključiti da su dužina lakatne kosti, žbice, golenjače i lišnjače različite u odnosu na do sada objavljivane vrednosti iz drugih populacija. U knjizi Simonina [9] navode se Rollet-ova istraživanja gde je srednja vrednost golenjače muškaraca 363,73 mm, lišnjače 359,93 mm, žbice 241 mm, a lakatne kosti 256,53 mm. Kod žena je srednja vrednost dužine golenjače 337,41 mm, lišnjače 333,35 mm, žbice 222,35 mm, a lakatne kosti 234,23 mm. Kod oba pola razlike između navedenih vrednosti i vrednosti dobijenih u našem istraživanju najveće su u dužini golenjače, a najmanje u dužini žbice. Golenjača muškaraca je za 51,4 mm, a žbica za 16,4 mm kraća od dužine do koje smo mi došli u ovom istraživanju. Kod žena žbica je kraća za 10,55 mm, a golenjača za 35,47 mm. U odnosu na Manouvrierova istraživanja koje navodi Balthazard [10] u knjizi *Medicine legale*, najveće razlike u odnosu na naša istraživanja su u dužini golenjače oba pola, a najmanje u dužini žbice. Istraživanjem savremene populacije Bosne i Hercegovine na skeletnim ostacima nađeno je da je dužina golenjače 308–460 mm, a lišnjače 310–455 mm, bez posebnog odvajanja polova [5]. Ove vrednosti su bliže vrednostima dužina kostiju ustanovljenim u ovom istraživanju.

Trotter i Gleser u svojim radovima [1, 2] ne preporučuju upotrebu lišnjače u antropološkim istraživanjima, zbog toga što je to tanka kost i lako se ošteti, iako rezultati njihovog istraživanja pokazuju da je najmanja standardna greška kod izračunavanja visine kada se u formuli koristi lišnjača.

U našem istraživanju najmanja standardna devijacija nađena je kod merenja lišnjače žena, međutim, lišnjača žena

pokazuje najmanju korelaciju sa telesnom visinom, dok je kod muškaraca ta korelacija znatno veća. Sarajlić [5] navodi da je na osnovu njihovih rezultata, mada nisu posebno analizirali polove, lišnjača pokazala najveću korelaciju sa visinom i preporučuje da se ona koristi kad god je očuvana, u procenjivanju zaživotne visine.

Lišnjača je kost koja zbog svoje anatomske građe daje najmanju mogućnost za greške i nedoumice prilikom merenja. S druge strane, dužina golenjače, pokazuje različite vrednosti [3, 4] zbog postojanja maleolusa i interkondilarne eminencije koje neki autori uvrste u merenje, a neki ne. Zbog postojanja olekranona, lakatna kost, takođe, daje različite rezultate prilikom merenja i pored jasno ustanovljenih antropometrijskih pravila [8].

Koeficijent koji označava međusobni odnos dužine lišnjače i golenjače je u našem istraživanju za oba pola 1,02, odnosno ne pokazuje polnu specifičnost, a odnos dužine lakatne kosti i žbice je za muški pol 1,07, a za ženski pol 1,08.

Usled postojanja razlika u dužini dugih kostiju i visini, formula za izračunavanje zaživotne visine do koje su Rollet i Manouvrier došli na osnovu mera tih kostiju [9, 10], primenjena na savremenu populaciju, neće dati precizan rezultat.

Rollet je naveo formule koje su do pojave formula Trotter-Gleser [1, 2] najčešće korišćene, a u kojima je koeficijent kojim se množi dužina golenjače kod muškaraca 4,53, a kod žena 4,61 [9]. Dužina lišnjače na osnovu Rolletovih merenja množi se kod muškog pola sa 4,58, a kod ženskog sa 4,66 [9]. Razlikuju se i koeficijenti za izračunavanje visine na osnovu ostalih dugih kostiju. Rollet je dao koeficijente za žbicu muškaraca 6,86, a žena 7,14, a za lakatnu kost muškaraca 6,41, a žena 6,66 [9]. Manouvrier je dao različite koeficijente za osobe visine preko 183 cm i za niske osobe [10]. Prema njemu, za visoke osobe koeficijenti kojima se množe dužine dugih kostiju muškaraca iznose od 3,53 do 6,70. Koeficijenti za žene visokog rasta su od 3,68 do 7,00. Za niske osobe muškog pola, ti koeficijenti iznose od 3,66 do 6,86, a ženskog pola od 3,71 do 7,16 [10]. Duyar i sar [11–13] su, takođe, izvodili različite formule za izračunavanje visine osoba niskog, srednjeg i visokog rasta. Postavlja se pitanje kako kod pronalaženja skeletnih ostataka znamo da li je osoba bila niska, srednje visine ili visoka, a ako uzimamo sve mogućnosti u obzir, izračunata visina ima veliki raspon i veliku grešku.

Vrednosti ovih koeficijenata u našem istraživanju niže su zbog većih izmerenih dužina kostiju naših ispitanika, a vrednosti su približnije koeficijentima kod izračunavanja za visoke osobe. To ukazuje na mogućnost da je prosečna visina u našoj savremenoj populaciji veća od visine stanovništva Francuske XIX veka, od kada datiraju navedena istraživanja. Srednja vrednost visine muškaraca koju navodi Rollet je 166 cm, a žena 156 cm [9]. Kod Manouvriera je srednja vrednost visine žena 154,97 cm, a muškaraca 167,9 cm [10]. U našem istraživanju, srednja visina muškaraca je 177,42 cm, a žena 162,53 cm.

Najveću korelaciju sa telesnom visinom u našem istraživanju pokazuje golenjača kod osoba muškog pola, (r = 0,859) i lakatna kost kod osoba ženskog pola, (r = 0,679). Različita korelacija kod oba pola za istu kost ukazuje na postojanje razlika u proporciji tela ženskog i muškog pola. Kod osoba ženskog pola faktor korelacije sa telesnom visinom za sve kosti manji je nego kod muškaraca.

Formule za izračunavanje zaživotne visine na osnovu dužine dugih kostiju koje su dali Rollet, Manouvrier i dr. nisu izračunate na osnovu regresionih formula, pa samim tim daju manje tačne razultate [9, 10]. Sarajlić [5] i Nath i Badkur [14, 15] navode prednosti linearne regresije u dobijanju formula. Trotter-Gleser [1, 2] došli su do formula linearnom regresijom, ali zbog prethodno navedenih razlika u merenju, starosti skeletnih ostataka i evidentnog antropometrijskog rasta stanovništva, njihove formule ne daju dovoljno precizne rezultate. Kod izračunavanja zaživotne visine na osnovu dužine dugih kostiju korišćenjem formule Trotter-Gleser [1, 2] najveće razlike dobijaju se kada se koristi lakatna kost žena 9,66 mm, a najmanja kada se koristi dužina žbice muškaraca 0,22 mm. Srednja vrednost razlike između izračunate i izmerene telesne visine iznosi 4,125 ± 2,97 mm. U istraživanju, linearnom regresijom dobili smo formule za izračunavanje visine muškog i ženskog pola (Tabela 3). Izračunavanjem telesne visine na osnovu tih formula dobili smo vrednosti koje se razlikuju od izmerenih visina za 0,181 ± 0,267 mm. Najveća razlika dobija se kada se za izračunavanje koristi dužina lišnjače, za žene 0,84 mm, a najmanja kada se koristi dužina golenjače i lišnjače za muškarce 0,05 mm.

Zaključak

Najveću korelaciju sa telesnom visinom u našoj populaciji pokazuje golenjača kod muškaraca i žbica kod žena. Korelacija između dužine dugih kostiju i telesne visine manja je kod žena nego kod muškaraca. Formule koje smo postavili daju manju razliku između izmerene visine i izračunate visine u odnosu na formule Trotter-Gleser, pa se nadamo da će njihova primena olakšati identifikaciju skeletnih ostataka u okviru naše populacije.

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Ultrazvučno praćenje hemodinamskih parametara kod simptomatskih i asimptomatskih bolesnika sa visokostepenom karotidnom stenozom pre i posle karotidne endarterektomije

Ultrasonografic monitoring of hemodynamic parameters in symptomatic and asymptomatic patients with high-grade carotid stenosis prior and following carotid endarterectomy

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Apstrakt

Uvod/Cilj. Dopler ultrasonografija danas je pouzdano dijagnostičko sredstvo za neinvazivno ispitivanje morfologije i hemodinamskih parametara ekstrakranijalnih segmenata krvnih sudova koji učestvuju u vaskularizaciji mozga. Ovaj dijagnostički modalitet u poslednje vreme postaje jedino dijagnostičko sredstvo koje prethodi hirurškoj intervenciji. Cilj rada bio je da se prikaže hemodinamski status pre i posle karotidne endarterektomije (CEA) kod simptomatskih i asimtomatskih bolesnika sa visokostepenom karotidnom stenozom. **Metode.** U ispitivanje su bila uključena 124 simptomatska i 94 asimtomatska bolesnika kojima je učinjena karotidna endarterektomija u Klinici za vaskularnu hirurgiju Instituta za kardiovaskularne bolesti „Dedinje" u Beogradu. Kod svakog bolesnika učinjeno je dopler ultrasonografsko ispitivanje neposredno pre operacije, kao i sedam dana nakon operacije. Mereni su maksimalna sistolna brzina (*peak systolic velocity* – PSV), brzina na kraju dijastole (*end dyastolic velocity* – EDV), srednjevremenska maksimalna brzina protoka (*mean velocity* – MV), indeks otpora (*resistance index* – RI) i volumen protoka (*blood flow volume* – BFV) operisane (ipsilateralne) i kontralateralne unutrašnje karotidne arterije (*internal carotid artery* – ICA). **Rezultati.** Dijabetes je jedini faktor rizika koji je statistički značajno češći u grupi simptomatskih bolesnika. Postoji statistički značajno veći broj bolesnika sa okludiranom kontralateralnom ICA u grupi simptomatskih bolesnika. Nakon operacije dolazi do statistički značajnog povećanja PSV, EDV, MV, kao i BFV operisane ICA. Nakon operacije ICA dolazi do statistički značajnog smanjenja PSV, EDV, MV, kao i BFV kontralateralne ICA. Jedini hemodinamski parametar koji se ne menja nakon operacije je RI kod obe grupe bolesnika. Upoređivanjem promena ispitivanih hemodinamskih parametara ipsilateralne i kontralateralne ICA, koje su nastale nakon operacije, nisu nađene značajne razlike kod ispitivanih grupa bolesnika.. **Zaključak.** Okluzija kontralaterealne ICA je faktor koji značajno doprinosi pojavi simptoma visokostepene karotidne stenoze. Uspešna CEA obezbeđuje poboljšanje hemodinamike cerebralne cirkulacije kod simptomatskih i asimptomatskih bolesnika.

Ključne reči:
endarterektomija a. carotis; ultrasonografija, dopler; faktori rizika; rizik, procena; lečenje, ishod; a. vertebralis.

Abstract

Background/Aim. Doppler ultrasonography is now a reliable diagnostic tool for noninvasive examination of the morphology and hemodynamic parameters of extracranial segments of blood vessels that participate in the brain vascularisation. This diagnostic modality in recent years become the only diagnostic tool prior to surgery. The aim of the study was to determine hemodynamic status in symptomatic and asymtomatic patients with severe carotid stenosis prior to and after carotid endarterectomy (CEA). **Methods.** A total of 124 symptomatic and 94 asymptomatic patients who had underwent CEA at the Clinic for Cardiovasculare Disease "Dedinje" in Belgrade were included in this study. Doppler ultrasonography examinations were performed one day before CEA and seven days after it. The peak systolic velocity (PSV), end-dyastolic velocity (EDV), time-averaged maximum blood flow velocity (MV), resistance index (RI) and the blood flow volume (BFV) of the ipsilateral and the contralateral internal carotid artery (ICA) were measured. **Results.** Diabetes was the only risk factor found signifi-

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cantly more frequent in symptomatic patients. There were significantly more occluded contralateral ICAs in the group of symptomatic patients. There was a significant increase in PSV, EDV, MV and BFV of the ipsilateral ICA after CEA and a significant decrease in PSV, EDV, MV and BFV of the contralateral ICA after CEA. RI is the only hemodynamic parameter without significant changes after CEA in both groups of patients. Comparing the values of hemodynamic parameters after CEA between the group of symptomatic and the group of asymptomatic patients no significant differences were found.

Conclusion. The occlusion of the contralateral ICA is an important factor differentiating between symptomatic and asymptomatic patients with severe carotid stenosis. Successful surgery provides good recovery of cerebral hemodynamics in both symtomatic and asymptomatic patients.

Key words:
endarterectomy, carotid; ultrasonography, doppler; risk factors; risk assessment; treatment outcome; vertebral artery.

Uvod

Dopler ultrasonografija (DU) danas je pouzdano dijagnostičko sredstvo za neinvazivno ispitivanje morfologije i hemodinamskih parametara ekstrakranijalnih segmenata krvnih sudova koji učestvuju u vaskularizaciji mozga. Ovaj dijagnostički modalitet u poslednje vreme postaje jedino dijagnostičko sredstvo koje prethodi hirurškoj intervenciji [1]. Ateroskleroza karotidnih arterija (karotidna stenookluzivna bolest) najčešće zahvata proksimalni deo unutrašnje karotidne arterije (*internal carotid artery* – ICA) i predeo karotidne bifurkacije. Ređe su zahvaćeni odstup srednje cerebralne arterije, distalni deo ICA i karotidni sifon. Progresija aterosklerotskog plaka dovodi do suženja lumena i hemodinamskih promena. Daljom progresijom bolesti dolazi do pojave ulceracija plaka, što povećava rizik od pojave embolije i tromboze. Ateroskleroza karotidnih arterija može biti simptomatska i asimptomatska. Simptomi karotidne stenookluzivne bolesti su simptomi moždane ili retinalne ishemije. Mogu se ispoljiti kao tranzitorni ishemijski atak ili moždani udar. Bolesnici sa kompletnim moždanim udarom koji dovodi do teškog neurološkog deficita nisu kandidati za operativno lečenje. Dosadašnje velike studije – (*North American Symptomatic Carotid Endarterectomy Trial* – NASCET), (*European Carotid Surgery Trial* – ECST), *The Veterans Administradion Symptomatic Trial* [2–4] pokazale su da je karotidna endarterektomija (CEA) značajno efikasnija u prevenciji moždanog udara u odnosu na medikamentoznu terapiju kod bolesnika sa simptomatskom stenozom ICA preko 70%. Velikom studijom efikasnosti CEA kod asimptomatske stenookluzivne karotidne bolesti, (*Asymptomatic Carotid Surgery Trial* – ACST) [5], dokazana je efikasnost ove operacije u prevenciji moždanog udara kod asimptomatskih bolesnika. Mnogi dosadašnji radovi bavili su se hemodinamskim promenama koje nastaju nakon ove operacije [6–8], a manji broj istraživača bavio se uticajem prisustva simptoma karotidne bolesti na ove promene.

Cilj ove studije bio je da se proceni i uporedi hemodinamski efekat CEA kod simptomatskih i asimptomatskih bolesnika sa visokostepenom stenozom jedne ICA tokom ranog postoperativnog perioda.

Metode

U ispitivanje je bilo uključeno 218 bolesnika kod kojih je dijagnostikovana visokostepena stenoza jedne, ipsilateralne ICA (≥ 70%). Kod svih bolesnika učinjena je CEA u Klinici za vaskularnu hirurgiju Instituta za kardiovaskularne bolesti „Dedinje" u Beogradu, u periodu od septembra 2007. do januara 2008. Podaci su prikupljani prospektivno, sa opservacijom više puta u toku trajanja studije. Za svakog ispitanika zabeležene su godine starosti, pol, kao i postojanje faktora rizika: hipertenzije, hiperlipidemije, dijabetesa, gojaznosti, pušenja, pozitivne porodične anamneze za cerebrovaskularne bolesti. Faktor rizika u vidu hronične bolesti (hipertenzija, hiperlipidemija, dijabetes) vrednovan je u slučaju trajanja izloženosti faktoru rizika tri godine ili duže. Gojaznošću smo smatrali povećanje telesne mase veće od 20% u odnosu na idealnu. Pušenje je vrednovano kao faktor rizika kod ispitanika koji su bili aktivni pušači, pušili 20 i više cigareta dnevno i nisu apstinirali poslednjih 5 godina. Pozitivna porodična anamneza definisana je kao pojava moždanog udara kod jednog od roditelja. Zabeležili smo i postojanje podataka o prethodnim simptomima karotidne bolesti u vidu tranzitornog ishemijskog ataka ili moždanog udara koji su nastali u slivu operisane ICA u periodu od šest meseci pre operacije. Na osnovu tih podataka podelili smo bolesnike u dve grupe, grupu simptomatskih bolesnika i grupu asimptomatskih bolesnika. Kod svakog ispitanika urađeno je DU ispitivanje obe ICA i obe vertebralne arterije (*vertebral artery* – VA) neposredno pre operacije i sedam dana nakon operacije. Ultrazvučni pregled obavljan je aparatom HDI 3500 Ultrasound system (A Philips Medical Systems Company, Bothell, USA). Pri ispitivanju smo koristili L-10-5 linearnu sondu. Beležene su dimenzije svih ispitivanih arterija u B modu (*gray-scale image*) u trenutku friziranja u sistoli. Spektralna analiza je obuhvatila merenja brzina protoka pulsnim dopler talasima, sa korekcijom ugla insonacije. Za svaku operisanu ICA beležen je stepen stenoze. Beleženi su parametri spektralne analize: maksimalna sistolna brzina (*peak systolic velocity* – PSV), brzina na kraju dijastole (*end dyastolic velocity* – EDV), srednjevremenska maksimalna brzina protoka (*mean velocity* – MV), indeks otpora (*resistance index* – RI), kao i volumen protoka (*blood flow volume* – BFV) operisane (ipsilateralne) i kontralateralne ICA. Sve brzine protoka su se automatski očitavale na aparatu. Za merenje volumena protoka korišćen je *sample volume* koji pokriva ceo krvni sud, a za spektralnu analizu jedan broj kompletnih srčanih ciklusa (3–5 ciklusa). Ovi parametri mereni su 2–3 centimetra iznad bifurkacije, iznad stenoze, u regiji gde je protok kroz ICA uvek laminaran. Beležen je broj okludiranih kontralateralnih ICA i broj okludiranih ipsilateralnih i kontralateralnih VA. Kada nije bilo moguće detekto-

vati protok kroz vertebralnu arteriju je vrednovana kao okludirana. U ispitivanje nisu uključivani bolesnici sa visokostepenom stenozom kontralateralne ICA, kao ni bolesnici sa subklavija stil sindromom kod kojih postoji visokostepena stenoza početnog dela arterije subklavije.

Kod svakog bolesnika ispitivanje je sprovedeno neposredno pre operacije (prvo merenje) i sedam dana nakon operacije (drugo merenje).

Dobijeni podaci uneseni su u formiranu komjutersku bazu podataka i statistički obrađeni pomoću programa SPSS 13.0. U radu su korišćeni χ^2 test, *t*-test i *General linear model repeated measures* (GLM RM).

Rezultati

U grupi simptomatskih bolesnika, od ukupno 124 ispitanika, srednje starosti 65,69 ± 7,11 godina 72 (58%) bili su muškarci, a 52 (42%) žene. U grupi asimptomatskih bolesnika od ukupno 94 ispitanika, srednje starosti 64,21 ± 7,76 godina, 52 (55,31%) bili su muškarci, a 42 (44,69%) žene. U tabeli 1 prikazani su demografski podaci i perioperativni faktori rizika kod simptomatskih i asimptomatskih bolesnika. U grupi simptomatskih bolesnika postojao je statistički značajan broj obolelih od dijabetesa melitusa (DM).

Hemodinamski parametri operisane ICA pre i posle operacije prikazani su u tabeli 2. Nakon operacije došlo je do statistički značajnog povećanja PSV, EDV, MV, kao i BFV operisane ICA.

Hemodinamski parametri kontralateralne ICA, pre i posle operacije, prikazani su u tabeli 3. Nakon operacije ipsilateralne ICA došlo je do statistički značajnog smanjenja PSV, EDV, MV, kao i BFV kontralateralne ICA. Nije ustanovljena statistički značajna promena u vrednostima RI nakon operacije kod ipsilateralne kao ni kod kontralateralne ICA.

U tabeli 4 pokazan je broj okludiranih kontralateralnih ICA, kao i broj okludiranih ipsilateralnih i kontralateralnih VA kod simptomatske i asimptomatske grupe bolesnika. Postojao je statistički značajan broj bolesnika sa okludiranom kontralateralnom ICA u grupi simptomatskih pacijenata. Broj okludiranih ipsilateralnih i kontralateralnih VA je bio veći u grupi simptomatskih bolesnika.

U tabeli 5 prikazane su vrednosti hemodinamskih parametara operisane ICA pre i posle operacije kod grupe simptomatskih i grupe asimptomatskih bolesnika. Ustanovljeno

Tabela 1

Demografski podaci i perioperativni faktori rizika kod simptomatskih i asimptomatskih bolesnika

Faktori rizika	Simptomatski bolesnici (n = 124)	Asimptomatski bolesnici (n = 94)	*p*
Starost (godine); $\bar{x}$ ± SD	65,69 ± 7,11	64,21 ± 7,76	$p > 0,05$
Pol, M/Ž	72/52	42/52	$p > 0,05$
HTA, n (%)	122 (98,4)	92 (97,9)	$p > 0,05$
DM, n (%)	26 (21,0)	6(6,4)	$p < 0,05$
Hiperlipidemija, n (%)	102 (82,3)	80 (85,1)	$p > 0,05$
Pušenje, n (%)	26 (21,0)	26 (27,7)	$p > 0,05$
Nasledni faktor, n (%)	36 (29,03)	30 (31,91)	$p > 0,05$
Gojaznost, n (%)	6 (4,83)	8 (8,51)	$p > 0,05$

HTA – arterijska hipertenzija; DM – dijabetes melitus; M – muški pol; Ž – ženski pol

Tabela 2

Hemodinamski parametri operisane ipsilateralne (ipsl) unutrašnje karotidne arterije (ICA) pre i posle operacije kod obe grupe bolesnika

Parametri	Preoperativno	Postoperativno	F/p
PSV ipsl ICA (cm/s)	59,90 ± 14,19	63,06 ± 14,87	F = 62,17 / $p < 0,001$
EDV ipsl ICA (cm/s)	19,14 ± 5,65	20,54 ± 6,9	F = 7,51 / $p < 0,05$
MV ipsl ICA (cm/s)	30,65 ± 7,52	34,0 ± 8,77	F = 26,52 / $p < 0,001$
RI ipsl ICA	0,68 ± 0,1	0,67 ± 0,1	F = 2,3 / ns
BFV ipsl ICA (mL/min)	165,8 ± 71,9	201,59 ± 77,9	F = 106,4 / $p < 0,001$

Analiza je izvršena kod svih 218 bolesnika: rezultati su prikazani kao $\bar{x}$ ± SD

PSV – *peak systolic velocity* (maksimalna sistolna brzina); EDV– *end dyastolic velocity* (brzina na kraju dijastole); MV – *mean velocity* (srednjevremenska maksimalna brzina); RI – *resistance index* (indeks otpora); BFV – *blood flow volume* (volumen protoka); ns – beznačajna razlika.

Tabela 3

Hemodinamski parametri kontralateralne (kontral) unutrašnje karotidne arterije (ICA) pre i posle operacije ipsilateralne ICA kod obe grupe bolesnika

Parametri	Preoperativno	Postoperativno	F / *p*
PSV kontral ICA (cm/s)	63,35 ± 18,13	60,53 ± 16,39	F = 21,15 7 / $p < 0,001$
EDV kontral ICA (cm/s)	20,32 ± 6,94	18,80 ± 5,80	F = 11,78 / $p < 0,001$
MV kontral ICA (cm/s)	33,84 ± 10,21	31,77 ± 9,20	F = 28,20 / $p < 0,001$
RI kontral ICA	0,69 ± 0,07	0,67 ± 0,07	F = 7,44 / ns
BFV kontral ICA (mL/min)	180,87 ± 79,44	172,31 ± 74,25	F = 9,40 / $p < 0,05$

Analiza je izvršena kod svih 190 bolesnika: rezultati su prikazani kao $\bar{x}$ ± SD

PSV – *peak systolic velocity* (maksimalna sistolna brzina); EDV – *end dyastolic velocity* (brzina na kraju dijastole); MV – *mean velocity* (srednjevremenska maksimalna brzina); RI – *resistance index* (indeks otpora); BFV – *blood flow volume* (volumen protoka); ns – beznačajna razlika

Tabela 4

Broj okludiranih kontralateralnih (kontral) unutrašnjih karotidnih arterija (ICA), okludiranih ipsilateralnih (ipsl) vertebralnih arterija (VA) i okludiranih VA kod simptomatskih i asimptomatskih bolesnika

Arterija	Simpt. (n = 124)	Asimpt. (n = 94)	*p*
	n	n	
Kontral ICA	26	2	< 0,05
Ipsl VA	28	16	ns
Kontral VA	30	22	ns

ns – beznačajna razlika

Tabela 5

Hemodinamski parametri operisane ipsilateralne (ipsl) unutrašnje karotidne arterije (ICA) pre i posle operacije kod simptomatskih i asimptomatskih bolesnika

Parametri	Simpt. (n = 124)		Asimpt. (n = 94)		F / *p*
	Preoperativno	Postoperativno	Preoperiativno	Postoperativno	
PSV ipsl ICA (cm/s)	59,33 ± 15,22	65,77 ± 15,56	53,70 ± 12,14	59,50 ± 13,25	PSV*simp, F = 0,165 / ns
EDV ipsl ICA (cm/s)	19,54 ± 6,42	21,53 ± 7,74	18,60 ± 4,45	21,53 ± 7,74	EDV*simp, F = 2,02 / ns
MV ipsl ICA (cm/s)	31,88 ± 7,97	35,58 ± 10,1	29,03 ± 6,63	31,92 ± 6,1	MV*simp, F = 0,40 / ns
RI ipsl ICA	0,68 ± 0,12	0,67 ± 0,11	0,68 ± 0,9	0,67 ± 0,9	RI*simp, F = 0,68 / ns
BFV ipsl ICA (mL/min)	169,46 ± 76,6	204,55 ± 81,3	161,0 ± 65,6	197,68 ± 73,9	BFV*simp, F = 0,002 / ns

PSV – *peak systolic velosity* (maksimalna sistolna brzina); EDV – *end dyastolic velosity* (brzina na kraju dijastole); MV – *mean velosity* (srednjevremenska maksimalna brzina); RI – *resistance index* (indeks otpora); BFV – *blood flow volume* (volumen protoka); ns – beznačajna razlika; rezultati su prikazani kao $\bar{x} \pm SD$

je da razlike između dve grupe bolesnika nisu statistički značajne. U tabeli 6 dat je uporedni prikaz promene u vrednostima hemodinamskih parametara kontralateralne ICA kod simtomatskih i asimptomatskih bolesnika. Njihovim poređenjem nisu ustanovljene statistički značajne razlike između ove dve grupe bolesnika.

krvlju odvija se preko karotidnih arterija, a 20–30% preko VA. Mehanizmi koji dovode do pojave simptoma karotidne bolesti nisu do kraja objašnjeni. Hemodinamski parametri dobijeni primenom DU koriste se za procenu hemodinamskih karakteristika cerebralne cirkulacije i procenu postojanja kolateralnog krvotoka [9–11]. Bai i sar. [12] kao i Fukuhara i

Tabela 6

Hemodinamski parametri kontralateralne (kontal.) unutrašnje karotidne arterije (ICA), pre i posle operacije kod simptomatskih i asimptomatskih bolesnika

Parametri	Simpt. (n = 98)		Parametri	Asimpt. (n = 92)		F / *p*
	Preoperativno	Postoperativno		Preoperativno	Postoperativno	
PSV kontral ICA (cm/s)	62,90 ± 19,13	60,02 ± 17,53	PSV kontral, ICA (cm/s)	63,83 ± 17,22	61,05 ± 15,30	PSV*simp, F = 0,007 / ns
EDV kontral ICA (cm/s)	20,35 ± 7,30	18,38 ± 5,86	EDV kontral, ICA (cm/s)	20,29 ± 6,62	19,24 ± 5,76	EDV*simp, F = 1,096 / ns
MV kontral ICA (cm/s)	33,70 ± 10,47	31,78 ± 9,74	MV kontral, ICA (cm/s)	33,98 ± 10,05	31,76 ± 8,69	MV*simp, F = 0,147 / ns
RI kontral ICA	0,68 ± 0,08	0,67 ± 0,07	RI kontral, ICA	0,69 ± 0,07	0,67 ± 0,07	RI*simp, F = 1,55 / ns
BFV kontral ICA (mL/min)	188,16 ± 80,75	179,17 ± 74,36	BFV kontral, ICA (mL/min)	173,11 ± 78,15	165,00 ± 74,23	BFV*simp, F = 0,0001 / ns

PSV – *peak systolic velocity* (maksimalna sistolna brzina); EDV – *end dyastolic velocity* (brzina na kraju dijastole); MV – *mean velocity* (srednjevremenska maksimalna brzina); RI – *resistance index* (indeks otpora); BFV – *blood flow volume* (volumen protoka); ns – beznačajna razlika

Diskusija

Brojni mehanizmi učestvuju u održavanju stalnog nivoa moždane cirkulacije u cilju snabdevanja moždanog tkiva dovoljnom količinom hrane i kiseonika. Danas se ne zna tačan mehanizam kontrole moždane cirkulacije, ali ulogu u održavanju stalnosti moždanog protoka imaju metabolički faktori, nivo ugljen-dioksida u krvi, neurogeni faktori, mehanizam autoregulacije. Oko 70–80% snabdevanja mozga

sar. [13] pratili su hemodinamske parametre kod simptomatskih bolesnika nezavisno od postojanja karotidne stenookluzivne bolesti i primetili da kod simptomatskih bolesnika postoje niže brzine protoka, povećani indeks rezistencije i veći prečnik karotidnih arterija. Našim istraživanjem praćene su promene vrednosti hemodinamskih parametara nakon CEA. Manji broj istraživanja bavio se upoređivanjem hemodinamskih promena kod simptomatskih i asimptomatskih bolesnika. Cilj našeg ispitivanje bio je da se odredi

uticaj CEA na cerebralnu hemodinamiku kod obe grupe bolesnika.

Karotidna bolest sa značajnom stenozom jedne karotidne arterije dovodi do hemodinamskih promena u predelu same stenoze, u celom krvnom sudu iznad stenoze, kao i do kompenzatornog aktiviranja kolateralne cirkulacije [6, 14]. Aktiviranje primarne kolateralne cirkulacije (ostvaruje se preko Willis-ovog kruga) dovodi do povećanja BFV u arteriji koja učestvuje u snabdevanju krvlju svog i kolateralnog sliva. Kod stenoze jedne karotidne arterije dolazi do aktiviranja kolateralnih puteva kontralateralnog karotidnog sliva, kao i vertebrobazilarnog sliva, i time kompenzatornog povećanja BFV tih arterija. Telman i sar. [7], u istraživanju promena parametara transkranijalnog doplera (TCD), pokazali su da su parametri koji odražavaju očuvanost autoregulatornih mehanizama značajno niži kod simptomatskih bolesnika. Kada postoji okluzija kontralateralne ICA autoregulatorni mehanizmi su značajno ugroženi. Nakon CEA dolazi do odstranjenja stenoze krvnog suda, kolateralna cirkulacija se normalizuje i to menja hemodinamiku svih arterija koje učestvuju u vaskularizaciji mozga. Nakon malog moždanog udara CEA ima ulogu u poboljšavanju cerebralne perfuzije i u sprečavanju novih embolijskih događaja u zoni irigacije ICA. Mnoga istraživanja pokazala su da nakon operacije dolazi do normalizovanja primarnog kolateralnog puta koji je bio kompenzatorno povišeno aktivan pre operacije. Istraživanje koje su sproveli Jeroen i sar. [15] 2003. godine obuhvatilo je analizu efekta karotidne endarterektomije na primarni kolateralni put, primenom MR arteriografije. Analizom je obuhvaćeno 48 bolesnika. Ustanovljeno je da nakon operacije dolazi do normalizovanja primarnog kolateralnog puta koji je bio kompenzatorno povišeno aktivan pre operacije. U slučaju postojanja okluzije kontralateralne strane, nakon endarterektomije ipsilateralne strane dolazi do kompenzatornog povećanja kolateralnog protoka kroz primarni kolateralni put [16]. Roddy i sar. [17] u svom istraživanju pokazali su da nema značajnih promena hemodinamskih parametara kontralaterlne ICA nakon CEA. Istraživanja Welch i sar. [18], sa druge strane, pokazala su da nakon CEA dolazi do značajnog smanjenja vrednosti PSV i EDV kontralateralne ICA. Dosadašnja ispitivanja [19] pokazala su da koristi od CEA zavise ne samo od stepena stenoze, već i od vremena koje je prošlo od pojave prvih simptoma karotidne stenoze do operacije. Zaključeno je da je optimalno vreme za operaciju period do dve nedelje od pojave simptoma karotidne stenoze. Svi asimptomatski bolesnici sa stenozom ICA $\geq$ 60% koji su planirani za CEA imaju prihvatljivo mali mortalitet i morbiditet [20].

Mnoga dosadašnja istraživanja na zdravim osobama pokazala su da se hemodinamski parametri ekstrakranijalnih segmenata krvnih sudova koji učestvuju u vaskularizaciji mozga menjaju sa godinama života i da zavise od pola [21–24]. Povezanost pojedinih faktora rizika sa pojavom karotidne stenookluzivne bolesti istraživana je i ranije [25]. Svi bolesnici obuhvaćeni našom studijom imali su neki od faktora rizika. Demografski podaci i podaci o zastupljenosti pojedinih faktora rizika pokazuju da je samo zastupljenost dijabetesa značajno povećana kod simtomatskih bolesnika. Najzastupljeniji faktor rizika kod obe grupe bolesnika bila je arterijska hipertenzija. Od ostalih faktora rizika za karotidnu stenookluzivnu bolest najviše je bilo ispitanika sa nekim od oblika hiperlipidemije. Treća po zastupljenosti bila je pozitivna porodična anamneza za cerebrovasularnu bolest, četvrti faktor rizika je pušenje, zatim neki od oblika dijabetesa, a najmanje je bilo gojaznih.

Kontralateralna ICA je češće okludirana kod simptomatskih bolesnika. Naše istraživanje pokazalo je da nepostojanje kolateralne cirkulacije preko kontralateralne ICA značajno utiče na pojavu simptoma karotidne stenoze. Postojanje funkcionalnog primarnog kolateralnog puta dovoljno kompenzuje nedovoljnu cerebralnu cirkulacuju kod karotidne stenookluzivne bolesti. Nepostojanje kolateralne cirkulacije preko jedne vertebralne arterije (ipsilateralne ili kontralateralne) nema značaja za pojavu simptoma karotidne bolesti.

Analizom dobijenih podataka možemo zaključiti da postoji statistički značajan porast PSV, EDV, MV kao i BFV operisane ICA nakon CEA, i to kod obe grupe ispitanika. Hemodinamski parametri kontralateralne ICA (PSV, EDV, MV i BFV) smanjuju se nakon CEA. Nakon CEA prestaje potreba za kolateralnom cirkulacijom i protok kroz kontralateralnu ICA smanjuje se i time vraća na nivo od pre pojave stenoze ipsilateralne ICA. Podaci govore i o tome da je povećanje BFV u operisanoj ICA veće od pada BFV kontralateralne ICA. Nema statistički značajne razlike između simptomatskih i asimptomatskih bolesnika kada se porede promene ispitivanih hemodinamskih parametara ipsilateralne i kontralateralne ICA nakon operacije. Jedini ICA hemodinamski parametar koji se ne menja nakon operacije jeste RI. Ova činjenica verovatno govori da je otpor u regiji ICA gde se vrši merenje stabilan, i nije podložan promenama nakon operacije. Ovaj parametar nije dovoljno senzitivan da bi govorio o hemodinamskim promenama nakon CEA.

Zaključak

Pri postavljanju indikacije za operativno lečenje i pri planiranju operacije treba imati u vidu da se postiže hemodinamski efekat koji se statistički značajno ne razlikuje kod simptomatskih i asimptomatskih bolesnika. Najvažniji efekat CEA je povećenje vrednosti hemodinamskih parametra operisane ICA, posebno BFV. Povećanje BFV ICA posredno govori o povećanju cerebralnog volumena protoka u irigacionom području ove arterije, što predstavlja hemodinamski efekat revaskularizacije koja se postiže primenom CEA.

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Procena postoperativnog analgetičkog dejstva ropivakaina posle hirurškog lečenja periapeksnih lezija sekutića gornje vilice

Assessment of ropivacaine postoperative analgesic effect after periapical maxillary incisors surgery

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Apstrakt

Uvod/Cilj. Ropivakain je jedan od novijih lokalnih anestetika sa dugotrajnim dejstvom. Cilj ovog istraživanja bio je da se uporedi postoperativno analgetičko dejstvo lokalnih anestetika, 0,75% ropivakaina i 2% lidokaina sa adrenalinom, u hirurškom lečenju periapeksnih lezija u gornjoj vilici. **Metode.** Ispitivanjem je bilo obuhvaćeno 60 ispitanika, podeljenih u dve grupe. U studijskoj grupi korišćen je 0,75% ropivakain bez vazokonstriktora, a u kontrolnoj grupi 2% lidokain sa adrenalinom (1 : 80 000). Korišćena je sprovodna anestezija za *n. infraorbitalis*, a lokalni anestetik dat je i sa palatinalne strane za završne grančice *n. nasopalatinusa.* Praćeni su sledeći parametri: vreme proteklo od davanja anestetika do pojave prvog bola posle operacije i uzimanja prve doze analgetika, intenzitet početnog bola i bola šest sati nakon aplikacije anestetika, kao i ukupan broj analgetika uzetih tokom 24 sata od završetka hirurške intervencije. **Rezultati.** Bol se javio statistički značajno ranije u grupi bolesnika kod kojih je korišćen lidokain sa adrenalinom ($p < 0,001$), a u istoj grupi je zapažena i statistički značajno viša srednja vrednost početnog postoperativnog bola ($p < 0,05$), kao i srednja vrednost intenziteta bola šest sati nakon intervencije ($p < 0,01$). U periodu od 24 sata posle intervencije, ispitanici studijske grupe uzimali su manje analgetika nego ispitanici kontrolne grupe (46,6% u odnosu na 73,3%), koji su ranije počinjali da koriste analgetik, mada u broju uzetih doza analgetika nisu zapažene statistički značajne razlike. **Zaključak.** Rezultati studije ukazuju na bolji postoperativni analgetički efekat ropivakaina u odnosu na kombinaciju lidokaina sa adrenalinom.

Ključne reči:
anestezija, lokalna; apikoektomija; sekutići; maksila; bol, merenje; bol, postoperativni; antiinflamatorici, nesteroidni.

Abstract

Background/Aim. Ropivacaine is a relatively new long-acting local anesthetic. The aim of this study was to compare the postoperative analgesic effect of topical anesthetics ropivacaine 0.75% and lidocaine 2% with adrenaline in the postoperative treatment of periapical lesions in the maxilla. **Methods.** The study was conducted on 60 subjects, divided into two groups. The study-group received 0.75% ropivacaine without a vasoconstrictor, while the control group was treated with 2% lidocaine with adrenaline (1 : 80.000). Block anesthesia for *n. infraorbitalis* was used and local anesthetics were applied also on the palatine side for the end branches of *n. nasopalatinus*. The following parameters were observed: time elapsed from the application of an anesthetic until the first occurrence of pain after the surgery and first intake of an analgesic, the intensity of initial pain, pain intensity 6 h after the application of anesthetics and the total number of analgesics taken within 24 h after the completion of surgery. **Results.** The pain appeared statistically significantly earlier in the patients who had been given lidocaine with adrenaline ($p < 0.001$), while statistically significantly higher mean values of initial postoperative pain ($p < 0.05$) and pain intensity 6 h after the intervention ($p < 0.01$) were also registered in the same group of patients. In the period of 24 h upon the intervention, the study-group patients were taking less analgesics as compared to the control-group subjects (46.6% vs 73.3%), who were given analgesics earlier, although no statistically significant differences were observed related to the number of analgesic doses taken. **Conclusion.** The results of our study indicate a better postoperative analgesic effect of ropivacaine as compared to lidocaine with adrenaline.

Key words:
anesthesia, local; apicoectomy; incisor; maxilla; pain measurement; pain, postoperative; anti-inflammatory agents, non-steroidal.

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Uvod

Lidokain je najčešće korišćeni lokalni anestetik u oralnoj hirurgiji i stomatologiji, pre svega zbog dokazane kliničke efikasnosti i retkih neželjenih efekata. Lidokain se odlikuje osobinama koje ga približavaju idealnom lokalnom anestetiku: brzo nastupanje anestezije, zadovoljavajuća dužina anestetičkog dejstva, pouzdanost i nizak potencijal toksičnosti. Međutim, dužina njegovog lokalnog anestetičkog dejstva ne obezbeđuje dobru postoperativnu analgeziju.

Lokalni anestetici dugog dejstva (bupivakain, etidokain) do sada su korišćeni u oralnoj hirurgiji, pre svega pri ekstrakciji trećih molara [1–5], zbrinjavanju fraktura vilica, uklanjanju torusa i multiplim ekstrakcijama sa alveolotomijama [4]. Takođe, korišćeni su i za lečenje hroničnog orofacijalnog bola [6]. Lokalni anestetici dugog dejstva pokazuju svoje prednosti prvenstveno u smislu ublažavanja postoperativnih bolova koji prate oralnohirurške zahvate, čime se redukuje broj analgetika uzetih u postoperativnom periodu [7].

Ropivakain je jedan od novijih lokalnih anestetika dugotrajnog dejstva. Hemijski je veoma sličan bupivakainu i mepivakainu (pKa = 8,1). Sva tri anestetika su iz grupe poznate kao pipekolil-ksilidini, koji kombinuju piperidinski prsten kokaina sa ksilidinom iz lidokaina. Supstitucijom metil, butil i propil grupa na piperidinskom prstenu nastali su mepivakain, bupivakain i ropivakain [8]. Ropivakain je prvi lokalni anestetik označen kao „čisti" enantiomer, koji sadrži više od 99% S-oblika. Ovo je od značaja jer je mnogobrojnim laboratorijskim ispitivanjima utvrđeno da S-enantiomeri poseduju znatno manju kardiotoksičnost u odnosu na R-formu [9]. Iako se ropivakain sa uspehom koristi u hirurškim granama medicine, nema dovoljno iskustva sa njegovom primenom u stomatologiji. Do sada je objavljeno svega nekoliko radova u kojima je ropivakain korišćen kod oralnohirurških intervencija [10–13].

Cilj ovog istraživanja bio je da se uporedi analgetičko dejstvo lokalnih anestetika 0,75% ropivakaina i 2% lidokaina sa adrenalinom, u postoperativnom periodu posle hirurškog uklanjanja hroničnih periapeksnih lezija u gornjoj vilici.

Metode

Kliničko ispitivanje analgetičkog dejstva 0,75% rastvora ropivakaina u hirurgiji hroničnih periapeksnih lezija sprovedeno je u Odeljenju oralne hirurgije Klinike za stomatologiju u Nišu. Ispitivanjem je obuhvaćeno 60 ispitanika kod kojih je bilo indikovano hirurško lečenje hroničnih periapeksnih lezija na jednom od prednjih zuba gornje vilice. Svi ispitanici bili su zdravi, bez podataka o sistemskim oboljenjima. Ni kod jednog ispitanika nije bilo znakova akutne infekcije u orofacijalnoj regiji. Svim ispitanicima je prethodno objašnjen protokol ispitivanja za koji su dali pisanu saglasnost. Nijedan ispitanik nije uzimao analgetike, sedative niti primao lokalne anestetike u orofacijalnoj regiji 24 sata pre hirurške intervencije. Nakon operacije, svim ispitanicima je savetovana upotreba nesteroidnog antiinflamatornog leka u cilju analgezije – ibuprofen tablete od 400 mg (Brufen® 400; Galenika, Beograd) u maksimalnoj dnevoj dozi od 1,6 g podeljeno u četiri doze, ali tek po početku postoperativnih bolova.

Ispitanici su bili podeljeni u dve grupe od po 30 ispitanika. U prvoj studijskoj grupi, kao lokalni anestetik korišćen je 0,75% ropivakain hidrohlorid bez vazokonstriktora (Naropin® 0,75%; Astra Zeneca, Švedska), a u drugoj, kontrolnoj grupi, korišćen je 2% lidokain sa adrenalinom, 1 : 80 000 (Lidokain 2% adrenalin, Galenika, Beograd).

U cilju hirurškog uklanjanja hroničnih periapeksnih lezija na jednom od prednjih zuba gornje vilice korišćena je sprovodna anestezija za *n. infraorbitalis* (s intraoralnim pristupom) primenom anestetika u zapremini od 1,8 ml. Takođe, kod svih ispitanika lokalni anestetik dat je i sa palatinalne strane za završne grančice *n. nasopalatinusa* u količini 0,2 ml.

Za svakog ispitanika formiran je istraživački karton u koji su unošeni odgovarajući podaci, kao i upitnik za ispitanika koji je lično popunjavao (uz prethodno dato objašnjenje), a koji je vraćao lekaru na kontrolnom pregledu, 24 sata nakon izvršene hirurške intervencije. Najveći prečnik periapeksne promene meren je na retroalveolarnom rendgen snimku upotrebom lenjira sa milimetarskom skalom.

Radi procene analgetičkog efekta primenjenih lokalnih anestetika praćeni su sledeći parametri: vreme proteklo od momenta primene lokalne anestezije do pojave prvog bola posle operacije – ispitanici su u upitnik unosili vreme kada se pojavio prvi bol na mestu hirurške intervencije po završetku operacije; vreme proteklo do momenta uzimanja prve doze analgetika posle operacije – ispitanici su u upitnik unosili vreme kada se javila potreba za uzimanjem analgetika posle hirurške intervencije; intenzitet početnog postoperativnog bola meren je korišćenjem vizuelno-analogne skale (VAS) na kojoj je ispitanik obeležavao jačinu bola koji je osećao u tom trenutku. Vizuelno-analogna skala je predstavljena horizontalnom duži od 100 mm, gde početni kraj sa leve strane označava stanje „bez bola", a drugi kraj stanje „najgoreg bola koji se može zamisliti". Ispitanik je na skali obeležavao tačku koja odgovara nivou intenziteta početnog bola koji je osetio po završetku intervencije. Nakon toga lenjirom je mereno rastojanje u milimetrima od početka skale do obeležene tačke, koje predstavlja numerički pokazatelj jačine bola; intenzitet bola šest časova nakon davanja lokalnog anestetika meren je, takođe, na VAS; ukupan broj doza (tableta) analgetika uzetih u toku prva 24 časa posle hirurške intervencije.

Eventualni neželjeni efekti povezani sa upotrebom lokalnog anestetika beleženi su od strane hirurga u istraživački karton.

Dobijeni rezultati statistički su analizirani primenom Studentovog *t*-testa i χ^2-testa, značajnosti.

Rezultati

Ispitanici su bili oba pola, starosti od 19 do 51 godine (tabela 1). Pre;nik periapeksne lezije, kao i trajanje hirurške intervencije, bili su približno slični u obe grupe ispitanika.

Od 30 ispitanika studijske grupe, njih šest (20%) nije imalo postoperativni bol. Kod ostalih ispitanika, koji su postoperativno imali bol, srednja vrednost vremena u kome se

Tabela 1
Raspodela ispitanika prema polu, prosečnoj starosti, prečniku periapeksne lezije i dužini operacije

Parametri		Ripovakain 0,75%	Lidokain 2% sa adrenalinom
Pol	muški	17	15
	ženski	13	15
Prosečna starost (god)		31,5	34
Prosečni prečnik periapeksne lezije (mm)		8,2	8,3
Prosečno trajanje operacije (min)		38,3	40,8

bol javio iznosila je nešto više od tri i po sata (222 minuta). Bol se pre pojavio kod ispitanika kontrolne grupe, što je bilo statistički visokoznačajno ranije u odnosu na grupu testiranu ropivakainom ($p < 0,001$) (tabela 2).

U tabeli 2 prikazan je intenzitet prvog postoperativnog bola, određen pomoću VAS. Statistički značajno viša, srednja vrednost početnog postoperativnog bola, utvrđena je kod ispitanika kontrolne grupe ($p < 0,05$). I posle 6 časova od operacije srednja vrednost intenziteta bola bila je statistički značajno veća kod ispitanika kontrolne grupe nego kod ispitanika studijske grupe (tabela 2). Štaviše, devet (30%) od 30 ispitanika studijske grupe nije imalo bolove u prvih 6 h od završetka operacije.

Od ukupnog broja ispitanika studijske grupe (n = 30), njih 16 (53,3%) uopšte nije imalo potrebu za analgeticima u prva 24 sata od završetka intervencije, a u kontrolnoj grupi njih osam (26,7%) nije uzimalo analgetike u prva 24 sata postoperativno. Ta razlika nije bila statistički značajna (tabela 2).

Ispitanici kontrolne grupe uzimali su prvu dozu analgetika pre ispitanika studijske grupe, ali to nije bilo statistički značajno (tabela 2). Nisu utvrđene statistički značajne razlike ni u pogledu broja uzetih tableta analgetika (tabela 2).

postoperativnom periodu [14]. Stoga se upotrebom lokalnih anestetika sa dugotrajnim dejstvom može prevazići upravo taj bolni period, zahvaljujući činjenici da lokalna anestezija traje više sati kada se primenjuje sprovodna (blok) anestezija [3]. Na osnovu dosadašnjih studija, bol nakon oralnohirurških intervencija javljao se značajno kasnije pri upotrebi bupivakaina u odnosu na lidokain sa adrenalinom [15]. Pojava postoperativnog bola obično se zapaža pre nego što se senzibilitet mekog tkiva vrati u normalu [4].

U našoj studiji, postoperativni bol u studijskoj grupi javljao se u proseku nakon skoro četiri sata, što je i statistički značajno duže ($p < 0,001$) u odnosu na kontrolnu grupu u kojoj je korišćen 2% lidokain sa adrenalinom. Svi ispitanici kod kojih je kao lokalni anestetik korišćen lidokain imali su postoperativne bolove, dok je takvih ispitanika u grupi sa ropivakainom bilo 80%. Ovo govori u prilog tome da 0,75% ropivakain obezbeđuje znatno dužu postoperativnu analgeziju od 2% lidokaina sa adrenalinom.

Takođe, intenzitet početnog postoperativnog bola, obeležavan od strane ispitanika na VAS, bio je značajno manji nakon primene 0,75% ropivakaina nego 2% lidokaina sa adrenalinom ($p < 0,05$). Do sličnog nalaza došli su Apostolo-

Tabela 2
Procena postoperativnog analgetičkog efekta ripovakaina i lidokaina 2% sa adrenalinom kod ispitanika podvrgnutih hirurškom lečenju periapeksnih lezija sekutića gornje vilice

Parametri	Ripovakain 0,75%		Lidokain 2% sa adrenalinom	
	n	$\bar{x} \pm SD$	n	$\bar{x} \pm SD$
Vreme pojave bola posle intervencije (min)	24	221,87 ± 108,14	30	131,33 ± 58,23
Intenzitet početnog postoperativnog bola (mm na VAS)	30	16,17 ± 17,13	30	24,13 ± 12,84
Intenzitet bola 6 h nakon intervencije (mm na VAS)	30	8,93 ± 8,71	30	14,63 ± 7,37
Broj bolesnika koji su uzimali analgetike				
da		14 (46,7%)		22 (73,3%)
ne		16 (53,3%)		8 (26,7%)
Vreme do uzimanja prvog analgetika (min)	14	227,14 ± 139,57	22	161,14 ± 111,63
Broj analgetika/bolesnik uzetih u prva 24 sata posle operacije	30	0,77 ± 1,01	30	1,20 ± 0,92

VAS – vizuelno-analogna skala

Diskusija

Hirurška intervencija aktivira složenu seriju biohemijskih i ćelijskih događaja, koja uključuje raznovrsne inflamatorne medijatore i algogene supstance. Bol nakon apikotomije relativno je kratkog trajanja (4–6 h) i javlja se u ranom

poulos i sar. [16] poredeći ropivakain i lidokain sa adrenalinom pri tonzilektomiji.

Po isteku perioda od 6 časova nakon intervencije, intenzivnije bolove imali su ispitanici u kontrolnoj grupi sa lidokainom, značajno izraženije, u poređenju sa ispitanicima iz grupe u kojoj je korišćen ropivakain ($p < 0,01$). Studije sprovedene

sa ciljem da se ispita upotreba lokalnih anestetika dugog dejstva u oralnoj hirurgiji ukazale su na činjenicu da se primenom ovih anestetika smanjuje upotreba analgetika u postoperativnom periodu [3, 4, 7, 17], ali je bilo i onih studija u kojima to nije bio slučaj [14, 18, 19]. Interesantno je zapažanje da upotreba potentnih nesteroidnih antiinflamatornih lekova (ibuprofen, 400 mg) može da smanji broj analgetika potrebnih za kontrolu bola i tako oteža merenje razlike između lokalnih anestetika [19].

No, kako bi bilo neetički lišiti bolesnike mogućnosti da u postoperativnom periodu koriste pouzdane analgetike samo radi praćenja analgetičke efikasnosti lokalnih anestetika, čini se neizbežnim da se ova činjenica, jednostavno, prihvati kao jedina moguća. Pojedini autori smatraju da se upotrebom lokalnih anestetika dugog dejstva u oralnohirurškim intervencijama umanjuje potreba za bar jednom dozom analgetika [3] i da dugo dejstvo anestetika sa postepenim nastupanjem postoperativnog bola čini kontrolu bola lakšom [3, 4]. El-Sharrawy i Yagiela [12] u svojoj studiji navode da 0,5% i 0,75% ropivakain nakon ekstrakcije donjih umnjaka uz sprovodnu anesteziju, obezbeđuju postoperativnu analgeziju koja traje duže i od utrnulosti mekih tkiva. Pri hirurškoj ekstrakciji gornjih umnjaka, međutim, ropivakain nije obezbedio uspešnu postoperativnu kontrolu bola, nakon infiltracione anestezije u maksili [13], što se može objasniti činjenicom da nije primenjena sprovodna anestezija. Pojedina klinička ispitivanja su ukazala na intenzivniji postoperativni bol nakon gingivektomije [20] kada je korišćen 2% lidokain sa adrenalinom (1 : 80 000) u pređenju sa drugim lokalnim anesteticima. Takođe, nakon primene većih količina 2% lidokaina sa adrenalinom zapažen je intenzivniji postoperativni bol nakon gingivektomije [21]. Kao jedan od mogućih uzroka autori navode povećanje količine vazokonstriktora, budući da lidokain sa adrenalinom 1 : 80 000 prouzrokuje redukciju u protoku krvi koja traje 60–90 min [22].

U našoj studiji manje od polovine ispitanika (46,6%) kojima je dat ropivakain uzimalo je analgetike tokom prva 24 sata postoperativnom, dok je u grupi u kojoj je primenjen 2% lidokain sa adrenalinom taj procenat bio znatno veći (73,3%).

Zaključak

Rezultati ove studije ukazuju na zadovoljavajući analgetički efekat ropivakaina posle hirurškog lečenja periapeksne lezije sekutića gornje vilice koji je bolji od analgetičkog efekta kombinacije lidokaina sa adrenalinom.

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Early postoperative complications in children with secretory otitis media after tympanostomy tube insertion in the Military Medical Academy during 2000–2009

Rane postoperativne komplikacije insercije aeracionih cevčica kod dece sa sekretornom otitis medijom u Vojnomedicinskoj akademiji u periodu 2000–2009.

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Abstract

Background/Aim. Secretory otitis media (SOM) is a chronic, nonpurulent inflammation of the middle ear, characterized by a long-term presence of liquids of different density in the middle ear for at least three consecutive months, different degrees of hearing loss and the absence of perforation of the eardrum. The aim of this study was to estimate the early postoperative complications after insertion of tympanostomy tube (TT) in children with secretory otitis media (SOM) in an 18-month period after TT insertion. **Methods.** This retrospective study included children with SOM (n = 478), aged from 2.5 to 16 years, operated from 2000 to 2009. During these ten years 365 children had TT in both ears, 131 children had TT in one ear and 55 children were operated two or more times. Totally 843 ears were operated on. Date were obtained by regular fallow up in Out-patient clinic concerning symptoms reported by children and parents, otomicroscopy findings and hearing measurements (audiometry and tympanometry). **Results.** Transient otorrhea was the most common early postoperative complication (16.5%), then obstruction (9.5%), premature extrusion of TT (3.9%), chronic otorrhea (3.1%), granulation tissue (1.1%) and medial displacement (0.5%). According to our experience gold and silicone TT were shown less successful than others. The incidence of premature extrusion of TT was significantly higher with gold TT, comparing to others (6/33, 18%; $p < 0.001$). We also found significantly more frequent medial displacement with silicone TT than with other ones (2/4, 50%; $p < 0.001$). **Conclusion.** There are many early postoperative complications of TT insertion, but they depend on the meticulous surgery techniques, regular postoperative examinations and the type of TT. The type of TT should be determined according to own experience.

Key words:
otitis media with effusion; otoscopy; middle air ventilation; postoperative complications.

Apstrakt

Uvod/Cilj. *Otitis media secretoria* (OMS) je hronični, negnojni zapaljenski proces srednjeg uva koji se karakteriše dugotrajnim prisustvom tečnosti u srednjem uvu, različite gustine, najmanje tri meseca u kontinuitetu, nagluvošću različitog stepena i odsustvom perforacije bubne opne. Cilj ovog rada bio je analiza postoperativnih komplikacija tokom 18-mesečnog praćenja bolesnika dečjeg uzrasta, lečenih od OMS implantacijom aeracionih cevčica (AC). **Metode.** Retrospektivnom studijom bilo je obuhvaćeno 487 bolesnika sa OMS, uzrasta 2,5–16 godina, operisanih u desetogodišnjem periodu (2000–2009) od kojih je 356 bilo sa obostranom i 131 sa jednostranom implantacijom AC, a njih 55 sa ponavljanom operacijom dva i više puta. Ukupno je implantirano 843 AC. Ambulantno praćenje operisanih bolesnika tokom 18 meseci bilo je bazirano na simptomima, autoanamnestičkim i heteroanemnestičkim podacima, otomikroskopskom pregledu, kao i merenju sluha audiometrijom i timpanometrijom. **Rezultati**. Tranzitorna otoreja bila je najčešća rana postoperativna komplikacija (16,5%), zatim zapušenost AC (9,5%), prevremeno ispadanje AC (3,9%), hronična otoreja (3,1%), granulacije (1,1%) i upadanje AC u bubnu duplju (0,5%). Prema našem iskustvu, silikonske i zlatne AC su manje uspešne za upotrebu. Postoji statistički značajna razlika između upadanja u bubnu duplju silikonskih AC u poređenju sa drugim tipovima (2/4, 50%; $p < 0,001$), kao i statistički značajna razlika zastupljenosti u ove komplikacije između zlatnih AC u poređenju sa drugim tipovima AC (6/33,18%; $p < 0,001$) **Zaključak.** Rane postoperativne komplikacije implantacije AC mnogobrojne su i mogu se svesti na razumnu meru minucioznom hirurškom tehnikom i izborom tipa AC prema sopstvenom iskustvu, kao i redovnim praćenjem stanja operisane dece.

Ključne reči:
otitis medija, serozni; otoskopija; uvo, srednje, aeracija; postoperativne komplikacije.

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Introduction

Secretory otitis media (SOM) is a chronic, nonpurulent inflammation of the middle ear, characterized by a long-term presence of liquids of different density in the middle ear for at least three consecutive months, different degrees of hearing loss and the absence of perforation of the eardrum. It occcurs in preschool and school children, mostly bilaterally, with a morbidity rate proportional to the latitude (follows moisture and cold). The average incidence of SOM is 2.5% in Serbia, in Finland 10%, and the average incidence in Europe is 6%. There are transudation (Politzer) and exudates (Tosh) theory of SOM origin. Reasons are numerous: allergies and immune factors, dysfunction of the Eustachian tube and many predisposing factors. Histopathological findings of SOM pass through three stages: initial, secretory and degenerative. Its clinical picture includes: impaired hearing, itching in the ears, autophony, nasal speech and slow speech development. Hearing loss is the main symptom, but many children get used to it, so if parents or teachers do not detect hearing loss on time, there is a potential risk for changes in the middle ear to become irreversible and cause permanent hearing loss. Diagnostic procedures include children's and parents' reports, microscopic examination of the ear, a complete ear, nose and throat (ENT) examination, tympanometry and hearing test. Therapy is conservative and surgical. Conservative therapy lasts up to 6 months after the onset according to Anglo-Saxon literature. If there is the presence of SOM on three consecutive examinations during a 6-month period, conservative therapy is unsuccessful. Surgical therapy is the next step.

Implantation of tympanostomy tubes (TT) is a surgical method of SOM treating. Eli and Riolanus treated hearing loss of children due to the appearance of mucus behind the Eustachian tube with paracentesis in the seventeenth century. Martill Frank was the first designer of TT from gold foil in 1845. Politzer recommended paracentesis with a blow tube in the mid-nineteenth century and gave up of implantation of TT because of numerous complications. Bourgeois introduced aspiration of secretions through the paracentesis and Armstrong redesigned and reactivated TT in 1954 [1]. After that TT implantation became a sovereign surgical procedure in the treatment of SOM. For example, in 1996 in the U.S. 500,000 children were operated with implantation of TT due to SOM, and even a million children per year in the last three years. Operation involves setting up a TT in the eardrum through a hole in the eardrum (paracentesis, myringotomy), thus making a communication between the middle ear and external ear to prevent accumulation of secretions in the middle ear and enabling aeration of the middle ear during a prolonged period of time. Effect on hearing is immediate, after aspiration of secretions from the middle ear and TT insertion [2, 3]. The result is sometimes accompanied by difficulties and complications which follow this operation. Armstrong and Charlotte said at the beginning of the TT era: "An ideal TT should not clog up or drop out prematurely, should be inserted and removed easily and should have a low rate of complications" [4].

The aim of our study was to analyze postoperative complications during 18 months after TT implantation in preschool and school children with SOM in a 10-year period.

Methods

We analyzed charts of 487 patients aged 2.5 to 16 years, treated in ENT Clinic of the Military Medical Academy in (MMA) Belgrade from 2000–2009 who had been TT implanted one or more times and followed postoperatively for 18 months. Indications for surgery were made after a 6-month period of conservative treatment (at least three findings), and included children's and parents' reports, otomicroscopy, a complete ENT examination, tympanometry and hearing test – pure tone audiometry for 5-year old or older children. Tympanometric findings were type B, or rigidity and hearing tests showed conductive hearing loss.

Surgery was performed under general anesthesia, mostly along with adenoidectomy or tonsilo adenoidectomy. Myringotomy was performed in classical front – lower section quadrant of the tympanic membrane. The length of myringotomy was between the internal and the external diameter of TT, on average 2–2.8 mm (Figure 1).

In a case of repeated TT implantation, we performed myringotomy in posterior – inferior quadrant of the tympanic membrane in order to avoid focal atrophy of the tympanic membrane. We used aspiration tubes with diameter 1.4, 1.8

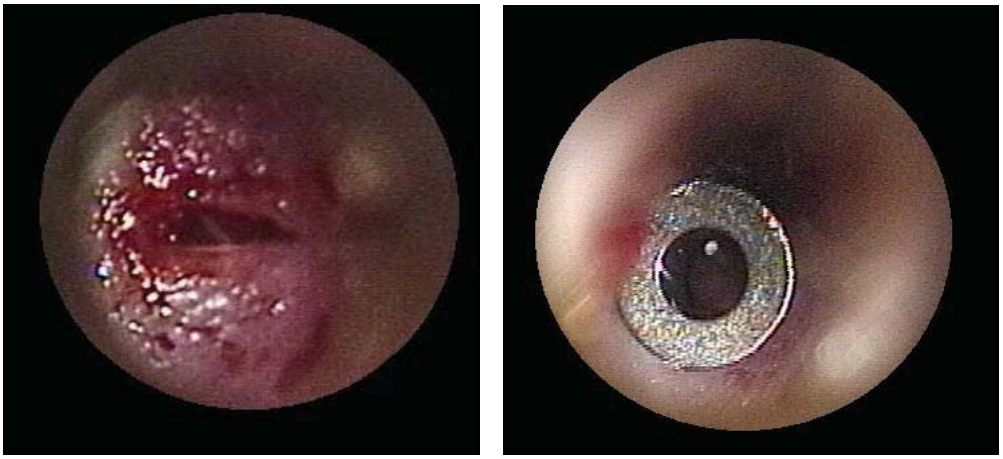

Fig. 1 – Surgical technique of myringotomy and tympanostomy tube implantation

and 2.2 mm for thorough and detail suction of secretions from the tympanic cavity. We placed a TT bilaterally in 356 children, in 131 children unilaterally (843 TT totally); 55 children were operated two or more times. We used TT made from various manufacturers, various materials and various designs and sizes. Technical characteristics of TT are given in Table 1.

Table 1

Technical characteristics of tympanostomy tubes (TT)

TT type	Inner diameter (mm)	External diameter (mm)	Length (mm)	Weight (mg)
Shepard fluoroplastic	1.14	2.4	2.4	10.3
Shepard teflon	1.14	2.4	2.4	15.4
Donaldson silicone	1.5	2.3	3.2	11.4
Kurtz titanium	1.25	2.55	1.6	10.6
Tuebingen gold	1.5	2.8	1.6	27.5

The first control examination was taken two weeks after surgery, and continued once monthly if the postoperative period was regular. Examinations were based on the otomicroscopy findings, hearing test and/or timpanometry. Findings were analyzed 18 months after surgery. Wearing TT for a period of 6–18 months was considered sufficient for the restitution and recovery of a sick middle ear from SOM. If TT did not spontaneously drop out in time, we pulled it out in outpatient clinic or in condition of one-day surgery under short-term inhalation anesthesia, rarely under general anesthesia.

Results

Early postoperative complications, such as bleeding from the ear, eardrum hematoma or hematoma of the skin of external auditory canal, were rare with spontaneous recovery in the next few days and they were not valuable for statistic analysis. We had no cases of intraoperative ossicular chain disruption or extended inflammatory disease such as labyrinthitis or endocranial complications. We had no complications of general anesthesia. Postoperative complications that appeared during 18 months after TT insertion, are given in Table 2.

Table 2

Postoperative complications 18 months after insertion of tympanostomy tubes (TT)

Complications after TT insertion	Operated ears [n(%)]
Transient otorrhea	139 (16.5)
Chronic otorrhea	26 (3.1)
Granulation tissue	8 (1.1)
Premature extrusion	33 (3.9)
Obstruction	80 (9.5)
Medial displacement	4 (0.5)

Functional and permanent structural sequelaes after TT extraction, such as tympanosclerosis, perforation, focal atrophy of the tympanic membrane, retraction pocket, cholesteatoma, were not included.

Transient otorrhea means occasional middle ear secretion leaking through TT up to 3 months after surgical procedure. It was the most frequent postoperative complication and occurred in 16.5%. This percentage fits the statistics of other authors and no statistical significance in relation to TT type was found ($\chi 2$ test = 1.357 for df = 4, $p = 0.852$). Secretions drainage through TT in the first week after insertion was not considered as a transient otorrhea and not treated with medications because it was considered as a result of incomplete intraoperative aspiration from tympanic cavity. Each subsequent episode of otorrhea was treated conservatively, as well as the exacerbation of recurrent acute otitis media. Occurrence of otorrhea more than 3 months after TT insertion was considered a chronic otorrhea. Chronic otorrhea was observed mostly equally in all groups, regardless of the used TT type (χ^2 test = 1.491 for df = 4, $p = 0.878$) with overall incidence 3.1% in 487 children. Frequency of granulation tissue formation (1.1%) was as in the literature (up to 5%). We solved it conservatively (with trichloracetic acid 20%), except in two cases where TT reinsertion was necessary with surgical removal of granulation tissue. There was no statistically significant differences in the formation of granulation tissue according to the TT type (χ^2 test = 0.265 for df = 4, $p = 0.992$).

Premature TT extrusion (3.9%) implies a TT dropped out earlier than 6 months after insertion, and it happened only in the group of children with transient otorrhea. According to the type of implanted TT, premature TT extrusion was the most frequent in the group of children with gold TT: 6 out of 24 gold TT dropped out before 6 months, with the incidence of 25%, and 6 out of 33 (18%) of all the premature TT extrusion. There was a statistically significant difference regarding gold TT comparad to other ones in the frequency of premature extrusion (χ^2 test = 30.311 for df = 4, $p = 0.000$). Figure 2 shows that a gold TT had the highest incidence of premature extrusion.

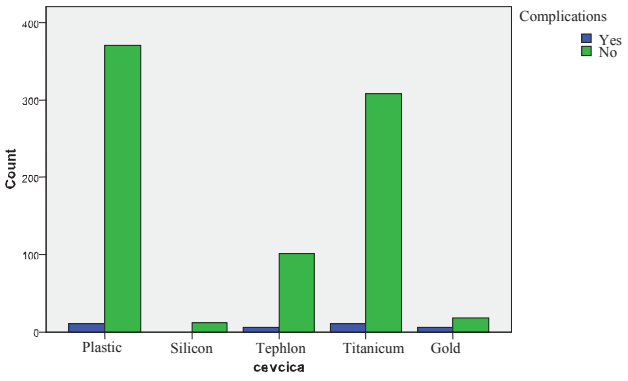

Fig. 2 – Premature extrusion of different tympanostomy tube types

TT obstruction with dried secretions occurred in 9.5% of the children which was similar to the global statistics (7% to 10.5%). There were no statistically significant differences among different types of TT regarding this complication (χ^2 test = 0.732 for df = 4, p = 0.947). Some cases were successfully treated with local seven-day therapy (3% hydrogen peroxide ear drops). Persistent TT obstruction was not an indication for reimplantation except cases with persistent conductive hearing loss during three months. Medial displacement of TT to the tympanic cavity occurred only in 4 cases. Two of them were with silicon TT, which represented 50% of the total number of TT medial displacement. There was a statistically significant difference between silicone TT and other TT types in medial displacement (χ^2 test = 66.766, df = 4 for p = 0.000). Silicone TT is soft and not at all easy to set up. Although we did not have not a case of premature extrusion of silicone TT, we gave up using silicone TT because of medial displacement (Table 3). We had the similar experiences with the implantation of "T" type of TT, which brought more postoperative complications and more difficulties in surgical work. "T" type of TT was used in cases with persistent SOM through many years. Persistent SOM was solved by repeated insertion of TT with a larger inner diameter of the TT (1.5 mm).

significant difference in premature extrusion of gold TT, comparing to other types. That is the reason for stop using gold TT in 2002 in MMA. The idea of making gold TT was good biocompatibility and antimicrobial activity of gold. The reason for the failure was the mass of gold TT, which is considerably larger than all the other TT types (Tuebingen gold TT weight = 27.5 mg which is almost three times higher than Shepard fluroplastic TT = 10.3 mg). The load of eardrum is therefore larger and the premature extrusion is more common. Premature extrusion was not an indication for TT reimplantation, but the repetition of the diagnostic protocol should be necessary.

Reinsertion of TT was necessary in case of granulation tissue with implanted fluoroplastic TT (one case), and the second was with titanium TT. Although there are many articles on granulation tissue frequently associated with titanium TT [5], we had no such experiences.

The presence of TT on the eardrum makes a new microenvironment in the middle ear. Foreign body reaction can result in one or more postoperative complications after TT insertion. Postoperative complications are connected, intensifying each other and in close connection with new microenvironment. There is definitely host reaction to all three layers of the eardrum in the presence of inserted TT and it depends on the material of TT. There is also a direct impact of air on all

Table 3

Postoperative complications according to tympanostomy tubes (TT) type

TT type	n	Transient otorrhea	Chronic otorrhea	Granulation tissue	Premature extrusion	Obstruction	Medial displacement
Plastic and fluoroplastic	382	66	12	4	11	36	1
Titanium	319	52	10	3	11	32	1
Teflon	106	17	3	1	5	10	0
Silicone	12	1	0	0	0	1	2
Gold	24	3	1	0	6	1	0
Total	843	139	26	8	33	80	4

n – number of TT implantation or number of operated ears

Discussion

Transient otorrhea after TT implantation is the most common postoperative complication in an 18-month follow-up after TT insertion. The nature of SOM is represented with chronic production and accumulation of secretion in a child's middle ear cavity and transient otorrhea is expected as a desirable appearance, because of TT drainage function. Successful conservative treatment of transient otorrhea, without any endocranial and exocranial complications, makes it a mild postoperative complication, like a minor or cosmetic complication according to the some authors [3]. However, transient otorrhea can be an introduction into further complications such as premature TT extrusion, obstruction of TT or chronic otorrhea. Besides that, one of the reasons for premature extrusion of TT is iatrogenic, such as too big myringotomy, which can be avoid by careful otomicroscopy work. The third reason is an inadequate reaction on foreign body in the ear drum. In our study, all the counted TT were extrusioned immediately after operation. There is no ideal material for making TT compatible with each patient. However, in our study there was a difference in the selection of TT type. There was a statistically

the threatening microbes to the tympanic cavity and the long lasting wound surface of myringotomy. The residual non infectious secretions in the middle ear can become contagious, even after a detailed aspiration during TT implantation. A biofilm is created on the contact surface of TT and eardrum. It is composed of dried secretion and microbes and sometimes it is infected with persistent strains of bacteria, such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Infectious biofilm or, occasionally, the presence of infectious discharge from the middle ear can cause even more secretion of mucus from hypertrophic glands in the middle ear, and lead to chronic otorrhea. Chronic otorrhea can be resistant to conventional antibiotics and discourages physicians. Attempts have been made using various antibiotics topically and orally before insertion, during or immediately after surgery, but without statistically significant reduction percentage of complications prevalence [6]. This has led to a series of investigations based on examination of bacterial biofilms, which often accompanies TT as a key reason for transient and chronic otorrhea [6]. Various substances put on a TT before insertion were examined in order to prevent the appearance of bacterial biofilms. A fluoroplastic TT coated with phosphorylcholine showed resistance to *S. aureus* and *P.*

aeruginosa [7], and silicone-coated TT with piperacillin-tazobactam showed resistance to ciprofloxacin- resistant strain of *P. aeruginosa in vitro* [8], and ion bombing silicon TT in guinea pigs showed resistance to *S. aureus in vivo* [9]. On the other hand, hearing improvement after TT implantation and consequently increase in quality of child's life [10, 11], justify this surgical procedure along with all the associated postoperative complications.

Conclusion

Early postoperative complications after TT insertion are numerous and may affect children's recovery from SOM. Regular and detailed postoperative monitoring of children who underwent TT insertion can diminish early postoperative complications and increase the effectiveness of surgical treatment of SOM.

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Procena zahvaćenosti aksilarnih limfnih nodusa u zavisnosti od veličine tumora i histološkog i nuklearnog gradusa kod bolesnica sa karcinomom dojke

Assessment of axillary lymph nodes involvement in patients with breast cancer depending on the tumor size and its histological and nuclear grades

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Apstrakt

Uvod/Cilj. Postoji dosta studija koje govore u prilog tome da zahvaćenost limfnih nodusa aksile raste u zavisnosti od povećanja veličine tumora, odnosno histološkog i nuklearnog gradusa. Cilj ovog rada bio je da se proceni rizik od zahvatanja aksilarnih limfnih nodusa kao i veza između veličine tumora, histološkog i nuklearnog gradusa u grupi bolesnica operisanih od karcinoma dojke kod kojih je urađena kompletna disekcija aksile. **Metode.** Ispitivanjem je obuhvaćeno 900 bolesnica operisanih u periodu od 2005 do 2008. godine kod kojih je rađena modifikovana radikalna mastektomija sa disekcijom aksile. Procenjivan je broj zahvaćenih limfnih nodusa u zavisnosti od makroskopske veličine tumora (T), histološkog gradusa (HG) i nuklearnog gradusa (NG). **Rezultati.** Ukupan broj pregledanih limfnih nodusa bio je 9 977. Broj zahvaćenih limfnih nodusa kod T1 bio je 18,6%, dok je kod T4 bio 60,2%. Za histološki gradus broj zahvaćenih limfnih nodusa kretao se od 14,2% (HGI) do 45,1% (HGIII). S obzirom na nuklearni gradus broj zahvaćenih limfnih nodusa kretao se od 17,4% (NGI) do 54,5% (NGIV). Korišćenjem χ^2-testa za trend i *odds ratio* (OR), pokazano je da zahvaćenost aksilarnih limfnih nodusa raste sa povećanjem veličine tumora, odnosno histološkog i nuklearnog gradusa. Rizik od zahvatanja aksilarnih limfnih nodusa bio je 1,43 puta veći kod tumora veličine T2 u odnosu na najmanje tumore (veličina T1), a čak 6,62 puta veći ukoliko je tumor bio veličine T4. Takođe, rastao je od 1,79 puta kod HGII do čak 4,98 puta za HGIII i od 1,44 puta za NGII do 5,71 puta za NGIV. **Zaključak.** Potvrđeno je da porast veličine tumora, histološkog i nuklearnog gradusa povećava rizik od zahvatanja aksilarnih limfnih nodusa kod bolesnica sa karcinomom dojke.

Ključne reči:
dojka, neoplazme; neoplazme, invazivnost; limfni čvor, ekscizija; neoplazme, metastaze; neoplazme, određivanje stadijuma; rizik, procena.

Abstract

Background/Aim. There are a lot of studies aiding to the opinion that the involvement degree of axilla lymph nodes grows depending on increase of breast tumor size, and its histological and nuclear grades. The aim of this study was to assess the risk of axillary lymph nodes involvement, as well as the relation between the tumor size, histological and nuclear grades in a group of female patients who underwent breast cancer surgery, including levels 1–3 axillary dissection. **Methods.** Investigation covered 900 patients operated on during 2005–2008 who underwent modified radical mastectomy including axillar dissection. We assessed a number of involved lymph nodes, depending on tumor macroscopic size (T), histological grade (HG) and nuclear grade (NG). **Results.** A total number of examined lymph nodes was 9977. The incidence of involved lymph nodes was from 18.6% with T1 tumor size up to 60.2% with T4 tumor size. Concerning histological grade, the number of involved lymph nodes ranged from 14.2% (HGI) to 45.1% (HGIII); while in terms of nuclear grade, the number of involved lymph nodes ranged from 17.4% (NGI) to 54.5% (NGIV). By using χ^2-test for trend and odds ratio (OR), the results showed that the axillary lymph nodes involvement degree was increased with the increase of the tumor size and its histological and nuclear grades. The risk of axillary lymphatic nodes involvement was 1.43 times higher in the group of T2 tumors size compared to the smaller tumors T1 size, and even up to 6.62 times higher in case of T4 tumor size. It was also increasied from 1.79 times for HGII to even 4.98 times for HGIII, and from 1.44 times for NGII to 5.71 times for NGIV. **Conclusion.** In breast cancer patients, there is a strong correlation between tumor size, its histological and nuclear grades and the risk of axillary lymph nodes involvement.

Key words:
breast neoplasms; neoplasm invasiveness; lymph node excision; neoplasm metastasis; neoplasm staging; risk assessment.

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Uvod

Proučavanje zahvaćenosti aksilarnih limfnih nodusa kod karcinoma dojke ima veliki praktični značaj. Pored ostalog, nalaz u limfnim nodusima pazušne jame predstavlja i izuzetno važan prognostički parametar.

Morton i sar. [1] iz *John Wayne Cancer Insitute* (Santa Monica) 1999. izneli su stav da prvi limfni čvor koji je na udaru tumorskih ćelija koje metastaziraju iz primarnog tumora, (*sentinel lymph node* – SLN) ili limfni čvor „stražar", odražava status preostalih limfnih čvorova u regionalnom limfnom drenažnom sistemu. Pomenuti autori su prvi uradili patohistološke analize *sentinel* detektovanih regionalnih limfnih nodusa kod bolesnica sa malignim melanomom, a potom i kod bolesnica sa karcinomom dojke i štitaste žlezde. Metoda je veoma korisna u smislu procene rasprostranjenosti kancerskog procesa kod karcinoma dojke. Negativan nalaz „stražarskog" limfnog nodusa ukazuje na odsustvo limfne diseminacije malignog procesa i pošteđuje bolesnicu od aksilarne disekecije i svih komplikacija koje nosi ova porocedura (bol, serom, limfedem ruke, itd), što je ujedno i glavni cilj ove metode.

Najveći rizik koji nosi ova procedura je pojava lažno negativnih rezultata. Oni se javljaju kao posledica nedostatka nekih *sentinel* nodusa, prisustva ekstraaksilarne lokalizacije pozitivnih *sentinel* nodusa, postojanja embolije limfnih puteva tumorskim ćelijama. Nekada prisustvo tumora u limfnim nodusima može ometati sposobnost nodusa da preuzme boju. Kod starijih bolesnica, limfni nodusi koji su zamenjeni masnim tkivom, ponekad, uslovljavaju niži kapacitet preuzimanja radiofarmaka ili boje.

Poseban značaj negativnog nodusa „stražara" jeste porast 5-godišnjeg preživljavanja, dok se sa povećanjem broja zahvaćenih limfnih nodusa metastazama, 5-godišnje preživljavanje znatno smanjuje [2].

Istražujući zahvaćenost aksilarnih limfnih nodusa aksile u zavisnosti od karakteristika tumora Leonard i sar. [3] na seriji od 15 719 karcinoma (duktalni, lobularni i tubularni) došli su do sledećih rezultata: broj pozitivnih aksilarnih limfnih nodusa značajno koreliše sa histološkom dijagnozom i povećanjem veličine tumora – duktalne i lobularne histologije.

Istražujući uticaj broja aksilarnih limfnih nodusa na preživljavanje Kuru [4] u svom istraživanju na seriji od 801 bolesnice sa T1–T3 tumorom dojke i pozitivnom aksilom, došao je do zaključaka da broj limfnih nodusa uklonjenih disekcijom aksile > 15 i broj negativnih limfnih nodusa > 15 značajno utiče na preživljavanje.

Kim i sar. [5] istražujući prognostičke faktore kod ranog karcinoma dojke, na seriji od 605 bolesnica, došli su do rezultata da je petogodišnje preživljavanje lošije kod bolesnica sa godištem ≤ 35 godina, pozitivnim limfnim nodusima i visokim nuklearnim gradusom. Takođe, petogodišnje preživljavanje lošije je kod bolesnica sa tumorom > 1 cm, pozitivnim limfnim nodusima i visokim nuklearnim gradusom u odnosu na bolesnice sa manjim tumorom, negativnim limfnim nodusima i nižim nuklearnim gradusom.

Ova studija ima za cilj procenu rizika od zahvaćenosti aksilarnih limfnih nodusa u zavisnosti od veličine tumora, (shodno *Tumor Node Metastasis* – TNM) klasifikaciji, histološkog i nuklearnog gradusa tumora.

Metode

Istraživanje je sprovedeno kao prospektivna, delom retrospektivna randomizovana studija koja je obuhvatila vremenski period od tri godine (2005–2008. godine).

Istraživanjem su bile obuhvaćene bolesnice Hirurške klinike Kliničkog centra u Nišu operisane zbog karcinoma dojke, kod kojih je rađena modifikovana radikalna mastektomija, i bolesnice Klinike za onkologiju Kliničkog centra u Nišu koje su bile na daljem postoperativnom lečenju. Ukupno, bilo je 900 bolesnica operisanih zbog karcinoma dojke. Limfni nodusi aksile sa tkivom dojke obrađivani su u Institutu za patologiju Kliničkog centra u Nišu.

Za analizu su korišćeni podaci iz istorija bolesti, operativni nalazi, izveštaji o patohistološkom pregledu, kao i onkološki protokoli bolesnica.

Istraživanje je obuhvatilo određivanje broja zahvaćenih limfnih nodusa u odnosu na ukupan broj pregledanih limfnih nodusa, a u zavisnosti od veličine tumora (T), kao i od histološkog (H) i nuklearnog (N) gradusa tumora.

U evaluaciji povezanosti veličine tumora, histološkog i nuklearnog gradusa sa zahvaćenošću limfnih nodusa istostrane aksile tumorskim procesom, koristili smo χ^2-test za linearni trend (*Chi Square for linear trend*) i *odds ratio* (OR) uz 95% interval poverenja (95% *Confidence interval* – 95% CI). Proračuni su vršeni korišćenjem Statcalc programa iz EPI-INFO programskog paketa u verziji 6. Kao prag statističke značajnosti korišćen je nivo greške procene manji od 5% ($p < 0,05$).

Kod svih bolesnica praćeni su: ukupan broj pregledanih limfnih nodusa i broj zahvaćenih limfnih nodusa u istostranoj aksili, veličina tumora, te histološki i nuklearni gradus tumora.

Rezultati

Najređa zahvaćenost limfnih nodusa nađena je u grupi tumora veličine T1 (18,6%), zatim je postepeno rasla i bila je najčešća u grupi bolesnica sa tumorom kategorije T4 (60,2%) (tabela 1). Između zahvaćenosti limfnih nodusa i veličine tumora dojke postojala je statistički značajna povezanost – porast veličine tumora pratio je porast pojave zahvaćenosti limfnih žlezda aksile ($p < 0,001$).

U grupi bolesnica sa tumorom dojke veličine T2 zahvaćenost limfnih nodusa iznosila je 24,6%. Pregledana su ukupno 3 172 aksilarna limfna nodusa operisana kod bolesnica sa veličinom tumora T1, od čega je 590 (18,6%) bilo pozitivno. Ova razlika bila je statistički značajna ($p < 0,001$). Rizik od zahvatanja aksilarnih limfnih nodusa bio je 1,43 puta veći u grupi tumora veličine T2, u odnosu na najmanje tumore (T1) (tabele 1–3).

U grupi bolesnica sa tumorom dojke veličine T3 zahvaćenost limfnih nodusa bila je 38,8%, što je značajno više u odnosu na grupu T1 ($p < 0,001$). Rizik za zahvatanje aksilarnih limfnih nodusa bio je 2,77 puta veći u grupi tumora veličine T3 u odnosu na najmanje tumore grupa T1 (95% CI = 2,34–3,28) (tabele 1–3).

Tabela 1

Zahvaćenost aksilarnih limfnih nodusa u zavisnosti od veličine tumora, histološkog i nuklearnog gradusa (n = 900)

Veličina tumora (T)	Limfni nodusi			OR (95% CI)
	Br. pregledanih	Br. zahvaćenih	% zahvaćenih	
T1	3172	590	18,6	1
T2	5434	1337	24,6	1,43 (1,28–1,59)
T3	851	330	38,8	2,77 (2,34–3,28)
T4	520	313	60,2	6,62 (5,41–8,10)
Σ	9977	2570	25,76%	
Histološki gradus (HG)		*χ^2 test za linearni trend; $p < 0,001$		
HG I	812	115	14,2	1
HG II	7523	1714	22,8	1,79 (1,45–2,21)
HGIII	1642	741	45,1	4,98 (3,98–6,25)
Σ	9977	2570	25,8%	
Nuklearni gradus (NG)		*χ^2 test za linearni trend; $p < 0,001$		
NG I	1238	215	17,4	1
NG II	6949	1614	23,2	1,44 (1,23–1,69)
NG III	1768	729	41,2	3,34 (2,79–3,99)
NG IV	22	12	54,5	5,71 (2,27–14,45)
Σ	9977	2570	25,76%	
* χ^2 test za linearni trend; $p < 0,001$				

OR – *adds ratio*; CI – *confidence interval*

Tabela 2

Zahvaćenost aksilarnih limfnih nodusa u zavisnosti od veličine tumora, histološkog i nuklearnog gradusa (n = 900)

Veličina tumora (T)	χ^2	*p*	OR	95% CI
T2 : T1	41,55	< 0,0001	1,43	1,28–1,59
T3 : T1	154,88	< 0,0001	2,77	2,34–3,28
T4 : T1	418,30	< 0,0001	6,62	5,41–8,10
T3 : T2	75,84	< 0,0001	1,94	1,66–2,66
T4 : T2	300,04	< 0,0001	4,63	3,83–5,61
T4 : T3	59,43	< 0,0001	2,39	1,90–3,00
Histološki gradus (HG)				
HGII : HGI	31,80	< 0,0001	1,79	1,45–2,21
HGIII : HGI	229,26	< 0,0001	4,98	3,98–6,25
HGIII : HGII	343,09	< 0,0001	2,79	2,49–3,12
Nuklearni gradus (NG)				
NGII: NG I	20,79	< 0,0001	1,44	1,23–1,69
NG III : NG I	192,47	< 0,0001	3,34	2,79–3,99
NG IV : NG I	20,21	< 0,0001	5,71	2,27–14,45
NG III : NG II	232,49	< 0,0001	2,32	2,07–2,59
NG IV : NG II	12,03	< 0,001	3,97	1,60–9,90
NG IV: NG III	1,59	> 0,05	1,71	0,69–4,29

OR – *adds ratio*; CI – *confidence interval*

Tabela 3

Rizik od zahvatanja aksilarnih limfnih nodusa u zavisnosti od veličine tumora (T), histološkog (HG) i nuklearnog gradusa (NG)

Odnos	Rizik od metastaze u aksilarne limfne noduse (x veći)
T2:T1	1,43
T3:T1	2,77
T4:T1	6,62
T3 : T2	1,94
T4 : T2	4,63
T4 : T3	2,39
HGII : HGI	1,79
HGIII : HGI	4,78
HGIII : HGII	2,79
NGII : NGI	1,44
NGIII : NGI	3,34
NGIV : NGI	5,71
NG III : NG II	2,32
NG IV : NG II	3,97
NG IV: NG III	1,71

U grupi bolesnica sa tumorom dojke veličine T4 zahvaćenost limfnih nodusa bila je 60,2%, što je, takođe, značajno više u odnosu na grupu sa veličinom tumora T1 ($p < 0,001$). Rizik od zahvatanja aksilarnih limfnih nodusa bio je 6,62 puta veći u grupi tumora veličine T4 u odnosu na najmanje tumore u grupi T1 (95% CI = 5,41–8,10) (tabele 1–3).

Najmanja zahvaćenost limfnih nodusa bila je kod tumora histološkog gradusa I (14,2%), a zatim je postepeno rasla i bila je najveća u grupi bolesnica sa tumorom dojke histološkog gradusa III (45,1%) (tabela 1). Između zahvaćenosti limfnih nodusa i histološkog gradusa tumora dojke postoji statistički značajna povezanost – porast histološkog gradusa prati porast zahvaćenosti limfnih žlezda aksile ($p < 0,001$).

U grupi bolesnica sa histološkim gradusom tumora dojke II zahvaćenost limfnih nodusa bila je 22,8%. U grupi žena sa histološkim gradusom I tumora dojke pregledano je ukupno 812 aksilarnih limfnih nodusa, od čega je 115 (14,2%) bilo pozitivno. Ova razlika je statistički značajna:

($p < 0,001$). Rizik za zahvatanje aksilarnih limfnih nodusa bio je 1,79 puta veći u grupi tumora histološkog gradusa II u odnosu na tumore sa najmanjim histološkim gradusom I (95% CI = 1,45–2,21) (tabele 1–3).

U grupi bolesnica sa histološkim gradusom tumora dojke III zahvaćenost limfnih nodusa bila je 45,1% što je značajno više u odnosu na grupu sa najmanjim histološkim gradusom ($p < 0,001$). Rizik od zahvatanja aksilarnih limfnih nodusa bio je 4,98 puta veći u grupi tumora histološkog gradusa III u odnosu na tumore sa histološkim gradusom I (95% CI = 3,98–6,25) (tabele 1–3).

Ustanovljena je najmanja zahvaćenost limfnih nodusa kod tumora nuklearnog gradusa I (17,4%), a najveća je u grupi bolesnica sa tumorom dojke nuklearnog gradusa IV (54,5%) (tabela 1). Između zahvaćenosti limfnih nodusa i nuklearnog gradusa tumora dojke postoji statistički značajna povezanost – porast nuklearnog gradusa prati porast zahvaćenosti limfnih žlezda aksile ($p < 0,001$).

U grupi bolesnica sa nuklearnim gradusom tumora dojke II zahvaćenost limfnih nodusa bila je 23,2% ($p < 0,001$). Rizik od zahvatanja aksilarnih limfnih nodusa bio je 1,44 puta veći u grupi tumora nuklearnog gradusa II u odnosu na tumore sa najmanjim nuklearnim gradusom (95% CI = 1,23–1,69) (tabele 1–3).

U grupi bolesnica sa nuklearnim gradusom tumora dojke III zahvaćenost limfnih nodusa bila je 41,2% što je opet bilo značajno više od grupe sa tumorom gradusa N1 ($p < 0,001$). Rizik od zahvatanja aksilarnih limfnih nodusa bio je 3,34 puta veći u grupi tumora nuklearnog gradusa III u odnosu na tumore sa najmanjim nuklearnim gradusom (N1) (95% CI = 2,79–3,99) (tabele 1–3).

U grupi bolesnica sa nuklearnim gradusom tumora dojke IV zahvaćenost limfnih nodusa bila je 54,5%. I ova vrednost bila je značajno viša u odnosu na grupu sa nuklearnim gradusom 1 N1 ($p < 0,001$). Rizik od zahvatanja aksilarnih limfnih nodusa bio je 5,71 puta veći u grupi tumora nuklearnog gradusa IV u odnosu na tumore sa najmanjim nuklearnim gradusom N1 (95% CI = 2,27–14,45) (tabele 1–3).

Diskusija

Veličina tumora uzima se kao važan prognostički faktor, ali i kao važan prediktor koji sa svoje strane utiče na metastaziranje u aksilarne limfne noduse. Metastaze u limfne noduse istostrane aksile često su prisutne, čak i kod ranih invazivnih karcinoma, pa i onda kada je aksila klinički negativna na palpaciju. Nalaz u limfnim nodusima pazušne jame predstavlja izuzetno važan prognostički parametar. Sa povećanjem broja zahvaćenih limfnih nodusa metastazama, 5-godišnje preživljavanje se znatno skraćuje [6].

Ahmad i sar. [7] došli su do rezultata da su T2 i T3 tumori povezani sa većom zahvaćenošću limfnih nodusa i da je većina bolesnika u istraživanju imala Nottingham prognostički indeks veći od 5,4 koji je, pak, bio povezan sa znatno lošijom prognozom.

Na preživljavanje, međutim, ne utiče samo broj zahvaćenih limfnih nodusa, već i veličina sekundarnog depozita, kao i ekstenzija van kapsule nodusa. Zato je neophodno potrebno mikroskopski odrediti broj limfnih nodusa zahvaćenih metastazama, stanje kapsule svakog nodusa i prečnik najveće metastaze. Važno je naglasiti, da je preživljavanje bolesnika sa mikrometastazama (depozit manji od 2 mm) skoro kompatibilno sa preživljavanjem bez metastaza [8]. Procenat prepoznatih mikrometastaza povećava se korišćenjem imunohistohemijskih metoda. Friedman i sar. [9] ustanovili su da prisustvo mikrometastaza povećava rizik od razvoja udaljenih metastaza za 1,7 puta. Tumori veći od 20 mm, visokog gradusa maligniteta zbog invazije limfatika imaju veću verovatnoću za razvoj mikrometastaza.

Andersson i sar. [10] u svom radu ističu lošiju prognozu za bolesnike koji imaju prisutne čak i mikrometastaze u aksilarnim limfnim nodusima, nego za one koje nemaju zahvaćene aksilarne limfne noduse.

U slučaju palpabilnih nodusa, koji češće nastaju kod lezija koje su većih dimenzija, nodus koji prihvata tumorsku metastazu uzrokuje opstrukciju distalnih limfatika i na taj način menja protok limfe, dovodeći do preusmeravnja njenog toka. Posledica toga je lažno negativna sentinel biopsija [11].

U radu Cartera i sar. [12] pozitivni limfni nodusi nađeni su kod tumora prečnika manjih od 10 mm kod oko 20% slučajeva, dok su kod tumora većih od 50 mm nađeni kod oko 70% slučajeva. Merenje veličine tumora kombinovano sa fizičkim pregledom aksile, nije dovoljno precizno za predviđanje metastaza u aksilarne limfne noduse.

Noguchi i sar. [13] našli su da aksilarne metastaze nastaju kod 21% slučajeva sa nepalpabilnim limfnim nodusima (uključujući i one manje od 2 cm) i kod 84% slučajeva sa palpabilnim limfnim nodusima.

Ahlgren i sar. [14] daju podatak o 25% histološki pozitivnih nodusa kod žena sa klinički negativnim limfnim nodusima i tumorima manjim od 2 cm.

Mala incidencija metastaza u limfnim nodusima javlja se kod bolesnica sa malim tumorima. Nažalost, postoji značajna varijabilnost stope aksilarnih metastaza posmatranih od strane Zajedničkog američkog odbora za kancer za T1 karcinome. Sveukupna stopa aksilarnih metastaza kod bolesnica sa T1 karcinomom dojke (< 2,0 cm) kreće se od 18 do 31% [15, 16].

Istražujući zahvaćenost aksilarnih limfnih nodusa kod tumora T1–T3, Grabau i sar. [17] analizom interakcije na seriji od 6 959 bolesnica (stadijum I–III, T1–T3, N0–N1, M0), pokazali su da broj zahvaćenih limfnih nodusa ima uticaja na porast rizika od smrti. Takođe, rizik od smrti zavisi i od toga da li se radi o mikrometastazama (depoziti manji od 2 mm) ili makrometastazama (povećan je u slučaju prisustva makrometastaza).

U vezi sa uticajem na metastaziranje u aksilarne limfne noduse kod (*Ductal Carcinoma In Situ* – DCIS) ≥ 2,5 cm i povezanost metastaziranja sa veličinom tumora, Maffuz i sar. [18], u seriji od 24 bolesnice došli su do rezultata da je incidencija aksilarnih metastaza direktno povezana sa veličinom tumora (od 0% za tumore 2,5–3,5 cm, pa do 28% za tumore 4,6–6 cm). Autori, stoga predlažu mapiranje limfatika za tumore koji su veći od 3,5 cm u prečniku i izvođenje *sentinel* biopsije.

Prateći značaj zahvatanja aksilarnih limfnih nodusa u zavisnosti od veličine primarnog tumora, Suzuma i sar. [19] u

seriji od 1 934 bolesnice sa tumorom T1–T2, izdvojivši 102 nodusa sa metastazama nivoa I–II, došli su do rezultata da je očekivana verovatnoća za tumor ≥ 6 mm, maksimalno zahvatanje šest nodusa nivoa I–II.

Wasuthit i sar. [20], uzimajući u obzir bolesnice mlađe od 60 godina, nizak mamografski denzitet dojke, kategoriju 5 mamograma i tumore veće od 1 cm u prečniku, kao i prisustvo limfovaskularne invazije, došli su do rezultata da je verovatnoća za zahvatanje aksilarnih limfnih nodusa 95%.

Viale i sar. [21] u seriji od 4 351 bolesnice došli su do saznanja da je rizik od zahvatanja aksilarnih limfnih nodusa kod tumora ≤ 1 cm bez patološke vaskularne invazije (PVI) 9,5%, a rizik kod tumora > 2 cm i sa PVI 77,2%.

Proučavajući zahvaćenost aksilarnih limfnih nodusa kod karcinoma dojke Wong i sar. [22] u seriji od 1 415 bolesnica ustanovili su da zahvaćenost limfnih nodusa aksile raste sa veličinom tumora: T1 (14–30%), T2 – 45%, T3 – 57% (gde se procenat odnosi na broj bolesnica, a ne na broj zahvaćenih limfnih nodusa).

Histološki gradus je još jedan važan prediktor zahvatanja aksilarnih limfnih nodusa, relapsa i preživljavanja. Uopšteno gledano, gradus je od strane Programa za nadzor, epidemiologiju i krajnje rezultate (*Surveillance, Epidemiology, and End Results Program* – SEER) definisan u četiri kategorije: gradus I kao dobro diferentovan, gradus II kao umereno diferentovan, gradus III kao loše diferentovan i gradus IV kao anaplastičan ili nediferentovan [23].

Druge studije, takođe, uzimaju histološki gradus kao važan prediktor kod bolesnica sa karcinomom dojke, koji individualno definiše status limfnih nodusa [24–28].

Poput histološkog gradusa tumora, i nuklearni gradus tumora u vidu tumorske anaplazije (ispoljene opet preko gradusa tumora), zajedno sa zahvaćenošću limfnih nodusa, uzima se kao važan prognostički faktor. Prognostičku vrednost nuklearnog gradusa karcinoma dojke dobro su objasnili Black i sar [29], i bili su prvi koji su opisali vezu između prognoze bolesnica sa karcinomom dojke i nuklearne anaplazije (gradus IV). Druga istraživanja pokazuju da je veći nuklearni gradus povezan sa lošijom prognozom i većom zahvaćenošću limfnih nodusa [30–33].

Istražujući zahvaćenost aksilarnih limfnih nodusa kod tumora veličine T1, u seriji od 117 bolesnika, Saiz i sar. [34] našli su 10,3% metastaza u aksilarnim limfnim nodusima. Kod tumora ≤ 0,5 cm nije bilo prisutnih metastaza. Kod karcinoma prečnika 0,6–1,9 cm bilo je 12,9% metastaza u aksilarnim limfnim nodusima. Visok nuklearni gradus korelisao je sa zahvaćenošću limfnih nodusa.

Istražujući prognostičke faktore kod ranog karcinoma dojke Kim i sar. [4] u seriji od 605 bolesnica našli su da je petogodišnje preživljavanje lošije kod bolesnika mlađih od 35 godina, sa pozitivnim limfnim nodusima i visokim nuklearnim gradusom. Takođe, petogodišnje preživljavanje lošije je kod bolesnica sa tumorom prečnika > 1 cm, pozitivnim limfnim nodusima i visokim nuklearnim gradusom [4].

Na našem materijalu i seriji od 900 bolesnica operisanih od karcinoma dojke, sa pregledanih 9 977 limfnih nodusa, pokazali smo da ukoliko postoji zahvaćenost aksilarnih limfnih nodusa, unakrsni odnos (OR) potvrđuje da rizik od zahvatanja aksilarnih limfnih nodusa veći je 1,43 puta ako žena ima tumor dojke veličine T2, nego ako ima T1.

Ukoliko postoji zahvaćenost aksilarnih limfnih nodusa, unakrsni odnos (OR) potvrđuje da rizik od zahvatanja aksilarnih limfnih nodusa veći je 2,77 puta ako žena ima tumor dojke veličine T3, nego ako ima T1, odnosno ukoliko postoji zahvaćenost aksilarnih limfnih nodusa, unakrsni odnos (OR) potvrđuje da rizik od zahvatanja aksilarnih limfnih nodusa veći je 6,62 puta, kod tumora dojke veličine T4, nego kod T1.

Vezano za rizik zahvatanja aksilarnih limfnih nodusa u zavisnosti od histološkog gradusa, rezultati su pokazali da ukoliko postoji zahvaćenost aksilarnih limfnih nodusa, rizik od zahvatanja aksilarnih limfnih nodusa veći je 1,79 puta ukoliko žena ima histološki gradus tumora dojke II nego I, rizik od zahvatanja aksilarnih limfnih nodusa veći je 4,78 puta ukoliko žena ima histološki gradus tumora dojke III nego I.

Rezultati vezani za nuklearni gradus pokazuju da ukoliko postoji zahvaćenost aksilarnih limfnih nodusa, rizik od zahvatanja aksilarnih limfnih nodusa je 1,44 puta veći ukoliko žena ima nuklearni gradus tumora dojke II nego I, a takođe rizik od zahvatanja aksilarnih limfnih nodusa veći je 3,34 puta ukoliko žena ima nuklearni gradus tumora dojke III nego I, odnosno rizik od zahvatanja aksilarnih limfnih nodusa veći je 5,71 puta ukoliko žena ima nuklearni gradus tumora dojke IV nego I.

Zaključak

U radu je potvrđena već poznata povezanost veličine i gradusa tumora sa zahvatanjem aksilarnih limfnih nodusa. Na osnovu dobijenih podataka može se reći da postoji značajna korelacija između veličine tumora (T), nodalnog statusa (N0 *vs*. N+) i histološkog i nuklearnog gradusa, odnosno da zahvatanje aksilarnih limfnih nodusa (broj zahvaćenih nodusa) raste sa porastom veličine tumora, i histološkog i nuklearnog gradusa.

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Prevencija preloma kuka u gerijatrijskoj populaciji – neiskorišćena prilika?

Missed opportunities for prevention of hip fracture in older patients

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Apstrakt

Uvod/cilj. Prevencija posledica osteoporoze postaje sve značajnija. Cilj rada bio je da se odredi prisustvo relevantnih faktora rizika od nastanka pada i preloma, stepen rizika od nastanka preloma, kao i adekvatnost lečenja osteoporoze pre povrede kod bolesnika hospitalizovanih zbog preloma kuka. **Metode.** Ispitivanjem su bila obuhvaćena 342 bolesnika, starosti ≥ 65 godina, koji su zbog akutnog preloma kuka lečeni na Klinici za ortopedsku hirurgiju i traumatologiju Kliničkog centra Srbije u periodu od 12 meseci. Kod svih ispitivanih bolesnika analizirani su faktori rizika od nastanka preloma i pada putem *Fracture Risk Assessment* (FRAX®) algoritma, a bolesnici su razvrstavani u odnosu na nivo rizika od nastanka preloma. **Rezultati.** Prelom kuka nastao je najčešće kod onih bolesnika koji su pripadali grupi sa visokim nivoom rizika (74,2%). Manje od 10% bolesnika je imalo dijagnozu osteoporoze pre povrede, dok je manje od 2% bolesnika lečeno od osteoporoye. Od faktora rizika od pada najzastupljeniji bili su: kognitivno oštećenje (95,3%), oštećenje vida (58,2%), sniženje aktivnosti dnevnog života (51,8%) i depresija (47,1%) **Zaključak.** Rezultati našeg istraživanja jasno ukazuju na nedovoljno prepoznavanje kliničkih faktora rizika od značaja za nastanak preloma i pada na nivou primarne zaštite, na neadekvatno lečenje osteoporoze, te, posledično, izrazito lošu prevenciju preloma kuka u gerijatrijskoj populaciji u našoj sredini. U lečenju starijih bolesnika savetuje se integrisani klinički pristup, koji podrazumeva merenje koštane gustine, kao i obaveznu rutinsku procenu kliničkih faktora rizika od nastanka preloma i pada.

Ključne reči:
osteoporoza; lečenje; stare osobe; kuk, prelomi; faktori rizika; rizik, procena.

Abstract

Background/Aim. Osteoporotic fractures are a major cause of morbidity in the population. Therefore, fracture prevention strategies should be a major concern, and one of the priorities in the primary health care system. The aim of the study was to assess fracture and fall risk factors, and fracture risk level in patients with acute hip fracture, and to evaluate if there had been adequate osteoporosis treatment prior to fracture in this group of patients. **Methods.** Fracture and fall risk factors were assessed in 342 patients, ≥ 65 years old, hospitalized due to acute hip fracture at the Clinic for Orthopedic Surgery and Traumatology, Clinical Centre of Serbia in a 12-month period. Fall risk factors were assessed with the Fracture Risk Assessment (FRAX®) algorithm, and patients were classified in respect to fracture risk level. **Results.** Hip fracture occurred in the majority of the patients in the high risk group (74.2%), where no additional bone mineral density testing was needed. Less than 10% of the patients had a diagnosis of osteoporosis before injury, while less than 2% were treated. Cognitive impairment (95.3%), visual impairment (58.2%), lower index of daily activities (51.8%), and depression (47.1%) were the most frequently observed fall risk factors. **Conclusion.** The results of our investigation reveal insufficient identification of clinical fracture risk factors in the primary care setting, inadequate treatment of osteoporosis and, consequently, ineffective prevention of hip fractures in the geriatric population. The introduction of FRAX® into clinical practice enables more effective acknowledgment of patients with elevated fracture risk, even if bone density measurement is not available. The results of this study have a special significance for everyday clinical practice, because they impose a need for reviewing the existing approaches to osteoporosis prevention, and precise definiment of hip prevention strategies.

Key words:
osteoporosis; therapeutics; aged; hip fractures; risk factors; risk assessment.

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Uvod

Osteoporoza predstavlja najčešće metaboličko oboljenje i rastući problem u populaciji koja stari [1]. Uprkos drastičnim posledicama, osteoporoza se često previđa i potcenjuje, u najvećoj meri zato što predstavlja tiho oboljenje sve dok se ne manifestuje prelomima. Uobičajena mesta osteoporotičnih preloma su kičma, kuk, distalna podlaktica i proksimalni humerus. Preko 8,9 miliona preloma godišnje u svetu nastane kao posledica osteoporoze, od toga više od 4,5 miliona u Americi i Evropi [2]. Oko 50% svih bolesnika koji su imali prelom kuka nikada se ne oporave u potpunosti, dok mortalitet unutar prve godine od nastanka preloma iznosi 20% [3]. Godišnja incidencija preloma kuka kod odraslih osoba na području Beograda u periodu od 1990. do 2000. god. iznosila je 51,7/1 000 00, što je slično incidenciji preloma u Italiji, Francuskoj i Velikoj Britaniji [3, 4].

S obzirom na učestalost i značaj osteoporotičnih preloma, prevencija ovih komplikacija ima sve veći značaj. Mineralna koštana gustina (MKG) smatra se zlatnim standardom za postavljanje dijagnoze osteoporoze. Međutim, mogućnost predviđanja rizika od nastanka preloma merenjem MKG ograničena je zbog niske senzitivnosti ove metode [3, 4]. S obzirom na to da je MKG samo jedan od parametara koji igraju ulogu u nastanku preloma neophodno je dodatno definisanje i preopoznavanje kliničkih faktora rizika koji pojedinačno doprinose nastanku preloma.

Savremeni pristup u lečenju osteoporoze odnosi se na procenu 10-godišnje verovatnoće rizika od nastanka velikih osteoporotičnih preloma (kičma, kuk, podlaktica, nadlaktica) i kuka primenom *Fracture Risk Assessment* (FRAX®), kliničkog intstrumenta definisanog od strane Centra za metabolička oboljenja kostiju Svetske zdravstvene organizacije, Sheffield, Velika Britanija [4]. Ovaj instrument objedinjuje značaj pojedinih faktora rizika od nastanka preloma uz ili bez podataka o MKG vrata butne kosti. Treba naglasiti da desetogodišnji rizik od nastanka preloma predstavlja samo smernicu za donošenje odluke o lečenju, i da svaka odluka mora biti individualno prilagođena [4–6]. Integrisanje rezultata FRAX®-a u odluku o načinu lečenja definisano je preoporukama različitih nacionalnih stručnih organizacija. U Velikoj Britaniji kategorizacija rizika od nastanka preloma, kao i preporuke za lečenje, vrše se u skladu sa odlukama *National Osteoporosis Guideline Group* (NOGG) [7]. Rizik od nastanka preloma, prema ovom modelu, može se klasifikovati kao nizak, srednji ili visoki. U skladu sa tim, bolesnicima sa visokim rizikom može se savetovati medikamentno lečenje osteoporoze bez dodatnog merenja MKG [7]. Nasuprot tome, kod bolesnika kod kojih je rizik nizak, odluka o nelečenju može se doneti i bez merenja MKG. Ponovna procena rizika kod ovakvih bolesnika savetuje se nakon pet godina. Kod bolesnika sa srednjim nivoom rizika savetuje se dopunsko merenje koštane gostine vrata butne kosti i ponovna procena nivoa rizika[7]. Primena ovakvog pragmatičnog modela naročito je pogodna zbog ograničenih kapaciteta za merenje MKG [8, 9].

Paralelno sa kliničkim faktorima koji utiču na kvalitet kostiju i doprinose riziku od nastanka preloma, padovi predstavljaju zaseban problem u etiologiji preloma [8, 9]. Parametri koji se odnose na rizik od nastanka pada u ovom trenutku nisu integrisani u FRAX® , što se i smatra njegovim glavnim nedostatkom. Prema podacima iz literature 30% osoba starijih od 60 god. i 50% onih starijih od 80 god. padne najmanje jednom tokom godine [10, 11]. Pored toga, poznato je da je najmanje 95% preloma kuka uzrokovano padom [12].

Cilj rada bio je da se kod bolesnika hospitalizovanih zbog akutnog preloma kuka odredi stepen rizika od nastanka preloma u odnosu na prisustvo relevantnih faktora rizika, prisustvo relevantnih faktora rizika od nastanka pada, kao i adekvatnost lečenja osteoporoze pre zadobijenog preloma kuka.

Metode

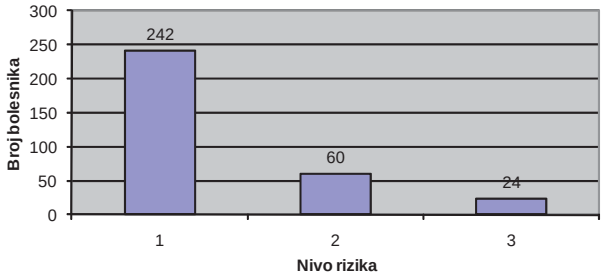
Ispitivanjem je bilo obuhvaćeno 342 bolesnika starijih ≥ 65 godina, hospitalizovanih u Klinici za ortopedsku hirurgiju Kliničkog centra Srbije zbog akutnog preloma kuka zadobijenog na malu traumu u periodu od 1. 3. 2009. do 1. 3. 2010. godine. Neposredno po prijemu, putem posebnog epidemiološkog upitnika i adekvatnih kliničkih testova, određivani su faktori rizika od nastanka preloma i pada. Relevantni podaci za procenu rizika od nastanka preloma – pol, životno doba, telesna visina i masa, prethodni prelomi, prelomi kuka kod roditelja, terapija kortikosteroidima, aktuelno pušenje, konzumiranje ≥ 1 jedinice alkohola dnevno, postojanje reumatoidnog artritisa i drugih sekundarnih uzroka osteoporoze obrađeni su putem FRAX® algoritma (model za Veliku Britaniju).[7] Vrednosti MKG i ukoliko su bile poznate izostavljene su iz FRAX®-a. Putem ovog kliničkog instrumenta, a na osnovu smernica NOGG-a, bolesnici su bili razvrstani u tri nivoa rizika (nisko-, srednje-, i visokorizični) od nastanka velikih osteoporotičnih preloma, kao i preloma kuka. Dodatno je ispitano prisutvo pojedinih relevantnih faktora rizika od nastanka pada na osnovu smernica Svetske zdravstvene organizacije [8]. U tom smislu, ispitivani su uslovi života, postojanje padova tokom prethodne godine, hod sa pomagalom, sniženje indeksa aktivnosti dnevnog života, prisustvo kognitivnog oštećenja, prisustvo depresije, prisustvo vaskularnih oboljenja, hronične opstruktivne bolesti pluća, artritisa, neurološkog oboljenja, uzimanje četiri ili više vrsta lekova, kao i oštećenje vida. Procena aktivnosti dnevnog života pre preloma vršena je primenom Katzovog indeksa aktivnosti dnevnog života [13]. Procena prisustva depresije vršena je putem kratke forme upitnika za depresiju u gerijatrijskoj populaciji [14], dok je kognitivni status procenjivan primenom kratkog upitinika za procenu mentalnog statusa (*Mini Mental Test*) [15].

U statističkoj analizi podataka korišćene su metode deskriptivne i inferencijalne statistike. U cilju deskripcije, korišćeni su aritmetička sredina, medijana, standardna devijacija, i relativni brojevi. Testovi statističke značajnosti (χ^2 test i Fišerov test) korišćeni su za analiziranje razlika između grupa po kategorijalnim varijablama (prikazani kao broj i procenat bolesnika). Korišćen je nivo značajnosti $p < 0,05$. Obrada podataka vršena je pomoću SPSS 8.0. (SPSS Inc, Chicago, IL, USA) programskog statističkog paketa.

Ispitivanje je sprovedeno u skladu sa Helsinškom deklaracijom [16]. Za ispitivanje je dobijena saglasnost Etičkog komiteta Medicinskog Fakulteta u Beogradu.

Rezultati

Od 342 operisana bolesnika prosečne starosti 78,2 ± 7,4 (65–96) god uključena u ispitivanje, 275 (19,6%) bile su žene, a 67 (80,4%) muškarci. Podaci relevantni za FRAX® dobijeni su za 326 (95,3%) bolesnika, dok su faktori rizika relevantni za nastanak pada dobijeni za sve ispitanike. Putem FRAX® algoritma utvrđeno je da je nizak nivo rizika postojao kod 24 (7,4%) bolesnika, srednji kod 60 (18,4%), dok je visok nivo rizika postojao kod 242 (74,2%) bolesnika (slika 1). Visok rizik



Sl. 1 – Rizik od nastanka preloma kod ispitivanih bolesnika prema *Fracture Risk Assessment* (FRAX®) algoritmu: 1 visok rizik; 2 – srednji rizik; 3 – nizak rizik

od nastanka preloma u značajno većem broju bio je prisutan kod žena nego kod muškarca ($\chi^2 = 95,569$; DF = 2; $p < 0,001$). Poređenjem bolesnika koji su imali 85 ili više godina sa bolesnicima mlađim od 85 nije utvrđena razlika u odnosu na nivo rizika od nastanka preloma ($\chi^2 = 0,418$, DF = 1, $p = 0,811$). Takođe, utvrđeno je da je kod 109 (32,4%) bolesnika prelomu kuka prethodio neki od osteoporotičnih preloma, i da se kod 25 (7,3%) bolesnika radilo o drugom prelomu kuka.

U ispitanom uzorku, kod 21 (6,3%) bolesnika pre povrede postojala je dijagnoza osteoporoze, pri čemu su samo tri (0,9%) bolesnika lečena adekvatnom terapijom, dok je dodatnih šest (1,8%) bolesnika uzimalo samo kalcijum i vitamin D.

Prisustvo više relevantnih podataka za nastanak pada među bolesnicima prikazano je u tabeli 1.

Diskusija

Rezultati našeg istraživanja ukazuju na to da je procenat bolesnika sa dijagnozom i lečenjem osteoporoze pre nastalog preloma kuka u ispitanoj populaciji bio izrazito nizak. Kod svega 6,3% bolesnika postojala je dijagnoza osteoporoze, dok je samo 0,9% adekvatno lečeno. Podaci iz literature koji se odnose na istu problematiku ukazuju na značajno bolju, iako i dalje nezadovoljavajuću, prevenciju preloma u drugim zemljama. Smith i sar. [17] prikazali su da je među bolesnicima sa prelomom kuka ili ručnog zgloba u Australiji 34% imalo neku vrstu medicinske informacije o osteoporozi, da je kod 32% rađena osteodenzitometrija, dok je 39% lečeno od osteoporoze. Najveći broj bolesnika lečen je samo kalcijumskim suplementima. Satomi i sar. [18] ukazuju na to da je od 123 bolesnika sa prelomom kuka u Brazilu 12,3% već imalo dijagnozu osteoporoze, pri čemu je 5,83% bolesnika lečeno medikamentozno [18].

Rezultati našeg istraživanja pokazuju da je do preloma kuka najčešće dolazilo kod bolesnika koji su pripadali grupi sa visokim nivoom rizika (74,2%). Kod te grupe bolesnika nije bilo neophodno dodatno merenje MKG, već je medikamentno lečenje osteoporoze moglo biti započeto samo na osnovu prisutnih kliničkih faktora rizika analiziranih primenom FRAX®-a. Viši nivo rizika od nastanka preloma kod žena nego kod muškaraca, nađen u našem uzorku, potvrđen je i u drugim radovima [19].

Poznato je da bolesnici koji su već imali neki prelom usled osteoporoze imaju pet puta veći rizik od nastanka novog preloma u poređenju sa populacijom bez prethodne dijagnoze osteoporoze ili bez prethodnog preloma[20]. Takođe, zna se da adekvatna terapija može smanjiti rizik od nastanka preloma za 40–60% [15, 16]. Naše ispitivanje pokazalo je da je mogućnost da se pravovremeno interveniše sigurno propuštena kod preko trećine bolesnika u našem uzorku, kod kojih je prelomu kuka prethodio neki drugi osteoporotični prelom. Podaci iz literature potvrđuju problem nedovoljno obuhvatne prevencije sekundarnih preloma [21–23].

Analizom naše grupe bolesnika dodatno smo utvrdili veliku zastupljenost faktora rizika od nastanka pada. Više od trećine naših ispitanika živelo je samo, imalo više od jednog pada tokom prethodne godine, uzimalo više od četiri leka,

Tabela 1

Faktori rizika od nastanka pada

Faktori rizika	Broj bolesnika, n (%)
Živi sam	116 (34,1)
≥ 1 pad tokom prethodne godine	127 (37,9)
Hod sa pomagalom	107 (31,6)
Sniženje nivoa aktivnosti dnevnog života	177 (51,8)
Kognitivno oštećenje	321 (95.3)
Depresija	161 (47,1)
Vaskularna oboljenja	61(18,0)
Hronična opstruktivna bolest pluća	22 (6,5)
Artritis	8 (2,4)
Neurološko oboljenje (moždani insult sa neurološkim deficitom/Parkinsonova bolest)	45 (13,16)
≥ 4 leka	124 (36,3)
Oštećenje vida	199 (58,2)

hodalo sa pomagalom i bilo depresivno, dok je preko polovine ispitanika imalo snižen nivo indeksa aktivnosti dnevnog života i oštećenje vida. Preko 90% ispitanika imalo je neki stepen kognitivnog oštećenja.

Osnovno ograničenje našeg istraživanja odnosi se na činjenicu da je za analizu faktora rizika od nastanka preloma korišćen FRAX® model za Veliku Britaniju. Za sada postoji samo 26 modela FRAX®-a specifičnih za određene zemlje, među kojima nije Srbija. Između ostalog, modeli za određene zemlje nastaju na osnovu specifičnih epidemioloških podataka vezanih za incidenciju osteoporotičnih preloma kuka. Odlučili smo se za model Velike Britanije, s obzirom na sličnu incidenciju preloma kuka u Srbiji i Velikoj Britaniji[24]. Neophodan je razvoj nacionalnog FRAX® modela kalibriranog prema relevantnim epidemiološkim podacima koji se odnose na incidenciju preloma i stopu smrtnosti u našoj zemlji, kako bi se još preciznije procenio rizik od nastanka preloma u rizičnim grupama bolesnika. Bez obzira na ograničenje koje smo izneli, smatramo da ovaj rad ima višestruki značaj i težinu za našu kliničku praksu. Uprkos izvesnom broju radova koji se bave problemima lečenja preloma kuka u domaćoj literaturi [25, 26], ovo je prvi rad koji se bavi analizom faktora rizika od nastanka preloma kuka u gerijatrijskoj populaciji upotrebom FRAX®-a kod nas. Dodatno, naš rad je na velikom broju bolesnika potvrdio efikasnost FRAX® instrumenta za procenu rizika od nastanka preloma kuka i bez podataka o MKG, čije merenje na našim prostorima često predstavlja logistički problem. Kao takav, on skreće pažnju kliničara na mogućnosti primene ovog jednostavnog kliničkog instrumenta u lečenju bolesnika sa osteoporozom i nameće potrebu za jasno definisanje strategije za prevenciju preloma. Rezultati našeg rada takođe nedvosmisleno pokazuju neophodnost strategije za prepoznavanje i sniženje rizika od nastanka pada u rizičnim grupama bolesnika.

Od budućih istraživanja, između ostalog, očekuje se i da daju odgovor na pitanje u kojoj meri se ispitivanje i lečenje osteoporoze vrši kod starijih bolesnika hospitalizovanih zbog prelomom kuka.

Zaključak

Rezultati našeg istraživanja jasno ukazuju na nedovoljno prepoznavanje kliničkih faktora rizika od značaja za nastanak preloma i pada na nivou primarne zaštite, na neadekvatno lečenje osteoporoze, te, posledično, izrazito lošu prevenciju preloma kuka u gerijatrijskoj populaciji u našoj sredini. Uvođenjem FRAX® kliničkog instrumenta omogućeno je prepoznavanje bolesnika sa povišenim rizikom od nastanka preloma, precizno definisanje stepena rizika, poboljšanje percepcije rizika, kome je izložen od strane samog bolesnika, kao i započinjanje odgovarajuće terapije kod bolesnika izloženih visokom riziku, čak i u uslovima u kojima merenje MKG nije dostupno. U lečenju starijih bolesnika savetuje se integrisani klinički pristup, koji podrazumeva merenje koštane gustine, kao i obaveznu rutinsku procenu kliničkih faktora rizika od nastanka preloma i pada.

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ORIGINAL ARTICLE

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Procalcitonin and BISAP score versus C-reactive protein and APACHE II score in early assessment of severity and outcome of acute pancreatitis

Prokalcitonin i BISAP skor naspram C-reaktivnog proteina i APACHE II skora u ranoj proceni težine i ishoda akutnog pankreatitisa

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Abstract

Background/Aim. Early assessment of severity and continuous monitoring of patients are the key factors for adequate treatment of acute pancreatitis (AP). The aim of this study was to determine the value of procalcitonin (PCT) and Bedside Index for Severity in Acute Pancreatitis (BISAP) scoring system as prognostic markers in early stages of AP with comparison to other established indicators such as C-reactive protein (CRP) and Acute Physiology and Chronic Health Evaluation (APACHE) II score. **Methods.** This prospective study included 51 patients (29 with severe AP). In the first 24 h of admission in all patients the APACHE II score and BISAP score, CRP and PCT serum concentrations were determined. The values of PCT serum concentrations and BISAP score were compared with values of CRP serum concentrations and APACHE II score, in relation to the severity and outcome of the disease. **Results.** Values of PCT, CRP, BISAP score and APACHE II score, measured at 24 h of admission, were significantly elevated in patients with severe form of the disease. In predicting severity of AP at 24 h of admission, sensitivity and specificity of the BISAP score were 74% and 59%, respectively, APACHE II score 89% and 69%, respectively, CRP 75% and 86%, respectively, and PCT 86% and 63%, respectively. It was found that PCT is highly significant predictor of the disease outcome ($p < 0,001$). **Conclusion.** In early assessment of AP severity, PCT has better predictive value than CRP, and similar to the APACHE II score. APACHE II score is a stronger predictor of the disease severity than BISAP score. PCT is a good predictor of AP outcome.

Key words:
pancreatitis, acute necrotizing; severity of illness index; prognosis; apache; treatment outcome.

Apstrakt

Uvod/Cilj. Rana procena težine i kontinuirano praćenje bolesnika sa akutnim pankreatitisom (AP) osnovni su preduslovi za adekvatno lečenje. Cilj rada bio je da se odredi značaj prokalcitonina (PCT) i *Bedside Index for Severity in Acute Pancreatitis* (BISAP) skoring sistema kao prognostičkih parametara u ranoj fazi AP u poređenju sa ostalim poznatim indikatorima kao što su C-reaktivni protein (CRP) i *Acute Physiology and Chronic Health Evaluation* (APACHE II) *score*. **Metode.** Ova prospektivna studija obuhvatila je 51 bolesnika (29 sa teškim oblikom AP). U prva 24 sata od prijema kod svih bolesnika određen je APACHE II skor, BISAP skor, i koncentracije CRP i PCT u serumu. Vrednosti koncentracija PCT u serumu i vrednosti BISAP skora upoređivane su sa vrednostima koncentracija CRP u serumu i APACHE II skora, u odnosu na težinu i ishod bolesti. **Rezultati.** Vrednosti PCT, CRP, BISAP i APACHE II skora, merene u prva 24 sata od prijema u bolnicu, bile su statistički značajno povišene kod bolesnika sa teškim oblikom bolesti. U proceni težine AP u prva 24 sata od prijema, utvrđene su vrednosti senzitivnosti i specifičnosti za BISAP skor (74%; 59%), APACHE II skor (89%; 69%), CRP (75%; 86%) i PCT (86%; 63%). Nađeno je da je PCT visokoznačajan prediktor ishoda bolesti ($p < 0,001$) **Zaključak.** U ranoj proceni težine AP, PCT je bolji indikator od CRP i sličan je APACHE II skoru. APACHE II skor je jači prediktor težine bolesti od BISAP skora. PCT je dobar prediktor ishoda AP.

Ključne reči:
pankreatitis, akutni, nekrotizujući; bolest, indeks težine; prognoza; apache; lečenje, ishod.

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Introduction

"Acute pancreatitis is the most terrible of all the calamities that occur in connection to the abdominal viscera. The suddenness of its onset, the illimitable agony which accompanies it, and the mortality attendant upon it, render it the most formidable of catastrophes." (Moynihan, 1925) [1]

This quotation still remains true because AP is unpredictable disease, while severity and outcome is difficult to predict with relatively few effective therapeutic options. The mortality rate of severe AP (SAP) is about 25%–50%, mainly due to multiple organ failure (MOF) and infection of the necrosis [2, 3]. Early identification of patients with SAP and their continuous monitoring are essential for adequate and timely treatment in order to prevent possible complications.

Several biochemical markers [4, 5], radiological imaging procedures [6–8], and multiple clinical and biochemical scores [9–12] have been used to assess severity and outcome of AP. An ideal prognostic method should be simple, inexpensive, routinely available and highly accurate. Such a method is not available yet.

Procalcitonin (PCT) is a 116-amino acids propeptide of calcitonin who has no known hormonal activity, and can be detected in high concentrations in serum during severe bacterial or fungal but not viral infections [13–15]. It is synthesized and secreted by the inflammatory and hepatic cells in response to proinflammatory mediators. PCT was introduced as an early marker of the systemic inflammatory response, sepsis, and MOF. Further, increased serum concentration levels of PCT have been suggested to be a reliable early predictor of a severe outcome and infected pancreatic necrosis [15–18].

In a recent multicentric cohort study a new prognostic scoring system, so-called Bedside Index for Severity in Acute Pancreatitis (BISAP), for prediction of mortality of AP was proposed [19]. Using blood urea nitrogen (BUN) level > 25 mg/dL, impaired mental status, systemic inflamatory response syndrome (SIRS), age > 60 years and pleural effusion in patients with AP, investigators were able to stratify patients within the first 24 hours of hospitalisation into distinct risk groups for in hospital mortality. These authors [19] presented BISAP score as an accurate scoring system in prediction of the outcome of AP, such as Acute Physiology and Chronic Health Evaluation (APACHE) II score.

The aim of this study was to assess the value of serum PCT concentrations and value of BISAP score as prognostic markers of severity of AP in early stages of AP in comparison with CRP and APACHE II score, as well as to estimate the value of PCT and BISAP score as predictors of AP outcome.

Methods

The study included of 51 consecutive patients with AP admitted to the Clinic for Abdominal and Endocrine Surgery, Military Medical Academy, Belgrade, Serbia, over a 14-month period (from June 2009 to September 2010). In all patients, the diagnosis of AP was established in the first three hours of admission by the presence of typical clinical symptoms for AP, serum concentrations of amylase and/or lipase above three times from the upper limit, and/or radiological evidence compatible with AP. The patients with confirmed AP were admitted to our hospital as primary or secondary referrals within 48 h after the onset of the symptoms and prospectively analyzed. The clinical course of patients was followed prospectively until discharge or death, with retrospective categorization into patients with mild AP (MAP) and severe form of the disease according to the Atlanta classification [20]. Ultrasonography was performed within 12 h of admission and contrast enhanced computed tomographic (CT) scan was performed according to the United Kingdom guidelines for the management of AP [21]. Serum CRP concentration levels were measured using a quantitatively immunoassay method (Cardio Phase, hsCRP BN2, Siemens, Germany) on admission, and 24 h and 48 h after admission. Serum levels of CRP determined at 24 h of admission with the cut-off value of 120 mg/L were accepted as an indicator for severe inflammation, as reported in previous studies [13, 22, 23]. PCT serum concentration levels were measured with a commercial quantitative assay (PCT sensitive, Kryptor, Brahms, Berlin, Germany) on admission, at 24 h and 48 h after admission, at the 8th and 10th hospital days and one more time in the 4th week of the disease. Serum concentrations of PCT measured at 24 h of admission were included in this study. In this study the value of APACHE II score calculated at 24 h of admission with the cut-off level of 8 and more was an accepted level indicator for severe inflammation, as reported in previous studies [20, 22, 24]. The BISAP score was calculated at 24 h of admission using BUN level > 25 mg/dL, impaired mental status, Systemic Inflammcetory Responsed Syndrome (SIRS), age > 60 years and pleural effusion (on chest radiography or CT) [25, 26]. Altered mental status was defined as any record of disorientation, lethargy somnolence, coma or stupor in the medical record [27]. The SIRS [28, 29] was defined by the presence of 2 ≥ of the following criteria: pulse > 90 beats/min; respirations > 20/min or PaCO2 < 32 mm Hg; body temperature > 38°C or < 36°C; white blood cells (WBC) count >12 000 or < 4000 cells/mm3 or >10% immature neutrophils (bands). Each point on the BISAP score worth 1 point [19,30], as presented in Table 1. The values of APACHE II score and BISAP score calculated at 24 h of admission were included in this study. Statistical analysis was performed using the SPSS software (Statistical package for the social sciences version 15.0, Chicago, IL, USA). The patients were divided into two groups according to severity and the outcome. Receiver operating characteristic (ROC) curves and the respective areas under the curves (AUC) were calculated. The diagnostic performances of the different parameters were further assessed by calculating sensitivity and specificity. Mann-Whitney U-test was used to test significance between the two groups. Z-test and Chi-square test were used to assess the value of the respective parameters as indicators of the disease severity and outcome. Z-test was further used to test differences between BISAP score and APACHE II score in early prediction of the AP severity. The results were expressed as median followed by the range, and mean followed by standard deviation (SD). Probability values less than 0.05 were considered as statistically significant, and probability values less than 0.001 were considered as highly statistically significant.

Table 1

The Bedside Index for Severity in Acute Pancreatitis (BISAP) scoring system [19, 30]

Blood urea nitrogen >25 (mg/dL)
Impaired mental status disorientation, lethargy somnolence, coma or stupor
SIRS (Systemic Inflammatory Response Syndrome)
Age > 60 years
Pleural effusion (on chest radiography or computed tomography)

- Each point on the BISAP score worth 1 point
Observed mortality risk with an increasing number of points: [30]
- 0 point: mortality rate of 0.1%
- 1 point: mortality rate of 0.4%
- 2 points: mortality rate of 1.6%
- 3 points: mortality rate of 3.6%
- 4 points: mortality rate of 7.4%
- 5 points: mortality rate of 9.5%

Results

A total of 51 patients, 34 (66.7%) males and 17 (33.3%) females, with the median age of 61 years (range 19–83) were included. Thirty-five patients (69%) were admitted within 0–12 h of symptoms onset, 5 (10%) within 12–24 h and 11 (21%) of patients within 24–48 h of symptom onset. Etiology was biliary in 28 (55%), alcoholic in 11 (21%), hyperlipidemia in 6 (12%), *post* endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis in 1 (2%), pancreatic tumor in 1 (2%) and of unknown cause in 4 (8%) patients. The values of the prognostic markers at 24 h of admission are listed in Table 2.

Twenty-two (43%) patients fully recovered and were classified into the group with MAP. Twenty-nine (57%) patients developed significant complications and were classified in the group with severe form of the disease. Seventeen of 29 patients with SAP had local complications. All patients with SAP had an organ failure of one or more organ systems during hospitalization. Overall mortality rate was 18% (9 patients), and 31% (9 patients) was in patients with SAP. Four patients died in the first week as a result of MOF, and the remaining 5 patients developed an organ failure (one or more organ systems) in addition to local complications.

The APACHE II scores calculated at 24 h of admission, and serum concentration of CRP and PCT values measured at 24 hours of admission were highly significantly higher in patients with SAP than in patients with MAD ($p < 0.001$). The BISAP scores calculated at 24 h of admission were significantly higher in the patients with SAP than those with mild attacks ($p = 0.008$, $Z = -2.668$). ROC curves for the observed values of BISAP and APACHE II score at 24 h of admission are shown in Figure 1, and sensitivity and specificity for the respective values are presented in Table 3.

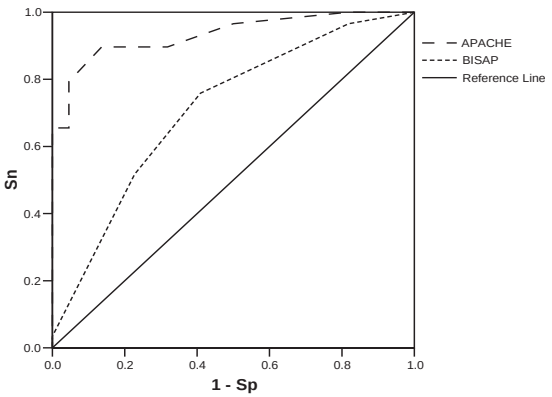

Fig. 1 – ROC curves for the BISAP and APACHE II score calculated at 24 h of admission in patients with acute pancreatitis

ROC – receiver operating characteristic, APACHE II – Acute Physiology and Chronic Health Evaluation II, Sn – Sensitivity; 1-Sp – Specificity, BISAP – Bedside Index for Severity in Acute Pancreatitis

Table 2

The values of the prognostic markers of acute pancreatitis (AP) at 24 h of admission

Parameters	AP	N	Mean	Median	Minimum	Maximum	Range	SD
APACHE II score [a]	Severe	29	15.79	16.00	7	23	16	4.701
	Mild	22	7.95	7.50	6	14	8	1.838
	Total	51	12.41	10.00	6	23	17	5.401
C-reactive protein (mg/L) [a]	Severe	29	161.45	160.00	67	332	265	63.138
	Mild	22	74.64	75.00	13	166	153	44.841
	Total	51	124.00	112.00	13	332	319	70.445
Procalcitonin (ng/mL) [a, b]	Severe	29	2.5072	0.7500	0.09	34.66	34.57	6.73732
	Mild	22	0.2600	0.2250	0.05	0.87	0.82	0.20281
	Total	51	1.5378	0.3600	0.05	34.66	34.61	5.16721
BISAP score [c]	Severe	29	3.2759	4.0000	1.00	5.00	4.00	0.95978
	Mild	22	2.4545	2.0000	1.00	4.00	3.00	1.05683
	Total	51	2.9216	3.0000	1.00	5.00	4.00	1.07412

[a] Mann-Whitney U test, $p < 0.001$; [b] Chi-square test, $p < 0.001$; [c] Z-test, $p = 0.008$.
N – number of patients, SD – standard deviation, APACHE II – Acute physiology and chronic health evaluation II
BISAP – Bedside Index for Severity in Acute Pancreatitis

Table 3

Ability of prognostic markers measured at 24 h of admission to predict acute pancreatitis (AP) severity

Test result variable(s)	AUC	SE	*p* value	Asymptotic 95% Confidence Interval		Cut off	Sensitivity	Specificity
				Lower Bound	Upper Bound			
APACHE II score	0.933	0.034	0.000	0.867	1.000	8	0.89	0.69
C-reactive protein	0.876	0.048	0.000	0.783	0.969	120 mg/L	0.75	0.86
Procalcitonin	0.830	0.055	0.000	0.721	0.939	0.25 ng/mL	0.86	0.63
BISAP score	0.710	0.074	0.011	0.565	0.855	3	0.74	0.59

AUC – Area under curve; SE – standard error, APACHE II – Acute Physiology and Chronic Health Evaluation II, BISAP – Bedside Index for Severity in Acute Pancreatitis

In testing differences between the BISAP score and APACHE II score (difference between AUC of respective parameters), and their strengths to predict a severe form of AP with accuracy, APACHE II score was significantly stronger predictor of disease severity than BISAP score (Table 4).

The values distribution of APACHE II score, BISAP score, CRP and PCT noted at 24 h of admission in survivors and nonsurvivos are presented in Figure 2.

Table 4

Differences in the strenghts of respective parameters to predict severe form of acute pancreatitis

Parameters	CRP	PCT	BISAP score
APACHE II score	Z = 0.969; *p* = 0.332	Z = 0.830; *p* = 0.111	Z=2.738; *p* = 0.006
C-reactive protein		Z = 0.630; *p* = 0.528	Z=1.882; *p* = 0.059
Procalcitonin			Z=1.302; *p* = 0.193

Z – Z-test, APACHE II – Acute Physiology and Chronic Health Evaluation II score; BISAP – Bedside Index for Severity in Acute Pancreatitis

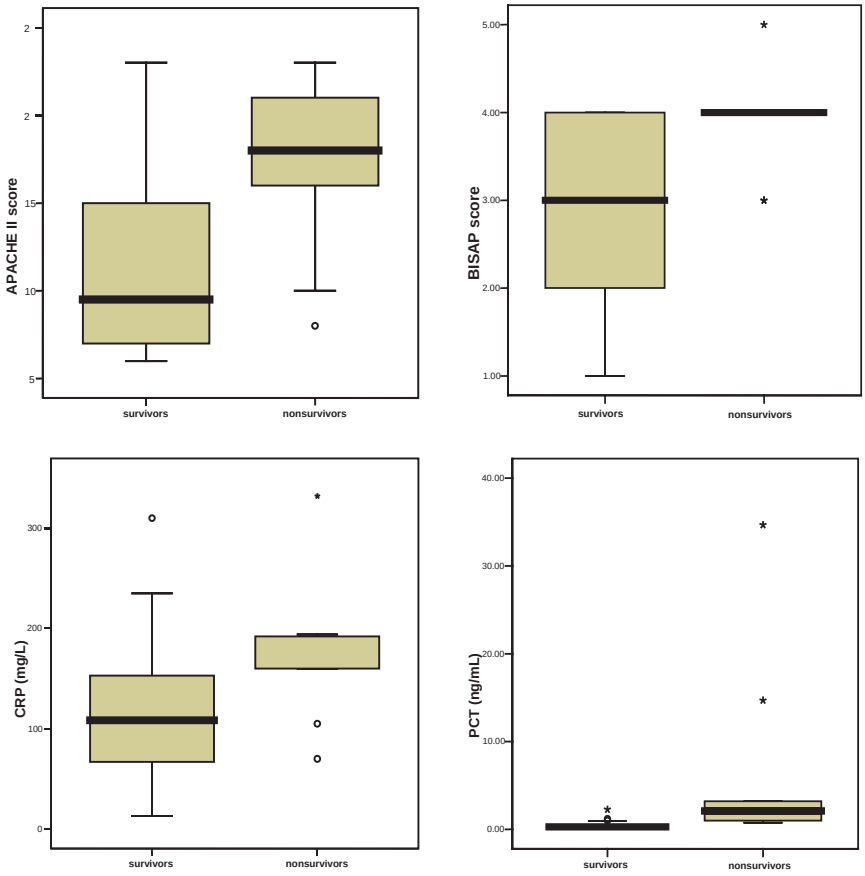

Fig. 2 – Distribution of values of APACHE II score, BISAP score, C – reactive protein, (CRP) and procalcitonin (PCT) noted at 24 h of admission in survivors and nonsurvivos

APACHE II – Acute Physiology and Chronic Health Evaluation II; BISAP – Bedside Index for Severity in Acute Pancreatitis

Between survivors and nonsurvivors there was a significant difference in APACHE II scores (Chi-square=9.222, p = 0.002; Z=-2.891, p = 0.004), BISAP scores (Z=-2.975, p = 0.003) and serum values of CRP (Chi-square=6.317, p = 0.012; Z=-2.434, p = 0.015), and a highly significant difference in serum concentrations of PCT (Chi-square=23.592, p < 0.001; Z=-4.177, p < 0.001) registered in 24 h of admission.

In serial measurements of serum concentrations of PCT it was registered that the most patients had maximal serum values of PCT noted in the first few days of hospitalization. The highest measured concentration values of PCT during hospitalization were significantly higher in nonsurvivors than survivors (Chi-square 33.157; p < 0.001).

Discussion

Early assessment of AP severity is essential for adequate and timely treatment. Moreover, it helps in reducing the mortality rate and can help in preventing numerous complications during the course of the disease. The scoring systems and biochemical markers which are being used for assessment of severity are also helpful for continuous monitoring of patients with AP. Although evaluation of AP severity demands a lot of procedures which are usually expensive, it can indirectly reduce a duration of hospital stay and improve cost benefit of the treatment. In this study, we investigated the value of PCT and BISAP score for prediction of severity and outcome in patients with AP. The predictive values were compared to the traditional biochemical marker and scoring system rutinely used in clinical practice, such as CRP and APACHE II score.

The APACHE II severity of the disease scoring system can be performed at admission and daily to help in identifying patients with SAP [22, 24, 31]. A variety of reports have correlated a higher APACHE II score at admission and during the first 72 h with a severe form of the disease and higher mortality rate. The sensitivity, specificity, as well as positive and negative predictive values ranges between 65%–81%, 77%–91%, 23%–69% and 86%–99%, respectively, have been reported [22, 32, 33]. Our results are similar to other studies. Agarwal et al. [34] reported that one of the potential weaknesses of APACHE II score is the fact that in patients older than 65 years there is a higher possibility of a false-positive score. We found that APACHE II score was highly significantly higher in patients with SAP than in patients with MAP. Also, APACHE II score in our study was significantly higher in nonsurvivors than survovors noted at 24 h of admission.

In the mid-1980s, several studies showed that the hepatic production of CRP was increased after any type of inflammation, and subsequently the protein was proposed as a prognostic factor in AP [2, 5, 7, 13]. Several investigators evaluated this marker as a predictor for severity when it was measured on admission, and in 24, 48 or 72 h after admission, and employed variable cut-off levels ranged between 110 mg/L and 150 mg/L [13]. With the CRP cut-off value of 115 mg/L measured at 24 h after admission Chen et al [35] reported the sensitivity of 44% and specificity of 96% in prediction of severity of AP. Leser et al. [36] reported the sensitivity and specificity rate of 67% and 79% for CRP as a predictor of severity of AP measured in 24/48 h after admission with the cut-off value of 100 mg/L. Just a few reports evaluated value of CRP as a predictor of severity of AP at 24 h of admission with the cut-off value of 120 mg/L [37, 38], but without exactly noted time of onset of symptoms or noted values of sensitivity and specificity. A possible flaw of this marker is the fact that it reaches its peak only after 36–72 h after admission, and the results of this test may not be entirely reliable at admission in assessing the severity of disease [39, 40]. As compared with other studies, we found a high sensitivity, but lower specificity in our research. Such finding could be a result of later appearance of the peak values. In our study serum concentration of CRP was highly significantly higher in patients with SAP, and significantly higher in nonsurvivors than survivors, registered at 24 h of admission.

The actual pathophysiologic role of PCT is still under investigation, and it was assumed that PCT might be also an acute phase protein [40]. In SIRS, regardless of the cause, the first released cytokines are tissue necrosis factor-alpha (TNF-a) and interleukin (IL)-1. Under their influence, the production of other proinflammatory cytokines such as IL-6, IL-8 and interferon gamma starts. These cytokines, especially IL-6, stimulate the release of CRP and PCT [41–43]. This is an indirect way of excretion, while the release of PCT is primarly induced *via* microbial toxins (*eg* endotoxin) [44]. Those various stimuli increase gene expression, which is responsible for secretion of PCT, and constitutive release of PCT from all parenchymal tissues and differentiated cell types throughout the body, including the liver, kidney, adiposities and muscle [45]. Serum concentrations of PCT was evaluated for its utility as predictor of severity and outcome of the AP in several studies [17, 46–51]. The predictive value of PCT in our study was comparable to the results of Kylanapa-Back et al. [17]. In the study of these investigators its sensitivity and specificity were 92% and 84%, respectively, with the cut-off value of 0.5 ng/mL. In our study these values were 86% and 63%, but with much lower cut-off value, such as 0.25 ng/mL. Pindak et al. [48] found that at 12 h after admission value of PCT was better than value of CRP in predicting the course and fatal outcome of the disease. In our study, the concentrations of PCT measured at 24 h of admission were highly significantly higher in nonsurvivors than survivors. Also, PCT levels measured at 24 h of admission were highly significantly higher in patients with SAP than in patients with MAP. While PCT was an excellent predictor of disease's course and fatal outcome, the serum levels of CRP measured at 24 h of admission were good predictor of disease’s course but not so good in predicting fatal outcome in AP. Confirmation for the fact that elevated serum concentrations of PCT can be found in acute inflammation, not only in infectious conditions, is that the maximal recorded PCT values were in the first few days of hospitalization in the most of patients, when there was relatively small possibility for pancreatic infection.

The most commonly utilised prediction scoring system for clinical studies on AP is APACHE II score. For calculating

the APACHE II score it requires the collection of a large number of parameters. An optimal scoring system for predicting severity and outcome of AP should be simple, accurate and able to be calculated in the first 24 h of hospitalization. With the usage of population-based data researchers from the United States developed and presented BISAP score, as a very simple and easy to use [19]. In addition, they cited that each of the parameters in BISAP score can be easily obtained early in the course of hospital admission. In the study of these authors there was no significant difference in the predictive accuracy between the BISAP score and the APACHE II score; in subgroup analysis, the BISAP score was effective in predicting mortality rates in patients without the evidence of early organ failure, and BISAP score was able to achieve a similar level of predictive accuracy to the more complex APACHE II score, with far fewer variables. We found that the APACHE II score was a better predictor of AP severity than BISAP score with sensitivity of 89% and specificity of 69%, while the BISAP score had specifity of 74%, asnd sensitivity of 59%. Further, with much greater AUC the APACHE II score was significantly stronger predictor of the disease severity than BISAP score ($Z=2.738$; $p = 0.006$). The value of the BISAP score in early prediction of AP mortality was similar to the APACHE II score. A possible explanation of why the BISAP score had lower ability to predict SAP than APACHE II score is because our study included a smaller number of patients then the study of authors from the United States [19]. Although difficult to perform, APACHE II score is multipoint system and provides a more objective clinical picture in patients with AP. Anyway, due to simplicity and easily obtained parameters, BISAP score should gain broad acceptance in routine use not by replacing clinical assessment, but rather by complementing and objectifying it.

Conclusion

In early prediction of AP severity, PCT has a better predictive value than CRP, and similar predictive value as the APACHE II score. PCT is a better predictor of fatal outcome in AP measured at 24 h of admission than CRP, BISAP score and APACHE II score. APACHE II score is a stronger predictor of disease severity than BISAP score. In early prediction of AP outcome, BISAP score has similar value to the APACHE II score. PCT analysis is simple, routinely available and a highly accurate method in early assessment of AP severity and outcome.

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Biohemijski markeri koštanog metabolizma i biološki efekti terapije za osteoporozu

Biochemical bone markers and biological effects of osteoporosis therapy

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Ključne reči:
osteoporoza; biološki markeri; lečenje lekovima; dijagnoza; lečenje, ishod.

Key words:
osteoporosis; biological markers; drug therapy; diagnosis; treatment outcome.

Uvod

Osteoporoza je poremećaj skeleta u čijoj osnovi se nalazi poremećaj koštane čvrstine koji vodi povećanju rizika od fraktura. Koštana snaga, odnosno čvrstina, integriše koštani kvantitet (mineralna gustina, prečnik kosti, debljina korteksa) i kvalitet (mikroarhitektonika, koštani promet) [1–4]. Više od 1,5 miliona vertebralnih i nevertebralnih fraktura javlja se na bazi osteoporoze od koje u svetu boluje približno 200 miliona ljudi. Osteoporoza se češće javlja u ženskoj populaciji, a za njen nastanak i razvoj odgovorni su genetski i negenetski faktori [5]. U okviru prevencije i terapije za osteoporozu bitna je individualna procena rizika od fraktura koja obuhvata analizu faktora rizika, osteodenzitometriju i određivanje biohemijskih markera koštanog metabolizma [6].

U osteoporozi povišeno je remodeliranje kosti uz dominaciju koštane resorpcije. Pored prvenstveno narušene trabekularne mikroarhitektonike dolazi do gubitka i kortikalne kosti te je povećana poroznost kostiju uz poremećaj koštane čvrstine [7]. Kod žena u postmenopauznom periodu života, kao i kod osteoporoze, dolazi do redukcije periostalne apozicije i porasta endokortikalne resorpcije, što rezultira povećanom koštanom fragilnošću [8, 9].

Koštano tkivo je visokodiferentovano tkivo čija se dinamičnost ogleda u stalnom procesu remodelovanja zasnovanom na koštanoj resorpciji i formiranju. Tokom navedenih procesa dolazi do razgradnje organskog dela matriksa kojeg čini preko 90% kolagena tipa 1. Razgradni produkti kolagena tipa 1 mogu se naći u serumu i urinu kao N-terminalni telopeptid (NTX), C-terminalni telopeptid (CTX) i prstenaste strukture pod zajedničkim imenom *piridinium-cross links*. Tokom procesa formiranja kosti, aktivisani osteoblasti sekretuju osteokalcin, prokolagen peptid tipa 1 N-terminalni prokolagen peptid (PINP) i C-terminalni prokolagen peptid (PICP) i alkalnu fosfatazu specifičnu za kost (ALP). Nivo osteokalcina, ALP, PINP i PICP koreliše sa stepenom koštanog formiranja. Osteokalcin, nekolageni protein, produkuju osteoblasti tokom procesa formiranja kosti, dok se tokom resorpcije izlaže iz koštanog matriksa tako da reflektuje celokupni koštani promet, mada se prvenstveno vezuje za proces formiranja kosti. Formiranje kosti kompletira se mineralizacijom koja se odvija u dve faze – u prvoj, odmah nakon formiranja osteida, dolazi do deponovanja kristala hidroksi-apatita, dok druga faza uključuje W „sekundarnu mineralzaciju“, proces koji traje mesecima i koji povećava koštanu gustinu (*bone mineral density* – BMD) ali ne i volumen nove kosti. Određen nivo biohemijskih markera reflektuje promene skeletnog metabolizma bez obzira na uzrok, tako da nisu vezani za određenu bolest ili stanje organizma [7, 10].

Biohemijski pokazatelji metabolizma kosti

Markeri koštanog formiranja su: ukupna i za kost specifična alkalna fosfataza (serum), osteokalcin (serum), C- i N-terminalni propeptidi prokolagena tipa 1, PICP, PINP (serum) i drugi nekolageni proteini kosti.

Markeri koštane resorpcije su: tartarat rezistentna kisela fosfataza (plazma), kalcijum (urin), hidroksiprolin (urin), *piridinium cross links* (urin), kolagen tipa 1 telopeptid *beta-cross laps* (urin, serum), C-terminalni telepeptid kolagena tipa 1 (ICTP – serum), NTX (urin).

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Izvori varijabilnosti markera

Izvori varijabilnosti biohemijskih markera koštanog metabolizma mogu biti preanalitički i analitički. Za svaki biohemijski marker koštanog metabolizma mora se odrediti analitička varijabilnost. U preporukama i direktivama date su procedure i mere za sniženje varijabilnosti određivanih biohemijskih koštanih markera u smislu sakupljanja uzoraka i protokola procesa korišćenih analiza. U analitičkoj fazi poboljšanje se postiže korišćenjem testova sa većom osetljivošću i preciznošću, kao i korišćenjem automatskih analizatora [11].

Preanalitička varijabilnost može se podeliti u dve kategorije: nekontrolisani i kontrolisani izvor varijabilnosti. Nekontrolisani izvor varijabilnosti obuhvata godine života, pol, sezonske varijacije i kondiciju pojedinca. U toku rasta i razvoja biohemijski markeri pokazuju viši nivo nego kod odraslih osoba nakon prestanka rasta. Porast biohemijskih markera događa se u postmenopauzi i u prisustvu pojedinih bolesti i stanja, sa reperkusijom na koštani metabolizam. Porast biohemijskih markera verifikuje se takođe nastankom frakture i može se održavati i do godinu dana. Smatra se da visok nivo parametara koštane resorpcije reflektuje postojanje mikrofraktura [12]. Sezonske varijacije koreliršu sa varijabilnošću metabolizma vitamina D [13]. Kontrolisana varijabilnost obuhvata diurnalnu i cirkadijalnu varijabilnost. Diurnalna varijabilnost koštanih markera može biti 40–70%, dok se cirkadijalna kreće 7–17%. Minimalne varijacije su od 8 do 10 h kada se preporučuje uzimanje uzorka našte i njegova brza obrada, što značajno smanjuje preanalitičku varijabilnost [14, 15].

U okviru adekvatne procene i interpretacije kontrolnih rezultata određivanih biohemijskih markera neophodno je koristiti najmanje značajnu promenu (*least significant change* – LSC). U odnosu na LSC procenjuje se stvarna promena nivoa biohemijskih markera koštanog metabolizma kao odgovor na terapiju, izbegavajući preanalitičke i analitičke varijabilnosti. Vrednosti LSC određene su za najčešće određivane biohemijske markere koštanog metabolizma i njihov raspon uopšteno iznosi 15–40%. Poznato je da antiresoptivna terapija redukuje 50–70% *beta-cross laps* u odnosu na bazalni nivo. Ovo pokazuje da se koštani markeri mogu uzeti za praćenje terapije uprkos velikoj varijaciji, s obzirom na to da je procenat promene veći od LSC [16].

Primena biohemijskih markera koštanog metabolizma

Predviđanje rizika od preloma

Prema mnogim preporukama, merenje koštane mineralne gustine predstavlja najbolji prediktor faktora rizika. Povišen nivo biohemijskih markera kosti povezan je sa ubrzanim koštanim metabolizmom koji se dovodi u vezu sa pogoršanjem koštanog kvaliteta. Koncept se zasniva na činjenici da povećan broj i intenzivnija aktivnost tzv. osnovnih multicelularnih jedinica koštane pregradnje dovode do malih mesta koštanog gubitka, ne moraju znatno sniziti koštanu gustinu ali znatno snižavaju koštanu snagu i, time, povećavaju rizik od frakture [14, 17]. Rezultati studije *Epidemiologie de l'Osteoporose* (EPIDOS) pokazuju da je relativni rizik od frakture definisan merenjem BMD sličan nivoima izmerenih biohemijskih markera (relativni rizik – RR ~2). Kombinovanim merenjem BMD kuka i koštanih resorptivnih markera kod starijih žena raste predviđanje frakture kuka (RR 5–6) [18]. Meier i sar. [19] iznose da kod postmenopauznih žena i zdravih muškaraca stepen koštane resorpcije ukazuje na povećani rizik od vertebralnih i nevertebralnih fraktura nezavisno od BMD, godina života i invaliditeta. Smanjenje markera formiranja za 50% snižava rizik od nevertebralnih preloma za 44% dok smanjenje markera resorpcije za 70% snižava rizik od nevertebralnih preloma za 40% [20].

Izbor terapije

Viši nivo određenih biohemijskih markera u serumu i/ili urinu odražava veći stepen koštanog remodeliranja, a samim tim i stepen koštanog gubitka. Nakon 30. godine života prosečan gubitak kosti iznosi oko 0,4% godišnje. Kod žena u postmenopauzi gubitak iznosi 1–2%. Međutim, kod oko 1/3 žena u postmenopauzi gubitak kosti je ubrzan i iznosi 3–6% godišnje. Određivanjem nivoa biohemijskih markera kosti mogu se identifikovati žene sa visokim koštanim metabolizmom, te sledstvenim brzim koštanim gubitkom i doneti odluka o adekvatnoj prevenciji i terapiji [21]. Antiresorptivna terapija dovodi do redukcije 30–70% nivoa biohemijskih markera resorpcije, dok anabolna terapija povećava za 30–50% nivo markera koštanog formiranja, kako prema našim iskustvima, tako i prema iskustvu drugih autora [22–24].

Bisfosfonati, estrogenska supstitucijska terapija, kalcitonin, raloksifen i denosumab imaju tendenciju redukcije resorpcije i formiranja kosti [25–33]. Stroncijum ranelat ima suptilan efekat na koštani promet, malu redukciju markera koštane resorpcije i blagi porast u markerima formiranja [34]. Teriparatid znatno povećava koštano formiranje i nakon pouzdanog perioda „mirovanja" ispoljava efekat na markere resorpcije [35–37]. Tranzitorni gubitak kosti u okviru endoostealne površine pri primeni teriparatida biva kompenzovan periostealnom apozicijom koji čuva koštanu čvrstinu [38]. Posmatranjem dugotrajnog efekta terapije, bolesnici sa određenim visokim stepenom koštane resorpcije imaju veću korist od antiresorptivne terapije, dok, suprotno, bolesnici sa niskim koštanim metabolizmom imaju veću korist od primene stimulatora koštanog formiranja [39].

Poznati su nepovoljni efekti hronične primene glikokortikoida na koštano tkivo. S obzirom na široko indikacijsko polje primene glikokortikoidne terapije, posebno mesto zauzima lečenje osteoporoze indukovane glikokortikoidima. Određivanjem markera koštanog metabolizma zapaža se da je efekat hronične primene glikokortikoida suprimovanje osteoblastne aktivnosti i koštanog formiranja osim u početnoj fazi terapije. Zbog toga, logična terapija za osteoporozu izazvanu glikokortikosteroidima bila bi primena teriparatida koja je, moguće, efikasnija od primene bisfosfonatne terapije [40–43].

Praćenje efekata lečenja

Rezultati studija efekata antiresorptivne terapije pokazuju da se redukcija rizika od faktora samo delom objašnjava porastom BMD i da je od značaja i poboljšan kvalitet kosti.

Cumming i sar. [44] izveštavaju da promene BMD objašnjavaju samo 4–28% redukcije rizika od vertebralnih fraktura, te imaju značaja i druge determinante koštane čvrstine, uključujući i stepen koštanog metabolizma. Pri praćenju terapijskog efekta, promene BMI možemo uočiti tek nakon 1,5–2 godine, dok promene u dinamici biohemijskih markera mogu se obično zapaziti za 3–6 meseci. Promena koštane mase i gustine kao reakcije na antiresorptivnu terapiju samo delom objašnjava predikciju redukcije rizika od fraktura. S obzirom na dinamičke promene koštanog *turnoveru*-a procena merenja biohemijskih markera u serumu i urinu mogu objasniti deo antifrakturnog efekta antiresorptivne terapije. Preporučuje se kontrolno određivanje biohemijskih markera koštanog metabolizma nakon tri meseca od početka primene bisfosfonata i raloksifena, šest meseci od primene hormonske supstitucijske terapije (*hormone replaecment therapy* – HRT, a potom za obe navedene nakon 12 meseci. Binkley i sar. [14] u svom istraživanju pokazali su da su vrednosti CTX snižene 70,2% nakon tri dana mesečne primene ibandronata. Greenspan i sar. [45] pokazuju da efekti alendronata i HRT pri višem koštanom metabolizmu, odnosno većoj urinarnoj eliminaciji NTX dovode do 10,1% povećanja BMD kičme i 6,1% BMD kuka, ali kada je eliminacija NTX u urinu niža, odnosno kada je sporiji koštani metabolizam, porast BMD kičme iznosi 5,9%, a kuka 2,1%. Delmas i sar. [46] saopštavaju da teriparatid redukuje relativni rizik od faktora, nezavisno od koštanog metabolizma pre terapije, i da ovaj lek ima najveći uspeh kod bolesnika sa težim stepenom osteoporoze. Od početka terapije alendronatom koštana resorpcija se suprimira nakon jednog meseca, a koštano formiranje za oko tri meseca. Redukcija koštanog metabolizma postiže se za šest meseci i traje 12 meseci. Najniži nivo markera resorpcije postiže se 3–6 meseci od početka HRT, a najniži nivo markera formiranja za šest meseci. Teriparatid povećava markere formiranja za jedan mesec, njegov efekat progredira tokom šest meseci i perzistira 12 meseci od započinjanja terapije [47]. Bisfosfonati snižavaju markere koštane resorpcije za 78%, dok ih HRT snižava za 67% [48–50].

Indeks uravnoteženosti kosti predstavlja relativnu vrednost odnosa osteokalcina i β-*crosslaps* (osteokalcin/β-*crosslaps* x 1000). Indeks uravnoteženosti kosti ispituje stepen odstupanja odnosa fizioloških procesa remodeliranja kosti (koštanog formiranja i razgradnje kosti) od idealnog ravnotežnog stanja. Vrednost indeksa u zdravoj populaciji iznosi oko 90 [51].

Praćenje adherencije i komplijanse

Na osnovu podataka iz literature može se reći da je prihvatanje (adherencija) terapije osteoporoze od strane bolesnika veoma niska. Približno 20–30% bolesnika prekida terapiju nakon 6–12 meseci, dok oko 50% pravi povremene prekide uzimanja lekova [52, 53]. Problem adherencije leži u nepoznavanju značaja osteoporoze, faktor rizika od pojave frakture i propisane terapije, mogućnosti uzimanja i dostupnosti propisane terapije, evaluacije praćenja efekata terapije, podnošljivosti i prisustvu neželjenih efekata primenjene terapije. Pored navedenog, značajna je starost bolesnika, postojanje komorbiditeta i uzimanje druge terapije [54].

Neodgovarajući pad markera za vreme terapije bisfosfonatima ukazuje na neadekvatno uzimanje leka (loša komplijansa), lošu intestinalnu resorpciju, ili nisku bioraspoloživost leka (starije bolesnice). Potrebne su češće kontrole, ponovno objašnjavanje postupka uzimanja terapije, neophodnosti uzimanja terapije i razmatranje uvođenja intravenske terapije.

Zaključak

U osnovi osteoporoze nalazi se poremećaj koštane čvrstine koja je pored ostalih parametara, određena i koštanim prometom. U okviru terapije i prevencije osteoporoze bitna je individualna procena rizika od fraktura koja obuhvata analizu faktora rizika, osteodenzitometriju i određivanje biohemijskih markera koštanog metabolizma. Potreba za određivanjem parametara koštanog metabolizma u proceni ovog rizika zasniva se na ideji da multicelularne jedinice koštane pregradnje ne moraju znatno sniziti mineralnu gustinu kostiju ali znatno snižavaju koštanu čvrstinu i koštani kvalitet i, time, povećavaju rizik od frakture. Analizom podataka iz literature, kao i analizom sopstvenih rezultata, ustanovljena je neophodnost određivanja biohemijskih markera koštanog metabolizma u izboru terapije za osteoporozu, kao i praćenju njenog biološkog efekta. Naime, određivanje biohemijskih markera koštanog metabolizma trebalo bi uključiti u rutinsku praksu prilikom vršenja izbora terapije u cilju što boljeg terapijskog efekta na rizik od frakture. Veoma je bitna adherencija bolesnika za terapiju što se može proceniti određivanjem biohemijskih markera i, posledično, preduzimanje mera za njeno poboljšanje.

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Screening, identification and evaluation of autism spectrum disorders in primary health care

Praćenje, identifikacija i evaluacija spektra autističkih poremećaja u primarnoj zdravstvenoj zaštiti

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autistic disorder; diagnosis, differential; mass screening; delivery of health care.

Ključne reči:
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Introduction

Autism spectrum disorders (ASD) is a terminology present in the literature over the past two decades. It represents a group of disorders with common basic expressions in different degrees [1–3] which are pervasive developmental disorders such as children's autism, Asperger syndrome and pervasive disorder – not otherwise specified [4, 5].

The reasons for separating and assembling these three disorders are that they have common basic behavioral manifestations (clinical signs) and are relatively well defined as autistic syndrome, although the degree of expression may vary in different extent. Precisely, these differences in the presence and degree of basic clinical characteristics represent the spectrum of autism disorders.

Conceptualization of disorders

The terminology "autism spectrum disorders" clearly reflects the current perception and understanding of autistic disorders and is a new concept accepted in this area [1–3].

This concept is based on a research which results showed that childrens` autism, Asperger syndrome and autistic disorder not otherwise specified, are just different kinds of a basic, autistic, behavioral phenotype.

Basically, these are clinical signs which correspond to the clinical picture of childrens` autism, the one first described by Kaner [6] in 1943, when he revealed eleven children in a group of mentally retarded children who showed "a strange and extreme isolation distance".

It also includes a disorder that the Austrian psychiatrist Hans Asperger discovered in 1944, describing amongst childrens' autism, children whose cognitive abilities and verbal skills were at a much higher level. This entity got its name – Asperger syndrome after him.

Terms of conceptualization of disorders, which means, comprehension and understanding of the disorder, have evolved over years in accordance with the degree of knowledge and understanding of the disorder, such as the prevailing doctrines [2, 3, 7].

For a long time, childrens' autism was placed in a group of psychotic disorders in childhood. Children's autism, as a separate clinical entity, showed up for the first time in 1980, when the National Council of the American Association for autism suggested a third edition of the Diagnostic and Statistical Manual of Mental Disorders [5] (DSM-III classification) to promote a rather different conceptual approach. Children's autism has been since then (and is now) understood and considered not as a psychosis but as a disease with damaged flow of normal developmental processes in the social, cognitive and psychological spheres. In other words, children's autism is a pervasive developmental disorder.

All "borderline" cases, in terms of incomplete clinical signs or associated with other disorders (comorbidity) since 1987 (in DSM III-R) are classified as not otherwise specified autistic disorder [4, 5].

Asperger syndrome, as a separate entity, is given the "right of citizenship" only in 1994.

Recognizing the presence of basic common "woof" in these three disorders makes the conceptualization of these disorders as a unity, defining them as autism spectrum disorders (ASD).

In both major international classifications, International classification of diseases and disorders (ICD-10) [4] and DSM-IV-R [5], these disorders are still today in the group of pervasive developmental disorders (with Rett syndrome and disintegra-

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tive disorder). One should also emphasize that the intention is clearly shown in their clustering within a continuum on the scale of autistic disorders. This concept has clear implications in respect to diagnostic and therapeutical approach.

Epidemiology and clinical manifestations

Epidemiological data for this group of disorders suggest that the prevalence is about 6 in 1000 [8]. It must be said that the data, at different times and from research to research, varied depending on the "width" and "strictness" of diagnostic criteria and some paramedical factors (involvement in special education, permanent housing ...). Research of disorders in relation to sex showed the ratio varying from 2 : 1 to 6,5 : 1 in favor of boys. This ratio is even more pronounced in cases where Asperger syndrome is found in only one girl towards 15 boys.

Autism spectrum disorder is a behavioral phenotype defined by clinical signs. That is why it is diagnosed as a behavioral disorder 1–5.

It should be emphasized that this grouping of ASD includes extremely heterogeneous phenotypes, including also those with vaguely defined expression as well as the prominence of different levels of behavioral manifestation, especially in the middle of the spectrum [9].

The essence of behavioral disturbances is expressed by inability to make reciprocal relations and communication with other human beings in a way that it is normal or common [7].

The core feature of the disorder consists of qualitative impairment of social interaction, qualitative impairment in communication and stereotyped, restrictive and repetitive forms of behavior, interests and activities.

Qualitative impairment in reciprocal socio-emotional reactions

These children lack the awareness of the presence of or feelings towards others, do not notice or treat them as pieces of furniture; passively uses people to meet their needs, has no interest in other children, do not participate in playing with others or make other children participate as mechanical "extensions"; do not register other persons` feelings (sadness, joy); show the lack of emotional responses to the messages of other people. These children do not posess or, if they do, their ability to imitate is damaged (they do not know to wave as a greeting, they mechanically imitate others' actions out of context).

Qualitative impairment in verbal and non-verbal communication

There may be a lack of communication in any way (mime, gesture, spoken language) and/or markedly abnormal nonverbal communication, without using gaze "eye to eye", without facial expression, body position and gestures to initiate or modulate social interaction. If speech is present, there are clear abnormalities in the production of speech (including volume, height, rhythm, intonation; for instance: squeaking or questioning melody etc.); in form and content (there are a lot of stereotypes and repetitive uses of speech – echolalia and metalalia; speech in the third person; there is idiosinkratic use of words and phrases); inability to start or to continue a conversation with others despite the preserved speech.

Extremely narrow repertoire of activities and interests and repetitive and stereotyped forms of behavior

These children have very limitated interests, such as the interest for important dates, driving schedule, telephone directory. They insist on maintaining the routine in detail (they have to go the same way to the kindergarten or a shop) and show extreme anxiety at a minimum change in the environment (change of lamps or flower pots, for instance). The lack of imagination when playing is evident. The game is stereotypical, often repetitive, and even bizarre. There is fascination (permanent preoccupation) in touching parts of objects or unusual objects (they can play for hours with the lid of some pot or a screw, or can touch the texture of some material). Motoric stereotypes are characteristic: bizarre stereotypical hand movements in the form of knocking, clapping or flapping, or swinging, bouncing and rolling the whole body.

These are the elements of clinical and diagnostic criteria for childrens' autism. All of these symptoms must be present, but the degree of their prominence varies from case to case, and this is what causes variation in the expression of the disorder.

In addition to these specific diagnostic criteria, autistic children have a range of non-specific problems from fear, sleep and eating disorders, temper tantrums and aggressiveness, to especially self-injury.

Certainly the most important "extra" coexsiting conditions, which does not make the core, are the cognitive deficit (general developmental slowing down). Intellectual abilities of children with autism vary in a wide range from normal ones (measured non-verbal techniques) to those whose intellectual development was heavily disturbed. The question of cognitive deficits, especially of mental retardation, was actualized in the 90s of the last century. In fact, attitudes that over 90% of children with this disorder show delayed mental development are somewhat questionned: the results of recent studies have shown that this percentage is under 50 and that it is actually about the difficult assessment of cognitive abilities of these children (assessment instruments and professional training are questionned). It must not be forgotten that people with Asperger syndrome are, by definition, characterized by normal intelligence. As some children with heavily impaired intellectual development can show "strange islands of skills on their general cognitive level, it is considered that cognitive abilities of children with autism do not follow the usual course of development.

In one third of children suffering from autism, epilepsy occurs during childhood or adolescence. Neurological and somatic tests in these children are normal.

Diagnosis

Diagnosis is based on the fact that the clinical manifestations (behavioral manifestations) fulfill the diagnostic criteria which are given in two of the world's leading classifications: ICD-10 and DSM-IV R [4, 5].

Diagnostic criteria (according to DSM-IVR) for children with autism–pervasive developmental disorder, are [5].

A. Qualitative impairment of social interaction; Qualitative impairment in communication; Restricted repetitive and stereotyped forms of behavior, interests and activities.

B. Delayed or abnormal functioning in each area, starting before 3 years of age: social interaction, use of language for the purpose of communication and symbolic or imaginative playing.

C. Disorder that does not fit in Rett syndrome and children`s desintegrative disorder.

Diagnostic criteria (according to DSM-IVR) [5] for Asperger's syndrome are: Qualitative impairment of social interaction; Restricted repetitive and stereotyped forms of behavior, interests and activities; Disorder causes clinically significant impairment in social, occupational and other important areas of functioning; No clinically significant slowdown in the development of language; No clinically significant lags in cognitive development or the development of appropriate self-help skills, adaptive behavior and curiosity about the school environment; The criteria can not be applied to another specific pervasive developmental disorder or schizophrenia. Diagnostic criteria for autism spectrum disorders are shown in Table 1.

in a coherent sequence, where the surveillance, in accordance with different compatible elements, structures one theoretical model encompassing many aspects.

Genetic basis

Certainly the most significant considerations are those regarding the genetic basis of this disorder [12]. Generally designed by researches of genetics within population and focused researches in the field of molecular genetics (targeted cytogenetics, screening the entire genome within families of children with autism spectrum disorders) they have given more than intriguing and promising results.

Research in the field of population`s genetics [10, 11] has shown that the behavioral manifestations of autism are related, more than randomly (1 of 4 "classic" cases of autism – about 10%), to a single gene disorders (neurofibromatosis, tuberous sclerosis, untreated phenylketonuria, Hurler`s syndrome). The nature of this connection is unknown.

The biggest incentive for the study of genetics of autism at the molecular level is the discovery of the relation between X fragile chromosome (Xq 27.3) and autism (1982). The presence of X fragile chromosome (and typical clinical picture), the so-called FRAXA syndrome, was discovered in 14% of all cases of autistic disorders. Although it is ac-

Table 1

Diagnostic criteria for autism spectrum disorders

Types of ASD	Common disorders	Different disorders
Children's autism	Manifests before 3 years	General slowing down or abnormal functioning in each of the above areas
Asperger syndrome	Characteristic abnormal functioning (limited, stereotyped and repetitive) in the field of social interaction, communication and behavior	There is no clinically significant slowdown in the development of speech
	Non-specific problems: phobias, sleep and eating disturbances, temper tantrums, aggression and self-injury	There is no clinically significant lags in cognitive development

Etiology

Autism spectrum disorders (ASD) etiology is not known, but today we consider that, although the spectrum of autism disorders is the behavioral phenotype defined by its clinical signs, it is biologically conditioned by neurodevelopmental disorder with a high degree of inheritance [7, 11, 12].

In fact, it is considered that the ASD neurobiological disorder occurs in genetically predetermined persons as a result of different unknown factors that act as triggers in the first two trimesters during the intrauterine life. These conclusions are based on facts as follows: Biological studies of central nervous system (CNS) in children with ASD (primarily autism in children) resulted in a number of interesting new findings. "Diversity" of pathological findings greatly hinders their integration into a single theoretical concept. However, different aspects of biological disorders combined knowledged that the X fragile chromosome is the marker for mental retardation rather than autism, the specific form of inheritance of autism (one group) is linked to the X chromosome.

Studies have shown that there is no genetic marker for autism. There are 2 to 10 genes "in the run" (identified abnormalities associated with autism). As candidate genes in autism spectrum disorders there are, among others, the genes assumed to have a role in the regulation of brain development (cell proliferation) or a neurotransmiter role [12].

Generally, it can be said that our heritage has an important, indispensable role in the development of autism spectrum disorders, more in terms of genetic predisposition than given completness. In fact, we assume that the disorder is caused in genetic predetermined persons under the influence of environmental factors in the first or second trimester of prenatal life.

Neurodevelopmental model

In autism caused by developmental damage of CNS there are two different groups of each of the findings that are the basis for the conceptualization of this model.

The first group – clinical observations of similarity between autistic behavior and behavior of adults in the verificated and known syndromes (neglect syndromes in the frontal lobe syndrome, Kluver Bucy syndrome, Korzhakov`s psychosis).

The second group – results of neuroanatomical and pathohistological researches.

Pneumoencephalography (in 1970s) and brain computerized tomography (CT) of patients with autism have shown a primary dilatation of the left temporal horn of lateral chambers in about 25% of these patients. Autopsy studies in patients with autism have shown major changes in cellular composition (number and size of neurons) in the nuclei amigdala and hypocampus (structures that are localized in the mesial temporal lobulus), which is a characteristic of immature configuration and de facto a sign of bacwardness in maturation [13].

The second structure where the CNS in patients with autism showed significant changes is the cerebellum (the reduction of Purkinje and granular cells, in the vermis and cerebellum hemispheres, with preserved neurons in the lower olivar nucleus which suggests that this loss of cells occurs during prenatal development). Abnormalities of cerebral cortex were also evidenced.

Based on these findings, it is assumed that these regions are dysfunctional due to immaturity, which is the result of distorted migration of cells in the CNS during the first 6 months of fetal life *ie* the result of early dysfunction caused by disorders of organogenesis con *causa ignota.*

Different functional MRI studies have shown that individuals with ASD use different cognitive strategies and, in many cases, other brain regions for processing specific information. Consequent damage has shown the connection between different cortical regions in the brain of people with ASD. Deficits in empathy, imitation and speech are due to abnormalities in the functioning of mirror neural systems. These functional brain differences promise intriguing connection between neuroanatomical substrate and the characteristic clinical manifestation in patients with ASD [9].

Immunological theory

The known facts about the participation of immunological processes as a "major player" in ethyopathogenetics of autism are, so far, unconvincing [10].

Identical (or very similar) clinical sign is a reflection of existence (involvement, participation) of the same anatomical structures of the CNS at a certain point of development (probably during the first months of gestation). Its consequence is the development of certain types of disorders in various domains of psychological functioning (so-called autistic behavior).

Why are these etyological considerations important if we say that the etiology of ASD is actually unknown?

First of all, because of a certain number (10–20%) of disorders which "look like" – have a clinical spectrum of autistic disorders or are associated with ASD and thereby have a clearly defined etiology (*eg* untreated phenylketonuria, X fragile chromosome syndrome, neurofibromatosis, tuberous sclerosis...). In some cases these disorders are considered in literature as secondary ASD as opposed to the primary ones with the basically unknown etiology. This is very important from the differential diagnostic point of view [13].

Screening, identification, evaluation of children with ASD in the primary health care

Basic items which model this issue and are present in the previous presentation are: autism spectrum disorder is a behavioral phenotype defined by its clinical signs (this is why it is diagnosed as a behavioral disorder); ASD is by its nature a neurobiological disorder generated by environmental factors on the genetic susceptible basis (most likely during the first two trimesters of intrauterine life); there are no specific biological tests for ASD.

These are also the guidelines for creating an "action plan" for screening and identification.

Developmental counseling in primary health care is conceived for developing a comprehensive monitoring and evaluation of child`s situation during regular visits to a pediatrician (in child`s 9 months, 18 months, 24 months and 30 months of age). This serves particularly to identify and track children 'at risk' (personal history, family history). It also helps to identify and evaluate children susceptible of having the ASD.

Screening

The key part for early identification of this disorder is screening – monitoring milestones of development expected for specific age and tracking of signs of development in the areas of speech, social and communication skills [14–16] as well. These milestones are monitored in the general population of children aged 0 to 3 years within monitoring in developing counseling centers, and especially in the population of children at risk for ASD (children at risk for ASD are those who have a positive family history or risk factors in the former development). As part of a periodic monitoring of pediatrician through visits (9, 18, 24, 30 months of age) all variations in the development of social relationships, communication and speech are registered.

Identification

What are the steps to make if there is a doubt regarding the existence of symptoms of Autism spectrum disorders [14, 15, 17, 19].

First of all, there is no pathognomonic clinical picture. For a good assessment, good knowledge of milestone development of social skills, communication and speech is indispensable (Table 2).

Signs of social skills deficits may be specific, but are often subtle and hardly recognized by parents. However,

Table 2

Milestones of development of social skills, communication and speech

Age of the child (months)	Area of development	
	Social skills – Communication	Speech
6	Reacts to the human voice turning in the direction of the head and eyes, and adequately respond to friendly and angry tones	Vocalizes, with intonation, cackle, a vocalization alternating between baby and parents
8–10	Recognized by parents, parental monitoring view and follow it, turning to (react) to your name	Yak, ingeminate syllables (mom, dad), respond to sounds
10–12	Track-view parental guidance ("Show me") and returns it to the parent (shared view and expression)	Use one or more words with meaning, understand simple instructions, understand the social aspect of speech
12–14	Shows things, began directing and "water" parents, protoimperative accent (stress required gestures)	Has vocabulary of about 50–20 words, combines two words, follow simple orders
24	Spontaneous behavior, share experiences with others (observation, participation) so. "Joint attention" looks at an alternative facility that is scored, and parents, the social interaction of multiple emotional expressions, voices and other gestures, respond to requests "show around" (nose, mouth ...)	It has a vocabulary of about 150–300 words, he can name objects in their environment, combining two words in a sentence (Noun, verb), it uses two pronouns: I, and you

signs of alarm *ie* “danger on the way” of development are: lack of appropriate gaze (“eye to eye”); lack of happiness in terms of exchange to-and-fro (here and there) vocal forms between infant and parents; lack of recognition of mother`s (father`s or a permanent caregiver`s) voice; lack of response to the name; disregard for vokalizations; delayed onset of babbling; decrease or absence of prespeech gestures (showing, waving, pointing); lack of expressions such as “oh oh”, “huh”; lack of interest or response to any kind of neutral statements; loss of speech (at any age).

The US Association of children neurologists considers as a sign of alarm [14, 16] “red flag” [20] when: the child does not babble or use other gestures by the age of 12 months; does not pronounce a single word by 16 months; does not make spontaneous 2-word sentences (not echolalic) by 24 months; loses speech or social skills at any age.

Diagnostics

After identifying the possibility of existence of Autism spectrum disorders, in order to verify, and before sending the child in a specialized institution, there is a need for general diagnosis, which in these cases involves the following steps [7, 14–17].

New detailed case history of the parents regarding: the child's development; the observed changes in its development; family case history. Surveillance of the child – intellectual level of functioning, specific developmental delays, behavior; assessment “meeting” the criteria for ASD; child`s tests – testing the existence of dysmorphia and neurological deficits; tests in terms of identification of syndromes whose etiology is known and show the picture or are associated with ASD (X fragile chromosome syndrome, tuberous sclerosis, untreated phenylketonuria, Rett syndrome...); audiological check up – AEP; genetic check up (X fragile chromosome, Mec P2); metabolic screening; electroencephalographic (EEG) examination; magnetic resonance (MR) examination of the endocranium – does not make part of a routine diagnostic.

Evaluation

After the diagnostic tests are carried out the evaluation of the results [14, 15] is made.

The evaluation is done at two levels and these are: evaluation of the child where there are manifestations of autism spectrum disorders. evaluation of the procedure in terms of "steps" to undertake in the identification-diagnostic procedure.

Basic principles of evaluation are: step by step evaluation; completeness – integration and analysis of the results; monitoring during a period of time.

When the existence of the disorder is confirmed a new interview with the parents must be performed. Parents are made aware of the child`s problem and the child is referred to children`s psychiatrist. The next step in the specialized institution is a general analysis and the individualized evaluation of child`s capacities. According to it, a program is made of specialized sociotherapeutic intervention and treatment (speech therapist, special teacher). Given the nature of the disorder (difficult, time consuming – often for a lifetime) and exceptional importance of early diagnosis, special attention is focused on facilitating and improving the quality of life of these children and their families [18–23].

For a definition of «how to follow the steps in the procedure» we use algorithms that give in a relatively simple and transparent way the «framework for action» in the field of diagnostics and therapy in a variety of possible situations. Certainly the most important (and most detailed) is the algorithm for monitoring and screening ASD of the American Pediatric Academy [14].

We give our algorithm of the Identification – Diagnostic Procedure for developmental counselings (Figure 1), which is a landmark and a reminder for “regular”, but also other cases whith concerns or doubts, or delicate cases in the diagnosis of ASD.

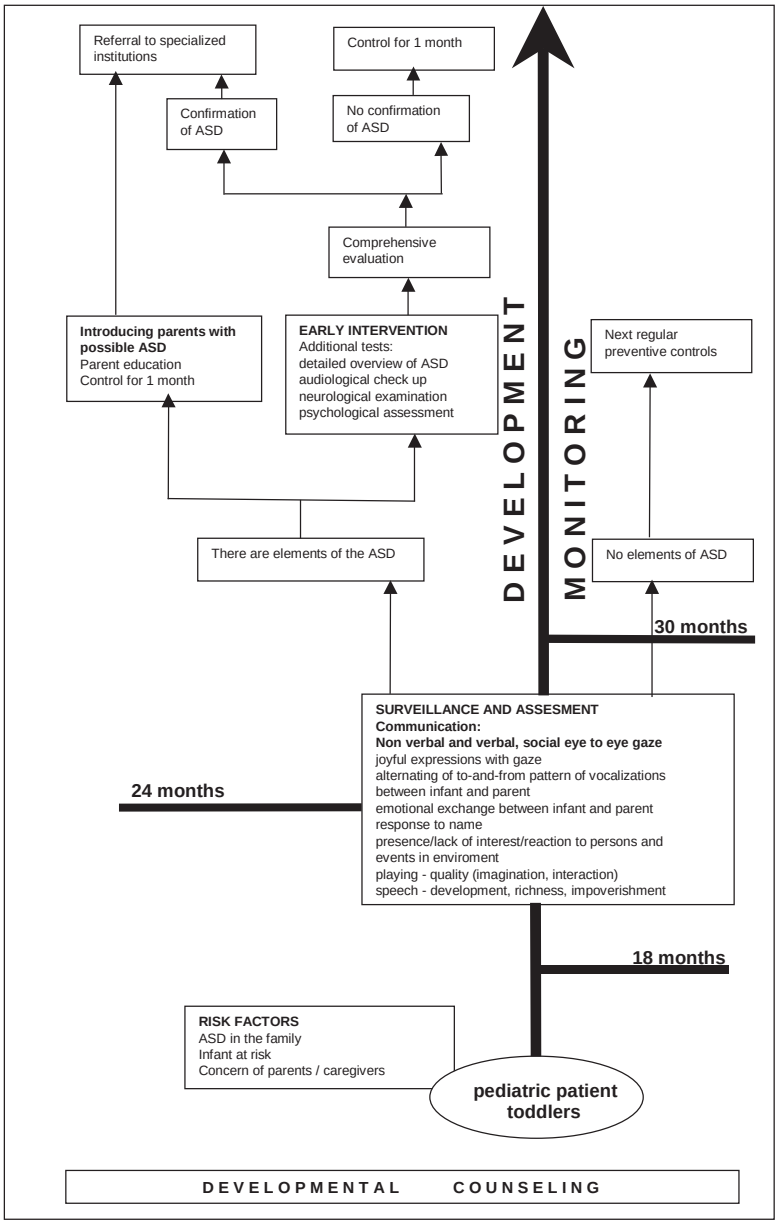

Fig. 1 – Identification – A diagnostic algorithm in cases of autism spectrum disorders (ASD)

Conclusion

Autism spectrum disorder is a new concept and approach to a group of disorders that include: children's autism, Asperger syndrome and pervasive disorder otherwise not specified. These disorders make a range of behavioral phenotypes (given the varying degree of prominence and representation of certain elements) which core makes the inability of reciprocal relations and communication with other human beings in a way that is normal/common.

Relatively homogenous (spectrum) behavioral phenotype, etiological heterogeneity, prevalence increase, graveness of disorders and chronicity (long-term – often for a lifetime) impose as an imperative good knowledge of all elements of this disorder with the aim of early identification. Early detection is a prerequisite for early intervention that can significantly alter the course of disorder and improve the quality of life of children with ASD and their families.

The first "meeting point" and the early diagnosis of this disorder is in the hands of the pediatrician in developmental counseling. Monitoring the development of common milestones expected for age and milestones in the development of social skills, communication and speech is a prerequisite, that is, the first step is screening. Registering variations in the development of social relationships, communication and speech is the second step – the identification of potential ASD in children patients. The third stepare the preliminary diagnostic tests, a comprehensive evaluation and assessment.

Three steps phase in early diagnosis of ASD in the developmental counseling is a major step in helping children with ASD. Early diagnosis allows appropriate planning and implementation of individually made behavioral and educational interventions, structured support of professional ASD specialists, program support and family assistance.

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CASE REPORT

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Malignant ameloblastoma metastasis to the neck – radiological and pathohistological dilemma

Metastaza malignog ameloblastoma na vratu – radiološka i patohistološka dilema

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Abstract

Introduction. Ameloblastomas are odontogenic epithelial, locally invasive tumors of slow growth and mostly of benign behavior. Their frequency is low (they account for 1% of all head and neck tumors and about 11% of tumors of dental origin). Malignant variations of ameloblastoma are malignant ameloblastoma and ameloblastic carcinoma. They constitute less than 1% of all ameloblastomas. We presented a case of malignant ameloblastoma of the mandible with neck metastasis. **Case report.** A patient, aged 72, presented with the following symptoms: pain in the lower jaw, swelling in the left submandibular area and difficult mouth opening. The patient was admitted to the Department of Oral and Maxillofacial Surgery, Clinical Center of Montenegro, two months after he had noticed the symptoms. Panoramic radiography (OPG) showed that both jaws were partially toothless with terminal stage of periodontitis of the remaining teeth. Also, OPG showed sharply limited semicircular defect in the retromolar region and along the front edge of the mandible rami. Conventional histopathologic examination of the neck masses showed malignant ameloblastoma which contained central fields of squamous differentiation. Immunoreactivity of several markers was determined using immunohistochemical analyses. After these diagnostic methods a definite histopathology diagnosis was made: *Ameloblastoma metastaticum in textus fibroadiposus regio colli (typus acanthomatosus)*. **Conclusion.** It is not possible to distinguish conventional, *ie* intraosseous, ameloblastoma from malignant ameloblastoma according to histopathologic features. It is necessary to pay special attention, especially in elderly patients, and to carry out further clinical, radiological and pathohistological diagnostic procedures, such as immunohistochemical analysis. A timely and correct diagnosis and treatment of malignant ameloblastoma require a multidisciplinary approach.

Key words:
ameloblastoma; neoplasm metastasis; diagnosis, differential; immunohistochemistry.

Apstrakt

Uvod. Ameloblastomi su odontogeni epitelni tumori, lokalno invazivni, sporog rasta, i u većini slučajeva pokazuju benigno ponašanje. Veoma su rijetki. Njihova učestalost je 1% u grupi tumora glave i vrata, kao i 11% kod tumora koji potiču od zubnih tkiva. Maligne varijante ameloblastoma su maligni ameloblastom i ameloblastički karcinom. Oni čine manje od 1% svih ameloblastoma. U radu je prikazan bolesnik sa malignim ameloblastomom donje vilice sa metastazom na vratu. **Prikaz bolesnika.** Prve subjektivne tegobe bolesnika, starog 72 godine, manifestovale su se kao bolovi u predelu donje vilice, otok u podviličnom predelu sa leve strane i otežano otvaranje usta. Bolesnik je primljen u Odeljenje oralne i maksilofacijalne hirurgije Kliničkog centra Crne Gore dva meseca nakon što je primetio prve tegobe. Ortopantomografski snimak pokazao je suptotalnu bezubost obeju vilica sa terminalnim stadijumom parodontopatije na preostalim zubima. U retromolarnoj regiji i duž prednje ivice ramusa donje vilice, uočen je jasno ograničen polukružni defekt. Biopsija promene na vratu pokazala je metastazu malignog ameloblastoma, sa prisutnim centralnim poljima skvamozne diferencijacije. Imunohistohemijskom analizom određivana je imunoreaktivnost više markera. Nakon ovih dijagnostičkih metoda postavljena je definitivna patohistološka dijagnoza: *Ameloblastoma metastaticum in textus fibroadiposus regio colli (typus acanthomatosus)*. **Zaključak.** Na osnovu histopatološkog nalaza nije moguće razlikovati konvencionalni, tj. intraosealni, ameloblastom od malignog ameloblastoma. Zbog toga je potrebno obratiti posebnu pažnju, naročito kod bolesnika starijeg životnog doba, i sprovesti sve dodatne kliničke, radiološke i histopatološke, ali i imunohistohemijske dijagnostičke procedure. Za postavljanje blagovremene i tačne dijagnoze, kao i sprovođenje adekvatnog terapijskog tretmana malignog ameloblastoma, neophodan je multidisciplinarni pristup.

Ključne reči:
ameloblastom; neoplazme, metastaze; dijagnoza, diferencijalna; imunohistohemija.

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Introduction

Odontogenic tumors are mostly benign lesions (97% of cases) [1], which are predominantly developed in the mandible [1,2].

Ameloblastoma is an odontogenic epithelial tumor. It derives from odontogenic epithelium of *lamina dentalis* (from which during embryogenesis enamel organ arises), or from odontogenic cyst epithelium, or epithelial rests of Malassez, and from the basal cells of oral mucous membrane or enamel organ [3].

Ameloblastomas are locally invasive tumors of slow growth and in most cases they have a benign behavior. Despite their low frequency (they account for 1% of all head and neck tumors and about 11% of tumors of dental origin) [4], they are a subject of continuous interest because of their diversity of microscopic – histopathologic features, as well as difficulties in radical surgical therapy. The most frequent localization of the tumor is the lower molar region [5], and it rarely occurs in the upper jaw or maxillary sinus [4]. There are three clinical pathologic types of ameloblastoma: a conventional solid or multicystic (present in about 85% of cases), unicystic (present in about 15%) and peripheral ameloblastoma (extraosseous) – present in about 1% of cases.

Malignant variations of ameloblastoma represent a separate entity because of their clinical characteristics and pathohistologic features.

According to the World Health Organization (WHO) histological classification of odontogenic tumors published in 2005 there are: metastasizing (malignant) ameloblastoma; ameloblastic carcinoma – primary type; ameloblastic carcinoma – secondary type (dedifferentiated), intraosseous; ameloblastic carcinoma – secondary type (dedifferentiated) [6]. Peripheral malignant ameloblastoma is a neoplasm that shows histopathologic features of ameloblastoma in the primary tumor and metastatic deposits (cell signs of malignancy are absent). They constitute less than 1% of all ameloblastomas and are characterized by the aggressive growth and metastasis ability. It is not possible to distinguish conventional (intraosseous) ameloblastoma from malignant ameloblastoma, based on histopathologic findings. The diagnosis of malignant ameloblastoma is usually made *post festum* and based on the findings of metastasis of the same microscopic characteristics as the intraosseous ameloblastoma. Because of that reason, the clinical (not histological) finding could be of great importance for diagnosis of metastasizing ameloblastoma. The appearance of metastasis is a paradox considering that intraosseous conventional ameloblastoma is characterized by benign microscopic features.

Ameloblastic carcinoma is an ameloblastoma that demonstrates all the classic features of cancer including cytological atypia, recurrence and metastatic spread into the lymph nodes and the lungs [7].

A meloblastoma may be present radiographically as unilocular (often even lobular in appearance) or multilocular [8]. There are, however, several radiographic features which make one suspicious of the diagnosis. As it begins within the jaw and grows slowly, it expands the lingual cortex. Radiographically, this translates to a radiolucency which when unilocular is difficult to distinguish from a simple odontogenic cyst. Nearly one-half of all ameloblastomas exhibit an overlapping multilocular soap-bubble or honeycomb appearance. The margins of the defect are scalloped and well-defined in the majority of cases. When the tumor occurs adjacent to a tooth, the root of the tooth is typically eroded whereas displacement of teeth is more common in association with simple dentigerous cysts. The differential diagnosis of a multilocular radiolucency in the jaw includes cherubism, giant cell granuloma, odontogenic myxoma, aneurysmal bone cysts, odontogenic keratocysts, and others, and often the diagnosis is not made until the patient undergoes diagnostic biopsy.

Microscopic findings of conventional or classic intraosseous ameloblastoma show numerous variations, which are not associated with the biological behavior of tumors. The most common forms are follicular and plexiform ameloblastoma and much less frequent acanthomatous variation [9,10]. Microscopically, ameloblastoma is composed of nests, strands, and cords of ameloblastic epithelium, all separated by relatively small amounts of fibrous connective tissue stroma. In the follicular form, the epithelial islands contain central portions that are composed of a loose network resembling that of the enamel organ. The epithelium at the periphery is composed of tall columnar cells with polarized nuclei. In the plexiform type, the epithelium is arranged in anastomosing strands and cords. Epithelial cells are closely apposed and with basaloid or cuboidal appearance [3].

Case report

The patient, aged 72, was treated for 10 years in Neuropsychiatry Department due to dementia and Alzheimer's disease. The disease gradually progressed, and it was manifested by obliviousness to daily things. At the time of first examination by the dentist the patient was completely disoriented, could not recognize his family members, and was occasionally aggressive. Cooperation with the patient was extremely difficult.

The patient noticed the first symptoms, such as pain in the lower jaw, swelling in the left submandibular area and difficulty opening mouth, two months before the visit to the dentist. The dentist prescribed him an antibiotic therapy for 10 days because of the limited mouth opening (first degree trismus – mouth opening about 25 mm).

As there was no improvement after the implementation of oral therapy, the antibiotic therapy was given intravenously (*iv*) for a period of 10 days. Ten days after the patient stopped using antibiotics, the patient was unable to open the mouth (third degree trismus).

After a month of antibiotic therapy prescribed by his dentist the patient was admitted to the Department of Oral and Maxillofacial Surgery, Clinical Center of Montenegro. Heteroanamnesis revealed that the patient had lower left wisdom tooth extracted 3 years ago. This was confirmed by the patient's daughter. Clinical examination established changes in the upper neck area of approximately $30 \times 30 \times 25$ mm in size, of irregular shape, clearly limited, that erected the surrounding

skin by about 10 mm. Palpation revealed painless, hard elastic, mobile lesion that mostly looked like conglomerate of enlarged lymph nodes.

Panoramic radiography (OPG) showed that both jaws were partially toothless with terminal stage of periodontitis of the remaining teeth (Figure 1). Also, OPG showed sharply limited semicircular radiolucency of the osseous tissue in the retromolar region and along the front edge of the mandible rami. This radiolucency extended up till almost half of the front edge of the ramus and its posterior wall was very close to the mandibular channel. The dimension of bone lesion was approximately 25 × 25 mm. The defect was relatively homogenous and it spreaded over the distal root of the second molar. From the mesial side of that tooth there was also a defect of alveolar ridge, which reached half of the length of a mesial root and probably corresponded to advanced stages of periodontitis (less probable connection with retromolar defect).

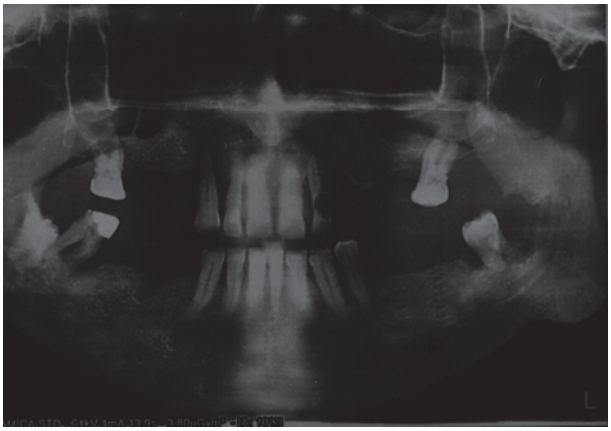


Fig. 1 – Radiological appearance of malignant ameloblastoma on the left side of the mandible

Computerized tomography (CT) examination of the neck region (made in 5 mm axial sections, native and postcontrast series) revealed in the left submandibular region, below the mandibular angle, a differentiated oval tumor formation, predominantly soft tissue density, relatively clearly designated, 38 × 35 mm in size, that did not intensify after *iv* application of contrast (Figure 2). CT also showed two to three lymphatic nodes, which were located anteriorly – medially and distally to the formation described before, up to 15 mm and 23 mm in size.

Bioptic material was sent to the Center of Pathology, Clinical Center of Montenegro. Biopsy (conventional histopathological finding) of the neck masses showed malignant ameloblastoma that contained central fields of squamous differentiation (Figure 3). After histomorphologic analysis of the

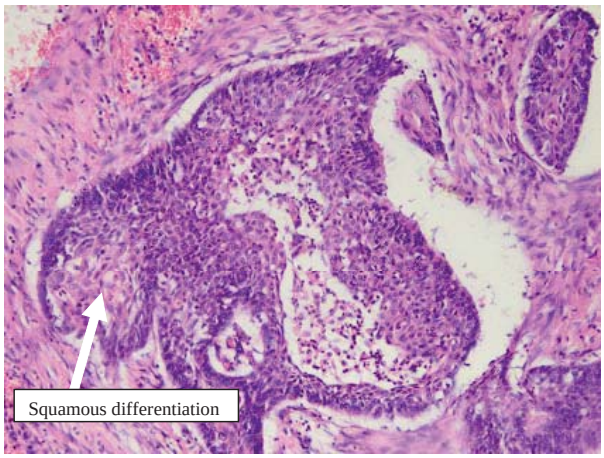


Fig. 3 – *Ameloblastoma metastaticum in textus fibroadiposus regio colli – typus acanthomatosus*
(H/E – hematoxylin – eosine, ×100)
The arrow shows fields of squamous differentiation with keratin formation in central parts of tumor tissue.

tumor tissue in the standard hematoxylin-eosine (H&E) products, the immunohistochemical analysis was done. Using this method, immunoreactivity of several markers was analyzed: epithelial membrane antigen (EMA, Figure 4a), pancytokeratin (PCK, Figure 4b) and vimentin (Figure 4c). The following results were obtained: EMA and PCK showed focal, medium immunohistochemical positivity, while vimentin gave a negative result. After these diagnostic methods definite histopathology diagnosis was made: *Ameloblastoma metastaticum in textus fibroadiposus regio colli (typus acanthomatosus*).

The patient was presented in the consilium of medical doctors for malignant tumors of the head and neck of the Clinical Center of Montenegro. Having in mind general

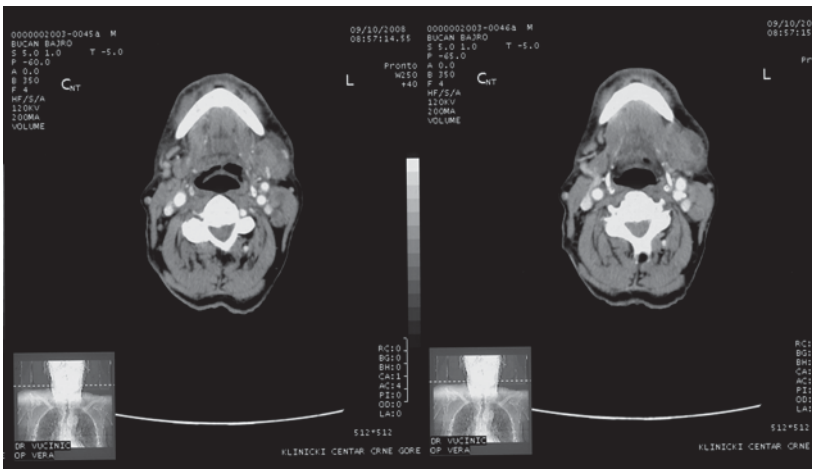
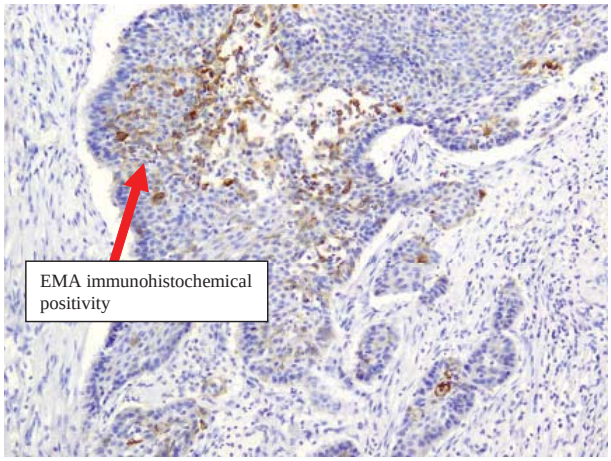
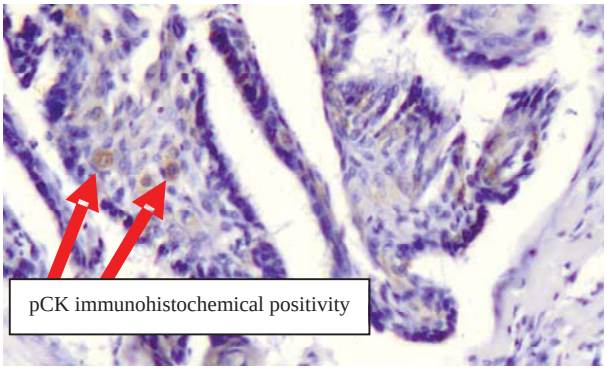


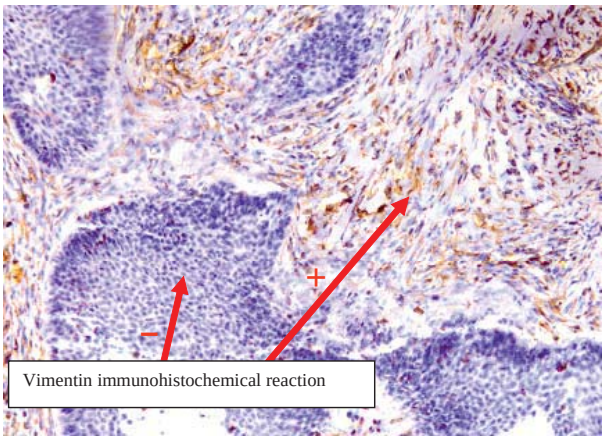
Fig. 2 – Computerized tomography of the neck shows oval tumor formation in the left submandibular region



a) The arrow indicates tumor cells with focal, middle immunohistochemical positivity (epithelial membrane antigen, ×100).



b) The arrow indicates tumor cells with focal, middle immunohistochemical positivity (pancytokeratin, ×200)



c) The arrow indicates tumor cells with focal, middle immunohistochemical positivity (vimentin, ×100)

Fig. 4 – *Ameloblastoma metastaticum in textus fibroadiposus regio colli – typus acanthomatosus*

health status and the primary illness of the patient, it was decided that symptomatic therapy should be administered. Surgery was not possible in this case.

Discussion

Malignant ameloblastomas occur in patients aged between 4 and 75 years [11]. The etiology of ameloblastoma is unknown. Some authors consider that the lesion arises in association with the difficult eruption of a third molar, or in association with previous infection or cyst, while the others suggest that trauma and inflammation are common etiologic agents [3].

Radiographic image of ameloblastoma in this case was atypical, and therefore the diagnosis of ameloblastoma could not be made by radiography alone.

In this case, the acanthomatous variation of malignant ameloblastoma was represented, showing strong squamous metaplasia (Figure 4). There have been some cases with microscopic features of ameloblastoma represented by the three previous types of ameloblastoma [12].

Only recently malignant potential for ameloblastoma has been described [13, 14]. Metastatic deposits of ameloblastomas are frequently developed in the lungs but have also been reported at other sites [15–17]. Verneuil et al. [13] have described malignant ameloblastoma of the mandible with metastasis in submandibular region.

Ciment et al. [14] described metastasis of malignant ameloblastoma in the lung 29 years after the excision of the primary tumor. Hayakawa et al. [18] described a case of metastatic ameloblastic carcinoma in both kidneys while Hayashi et al. [19] described the case of mandibular ameloblastoma metastasis to the orbit.

Some authors have described metastasis of malignant ameloblastoma to the lungs seven years after removal of the primary tumor in the lower jaw [20] and that metastatic ameloblastoma in the region of the lung and pleura responded well to hemiotherapy [21].

Histologically, ameloblastomas that may metastasize cannot always be differentiated from the more classic benign ameloblastoma. It appears that inadequate surgical resection and a long duration of the tumor have a significant relationship with metastatic disease appearance [3].

Conclusion

Considering that it is not possible to distinguish conventional, *ie* intraosseous ameloblastoma from malignant ameloblastoma, according to the histopathologic features it is necessary to pay attention, especially to elderly patients, and carry out all clinical, radiological and pathohistologic procedures including immunohistochemical ones. Complete radical excision of the primary tumor with jaw resection and radical neck dissection is recommended as the method of choice in the surgical treatment of this disease. Regular postoperative clinical control should certainly be implemented as a form of local control and disease prevention. A timely and correct diagnosis and treatment of malignant ameloblastoma require a multidisciplinary approach.

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CASE REPORT

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Subdural empyema, retropharyngeal and parapharyngeal space abscess: unusual complications of chronic otitis media

Subduralni empijem, retrofaringealni i parafaringealni apsces: retke komplikacije hroničnog zapaljenja srednjeg uha

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Abstract

Introduction. Otitic complications arise from expansion of the middle ear infection. Subdural empyema is a rare otitic complication, and both retropharyngeal and parapharyngeal abscesses have been described in just a few cases. **Case report.** A 30-year-old male was, admitted as an emergency case because of breathing difficulties, secretion from the ear, and fever. Clinical examination had shown a purulent, fetid secretion from the ear, swelling on the roof of epipharynx, left tonsil pushed medialy, immobile epiglottis, reduced breathing space. Computed tomography revealed thick hypodense content filling cavity, mastoid entering the posterior cranial fossa, descending down throw the parapharyngeal space to the mesopharynx. On the roof and posterior wall of the epipharynx hypodense collection was also present. Tracheotomy was conducted, and incision of the parapharyngeal and retropharyngeal abscess and radical tympanomastoidectomy were performed. The patient's state deteriorated on the tenth postoperative day with hemiparesis and consciousness disorder. Magnetic resonance imaging was done. It showed subdural empyema of the left frontoparietal region and next to the falx, so craniotomy and abscess drainage were conducted. **Conclusion.** Parapharyngeal, retropharyngeal abscess and subdural empyema are rare otitic complications. Adequate antibiotic therapy and radical surgical treatment make possible an outcome with survival.

Key words:
empyema, subdural; retropharyngeal abscess; otitis media; treatment outcome.

Apstrakt

Uvod. Otogene komplikacije nastaju širenjem infekcije iz srednjeg uha. Subduralni empijem je retka otogena komplikacija, a retrofaringealni i parafaringealni apscesi su opisani kod samo nekoliko bolesnika. **Prikaz bolesnika.** Prikazan je bolesnik, star 30 godina, primljen zbog gušenja, sekrecije iz uha i povišene temperature. Kliničkim pregledom nađena je gnojna, fetidna sekrecija iz uha, otok na krovu epifarinksa, izbočena leva tonzila, nepokretan epiglotis koji je ispunjavao kavum, mastoid i ulazio u zadnju lobanjsku jamu, spuštao se parafaringealno do mezofarinksa. Na krovu i zadnjem zidu epifarinksa nađena je hipodenzna kolekcija. Urađena je traheotomija, incizija parafaringealnog i retrofaringealnog apscesa i radikalna timpanomasfoidektomija. Desetog dana posle operacije, kod bolesnika je utvrđeno pogoršanje sa hemiparezom i poremećajem svesti. Magnetnom rezonancom otkriven je subduralni empijem levo frontoparijetalno i uz falks, te je učinjena kraniotomija i drenaža apscesa. **Zaključak.** Parafaringealni, retrofaringealni apsces i subduralni empijem su retke otogene komplikacije. Uz adekvatnu antibiotsku terapiju i radikalnu hiruršku intervenciju moguće je preživljavanje.

Ključne reči:
empijem, subduralni; apsces, retrofaringealni; otitis medija; lečenje, ishod.

Introduction

Otitic complications arise from spreading of infection of middle ear, usually with chronic inflammation with cholesteatoma. With the advent of antibiotics the number of otitic complications has been significantly reduced, but it still poses a problem and needs early detection and adequate treatment. The incidence is 0 : 24 to 0 : 45, and in the preantibiotic era it was 6%. Mortality is 18%–31%, and before the discovery of antibiotics it was 76% [1–3].

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The most common extracranial complications are facial palsy, subperiosteal abscess and labyrinthitis and intracranial: meningitis, cerebral abscess and sigmoid sinus thrombosis. Causes of infections are Gram-negative bacteria, but anaerobes also have to be taken into account. Common symptoms are fever, such is headache with secretion from the ear.

Computed tomography (CT) and magnetic resonance imaging (MRI) make diagnostic procedure much faster and more accurate. The sensitivity of CT for intracranial otitic complications is 92.75%, and diagnostic method of choice for intracranial focal infection is MRI [4].

Antibiotic therapy (combination of of the third- or fourth- generation cephalosporin, aminoglycosides and metronidazole) provides good results. Surgical intervention involves mastoidectomy or radical tympanomastoidectomy. In focal intracranial infections craniotomy and abscess drainage are preferred.

The death rate decreases by using CT and MRI because of faster and more accurate diagnosis, timely surgical intervention and appropriate antibiotic therapy. Postsurgical morbidity due to intracranial infection includes hearing loss, hemiparesis, hydrocephalus, mental retardation, neuropathy, and epilepsy [4–6].

Multiple ototic complications occur in 25% of extracranial and 44% of intracranial complications [1]. Subdural empyema is a rare otitic complication represented by purulent collection between the dura and arachnoidea. It has been presented in 15%–22% of intracranial focal infections. It usually occurs as a complication of rhinosinus infections, meningitis and injuries. Infection from the ear spreads directly or venously [7, 8]. Retropharyngeal and parapharyngeal abscesses, as ototic complications, are described in a few cases [9, 10].

We reported a patient with multiple complications of chronic otitis media with cholesteatoma: subperiostal abscess, thrombosis of the sigmoid sinus and internal jugular vein, perisinus abscess, parapharyngeal and retropharyngeal abscess, supraglottitis, and subdural abscess.

Case report

A 30-years-old male, was admitted as an emergency because of choking, difficulties with swallowing, secretions from the ear, swelling behind the ear and fever. Preveously, in his tenth year, tympanoplasty had been done. On clinical examination we found a purulent, fetid secretion from the left ear, retroauricular edema which fluctuates, swelling on the roof of epipharynx, left tonsil pushed medialy, swelling of the left lateral hypopharyngeal wall down to sinus piriformis, immobile epiglottis, mucosa of the supraglottis hyperemic and edematous, reduced breathing space. The patient had a high fever and breathing with inspiratory stridor. C-reactive protein level was 210 mg/dL, white blood cells (WBC) 13 × 10^9/L.

CT of the endocranium and neck revealed thick hypodense content filling cavity, mastoid, entering the posterior cranial fossa, descending down through the parapharyngeal space to the mesopharynx. After injecting contrast CT revealed defect in the sinus sigmoideus, partially represented with gas, that spreads through the jugular foramen in hypodense tubular structure. Hypodense collection with gas content, 22 × 16 mm in diameter, descended down through the parapharyngeal space to the mesopharynx is shown in Figures 1 and 2. On the roof and posterior wall of the epipharynx hypodense collection 24 × 18 mm in diameter was observed (Figure 3). There was subdural pneumocephalus next to the falx and in the frontal region. In the region of the cerebellum no postcontrast changes in density were present. Supratentorial structures without changes in density were described.

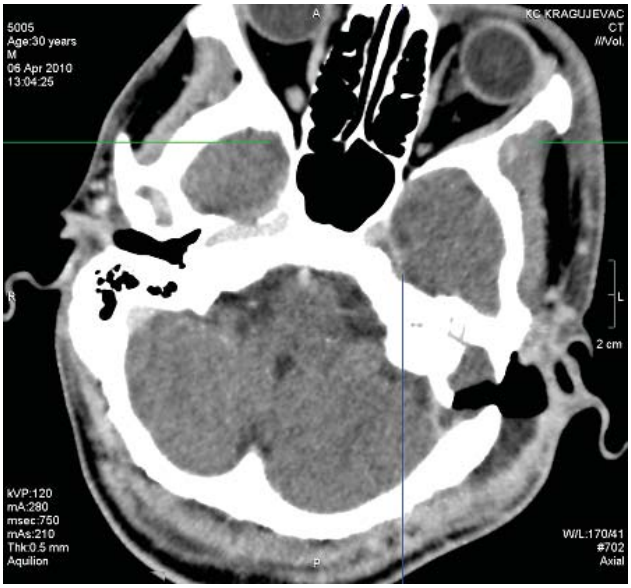

Fig. 1 – Computed tomography (CT) reveals hypodense collection with gas content subcutaneously in the left temporoparietal region, filling the mastoid cavity and entering into the sinus sigmoideus and posterior cranial fossa

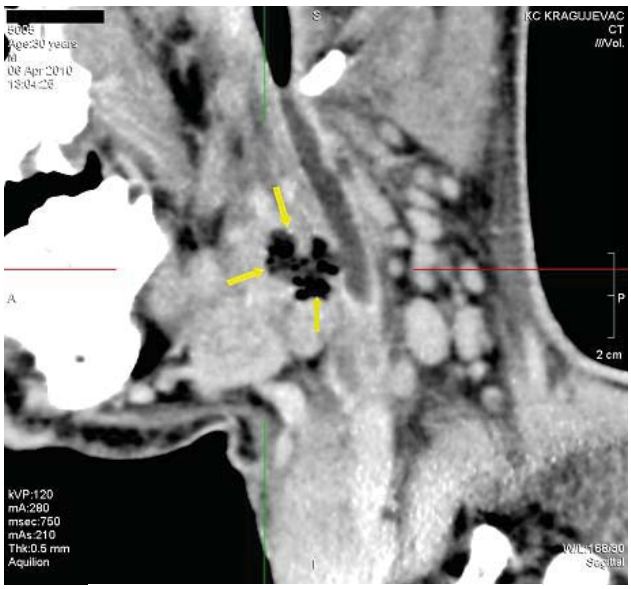

Fig. 2 – Computed tomography (CT) reveals parapharyngeal inflammatory collection with gas content in a direct contact with the internal jugular vein filled with hypodense content and gas

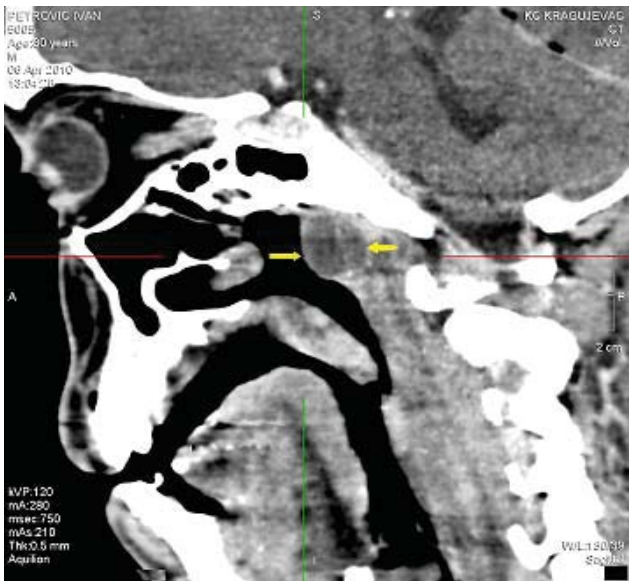

Fig. 3 – Computed tomography (CT) reveals retropharyngeal hypodense lesion, 24 × 18 mm in diameter, at the level of nasopharynx

The patients state deteriorated on the tenth postoperative day with hemiparesis, WBC 8 × 10^9/L, C-reactive protein 61 mg/dL. CT revealed supratentorial, frontoparietal left subdural effusion with free gas, without moving mediosagital structures. Because of the suspected hygroma neurosurgical intervention was not indicated. Antiedematous, along with antibiotic therapy was instituted. Because of further deterioration with consciousness disorder and signs of pyramidal lesions on the right, MRI was done. It showed subdural empyema of the left frontoparietal region and next to the falx, chamber system dislocated towards the right along with cerebelar falx (Figures 4 and 5). Infratentorial, nor intraspinally, no visible pathological changes were detected. The patient underwent craniotomy with wide excision of the dura mater and abscess drainage. The patient experienced postoperative improvement of consciousness level and general condition. Repeated CT scan did not show signs of any residual collection. The patient had been decanullated and retroauricular fistula was resutured. Control CT, after a month, showed regular findings, so the patient was discharged from the Clinic without neurological deficiency.

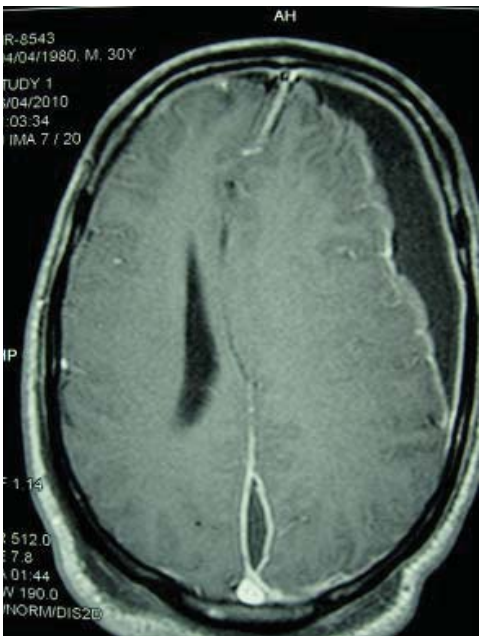

Fig. 4 – Magnetic resonance imaging (MRI) interpreted as subdural collections of thick fluid, 17 mm in width, in the frontoparietal region and also next to the cerebral falx in the occipital region (T1W transverse cross-section and postcontrast)

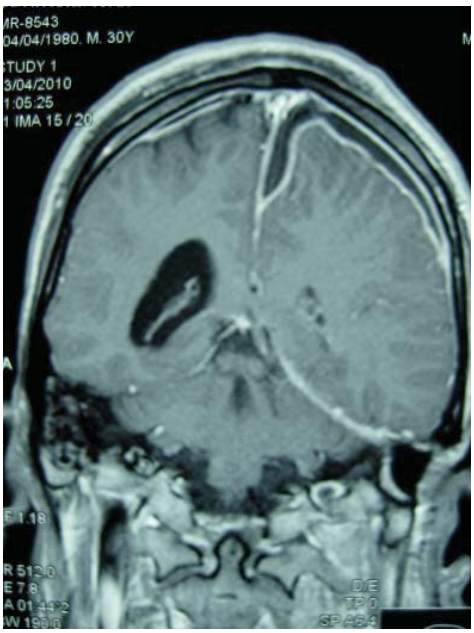

Fig. 5 – Magnetic resonance imaging (MRI) interpreted as subdural collections of thick fluid, in the frontoparietal region and also next to the cerebral falx in the parietal region (T1W coronal cross-section and postcontrast)

Antibiotic therapy including ceftriaxon, amikacin and metronidazole, as well as anticoagulation therapy, had been instituted. Tracheotomy had been conducted, incision of the parapharyngeal and retropharyngeal abscess and radical tympanomastoidectomy with denudation of the dura mater. Proteus vulgaris was isolated, and the presence of gas suggested anaerobic infection.

Postoperatively, the patient recovered without fever, WBC count was 9.1 × 10^9/L, C-reactive protein 29 ng/dL, without swelling and secretions in the pharynx and larynx.

Discussion

Ototic complications are still relatively common, despite the discovery of antibiotics and the possibility of early diagnostic through the use of CT and MRI. The mortality rate is still alarmingly high (18%–31%) and higher in undeveloped countries. Two or more complications of purulent otitis media are often associated, 25% of extracranial and 44% of intracranial ototic complications [1, 2, 4–6].

The case we presented with eight otitic complications is extremely rare. Because of chronic psychosis communication with the patient was difficult. Lack of history data has caused the development of the disease without adequate treatment. He was admitted in a bad general condition with signs of sepsis. The extent of complications was probably a consequence of sigmoid sinus thrombosis, combined aerobic and anaerobic infection and untimely treatment. The infection had venous and direct spread from the mastoid region to the posterior fossa and below the base of the skull to the retropharyngeal space. A large amount of gas suggested anaerobic flora.

Only a few cases of parapharyngeal abscess have been described, explaining the spread of infection *via* the internal jugular vein or directly through the mastoid tip and deep muscles of the neck. Retropharyngeal abscess, as a result of acute otitis media, is described together with cervical vertebral osteomyelitis through direct spread down the skull base [9, 10].

Subdural empyema is a rare otitic complication, more often it is a complication of rhinosinus infections, meningitis and injuries.

Infection from the ear spreads directly or through the vein. Subdural empyema in the presented patient developed by hematogenous spread of infection. Initial lesion was in the frontoparietal region on the same side. Small subdural effusion, shown on CT scan, represented a differential diagnostic problem between empyema and hygroma (in case of which surgery is contraindicated). MRI is the method of choice in the diagnosis of intracranial infections. Craniotomy and wide excision of the dura mater and abscess drainage give the best results [7, 8].

Conclusion

Multiple otitic complications (subperiostal abscess, parapharyngeal abscess, retropharyngeal abscess, supraglottitis, thrombosis of the sigmoid sinus and internal jugular veins, perisinus abscess and subdural empyema) are rare, and the reason for its development is untimely treatment caused by underlying disease. Adequate antibiotic therapy and radical surgical treatment enable the outcome with survival.

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Disulfiramska polineuropatija

Disulfiram-induced polyneurophaty

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Apstrakt

Uvod. Disulfiram je lek koji se koristi za lečenje alkoholizma zato što izaziva neprijatne senzacija posle uzimanja alkohola. Lek se uglavnom dobro toleriše, a retko, kod jednog od 15 000 lečenih bolesnika godišnje, nastaje periferna neuropatija, koja se često pogrešno dijagnostikuje kao alkoholna neuropatija. **Prikaz bolesnika.** U radu su prikazani klinički, laboratorijski, elektrofiziološki i histopatološki nalazi kod bolesnika kod koga se razvila akutna distalna senzorimotorna neuropatija tokom lečenja od alkoholizma. Nakon 4-mesečnog uzimanja disulfirama u dozi od 250 mg dnevno, devetnaestogodišnji mladić osetio je nagli početak slabosti u nogama, osećaj pečenja u tabanima, utrnulost i bolove u listovima i stopalima, uz sniženje snage i ugašene Ahilove refleksе. Bolesnik se uspešno oporavio nakon obustavljanja disulfiramske terapije. **Zaključak.** Uprkos tome što je još uvek značajan broj polineuropatija nepoznatog uzroka, značaj toksičnih neuropatija ogleda se u tome što se prepoznavanjem njihove kliničke slike, identifikovanjem etiološkog faktora i njegovom eliminacijom može sprečiti evolucija bolesti. Time se omogućuje njihovo efikasnije lečenje za razliku od idiopatskih neuropatija koje se mogu lečiti samo simptomatski. Prikaz našeg bolesnika upravo je pokazao te mogućnosti u periodu dok još nisu nastupila teška i trajna oštećenja aksona.

Ključne reči:
alkoholizam; lečenje lekovima; disulfiram; polineuropatije.

Abstract

Introduction. Disulfiram is used in the treatment of chronic alcoholism, because of the unpleasant symptoms produced after ethanol intake. Although it is well tolerated in most patients, one in 15,000 patients will develop peripheral neuropathy every year, which is frequently misdiagnosed as alcoholic neuropathy. **Case report.** We report clinical, laboratory, electrophysiological and histopathological features in a 19-year-old patient who developed an acute distal sensorymotor neuropathy during the treatment of alcoholism. At the end of 4-month treatment with disulfiram 250 mg/day, the patient complained of weakness in distal segments of the lower limbs associated with burning dysesthesias, numbness and pain in the soles of the feet and the legs below the knees; reduction in foot strength, the absence of ankle jerk tendon reflexes, and tactile stocking pin-pick and vibratory sensory impairment in the lower limbs below the knee. Recovery was successful after treatment cessation. **Conclusion.** The significance of toxic neuropathy is shown by the fact that the recognition of clinical picture, identifying etiological factors and its elimination may prevent the evolution of polyneuropathy. This allows for more effective treatment of these neuropathies as apposite to idiopathic ones which can be treated only symptomatically. Our case report indicates the possibilities during a period with no serious damage to the axons manifested.

Key words:
alcoholism; drug therapy; disulfiram; polyneuropathies.

Uvod

U grupi stečenih neuropatija sve veći značaj imaju toksične neuropatije koje nastaju usled neželjenih efekata lekova. Jedna od retkih formi neuropatija nastaje pod dejstvom disulfirama (tetraetiltiuram disulfid) [1].

Disulfiram je lek koji se koristi kao pomoć u toku terapije hroničnog alkoholizma, izazivajući akutnu senzitivnost na alkohol. Ovaj učunak disulfirama otkrila su dva danska lekara koristeći ga kao antihelmintik. Lek je odobrila američka Uprava za hranu i lekove (*Food and Drug Administration* – FDA) 1951. godine. Uobičajeno se primenjuje u inici-

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jalnoj dozi od 500 mg 1–2 nedelje, a kasnije se prelazi na dozu održavanja od 125 do 500 mg. Unosi se peroralnim putem ili aplikacijom subdermalnih testova. Apsorpcija iz gastrointestinalnog trakta je spora, sa dugim vremenom poluživota od 60 do 120 sati, zbog čega efekat leka traje i do dve nedelje nakon unosa tablete [2].

Disulfiram zaustavlja oksidaciju alkohola blokadom acetaldehid-dehidrogenaze čime dovodi do povećanja koncentracije acetaldehida čak 5–10 puta više nego prilikom normalnog metabolizma iste količine alkohola. Akumulacija ovog metabolita alkohola dovodi do pojave takozvane disulfiram-alkoholne reakcije čija jačina zavisi od količine unetog alkohola. Simptomi ove reakcije uključuju: tahikardiju, osećaj nedostatka vazduha, nauzeju, povraćanje, glavobolju, poremećaj vida, konfuznost, malaksalost, cirkulatorni kolaps. Efekat počinje oko 5 min. nakon unosa alkohola i traje od 30 min. do nekoliko sati. Dejstvo se javlja kada je alkohol konzumiran 12 sati pre uzimanja leka. Primena leka ne dovodi do pojave tolerancije, čak se efekat pojačava sa dužinom uzimanja [2].

Moguća neželjena dejstva disulfirama su: optički neuritis, periferni neuritis, polineuropatija. Prijavljeni su slučajevi holestatskog i fulminantnog hepatitisa, dok je kod manjeg broja bolesnika moguća pojava prolazne mučnine, slabosti, impotencije, glavobolje, alergijske reakcije, osjećaja metalnog ukusa u ustima, koji obično prestaje nakon dve nedelje od početka uzimanja terapije. Opisane su i psihotične reakcije kod bolesnika koji su bili tretirani visokim dozama leka, osobito u kombinaciji sa drugim lekovima (metronidazol ili izoniazid) [2].

Iako većina bolesnika dobro podnosi disulfiram, svake godine kod jednog od 15 000 lečenih bolesnika nastaje neuropatija koja se najčešće pogrešno dijagnostikuje kao alkoholna neuropatija. U zavisnosti od doze i dužine lečenja disulfiramom, ovaj oblik toksične neuropatije može biti različite težine. Neuropatija ima karakteristike simetrične, distalne senzorimotorne aksonalne polineuropatije. Žareće dizestezije i gubitak senzibiliteta u stopalima prethode mišićnim slabostima nogu, da bi se kasnije ispoljili simptomi i na šakama [3].

Prikaz bolesnika

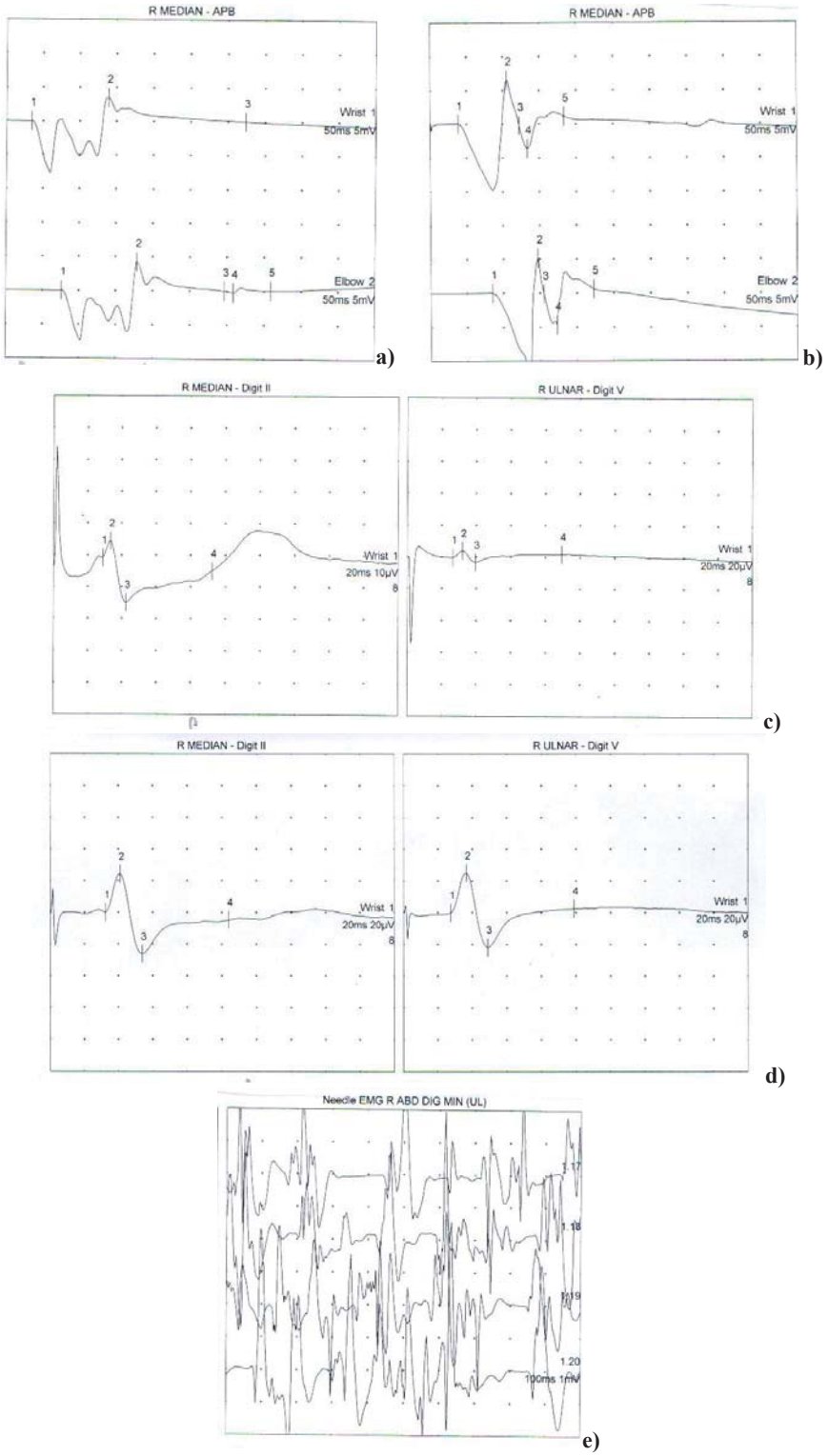
Devetnaestogodišnjem mladiću, ugostiteljskom radniku, kod koga je od 15 godine prisutna zloupotreba alkohola, od strane nadležnog neuropsihijatra ordinirana je terapija disulfiramom u cilju lečenja alkoholizma. Nakon četiri meseca od uvođenja terapije (250 mg disulfirama dnevno), bolesnik je vraćajući se sa posla iznenada osetio slabost i bolove u nogama. Rastojanje od 2 km od posla do kuće savladao je veoma teško, uz odmaranje više puta po nekoliko minuta. Ranije je isti put prelazio bez odmaranja i bez teškoća. U naredna tri dana kod bolesnika razvio se neprijatan osećaj pečenja prstiju i tabana oba stopala uz istovremeni bolni doživljaj dodira i pritiska na tabanima oba stopala. Pokušaj lečenja nesteroidnim antireumaticima i vitaminima grupe B nije dao rezultate. Tri nedelje od početka bolesti, pored pojačanih i konstantnih bolova u nogama koje je mogao da ublaži odmaranjem i ležanjem, bolesnik je primetio i podrhtavanje ruku. U takvom stanju primljen je u Neurološku kliniku u Podgorici radi ispitivanja i lečenja.

Bolesnik je u 3. godini života imao jedan epileptički napad, prema opisu majke generalizovanog toničnokloničnog (GTK) tipa. Do 10. godine života lečen je fenobarbitonom sa punom kontrolom napada. Godinu i po dana nakon obustavljanja terapije dobio je drugi GTK napad i tada je u terapiju uveden valproat (Eftil®). Nakon dve godine bez epileptičkih napada isključena je antiepileptička terapija. Poslednje četiri godine nije uzimao antiepileptike i nije imao napade. Bolesnik je počeo da uzima alkohol u 15. godini života, vremenom sve češće da bi od svoje 17. godine života uzimao svakodnevno veće količine alkohola, do sedam žestokih pića i više piva. U porodičnoj anamnezi od značaja je podatak da je i otac bolovao od alkoholizma.

Pri prijemu bolesnik je u psihičkom statusu ispoljavao anksioznost. Dok je stajao, upadljive bile su bolne grimase lica i premještanje težišta s jedne na drugu nogu zbog intenzivnih neprijatnih senzacija u oba stopala. Fizikalnim pregledom ustanovljena je sinusna tahikardija uz hladnu i marmoriziranu kožu akralnih delova ekstremiteta. Funkcija svih kranijalnih nerava bila je uredna kao i nalaz na vratu uz negativne meningealne znake. Na gornjim ekstremitetima registrovana je uredna trofika i tonus kao i snaga svih mišićnih grupa uz uredne mišićne reflekse i uredan senzibilitet. Kožni trbušni refleksi uredno su se izazivali. Na donjim ekstremitetima trofika mišića bila je uredna, ali je tonus bio pojačan prema spastičkom tipu na nivou kolena sa klonusom patela i pojačanim patelarnim i prisutnim suprapatelarnim refleksima. Registrovana je laka slabost dorzifleksora stopala sa otežanim stajanjem na petama, uz ugašene Ahilove reflekse i simetrično snižene plantarne odgovore. Pregledom senzibiliteta nađena je hiperestezija i hiperalgezija (hiperpatija) tabana kao i taktilna alodinija tabana. Vibracioni senzibilitet bio je značajno skraćen od kolena naniže, a položajni senzibilitet oštećen. Cerebelarne probe izvodio je uredno, Rombergov test bio je negativan. Testovi istezanja, Lazarevićev i Bikelesov znak bili su negativni.

Rutinske analize krvi, kompletna krvna slika, biohemijske analize i reaktanti akutne faze bili su normalnih vrednosti sa izuzetkom lako povišene serumske kreatin kinaze, 219 U/L. Nije bilo znakova hepatičke disfunkcije. Koncentracije bakra i ceruloplazmina u serumu bile su u granicama referentnih vrednosti kao i koncentracije svih klasa serumskih imunoglobulina. Virusološke analize na HCV, HbsAg i HIV bile su negativne. Nivo vitamina B12 u serumu, kao i koncentracije kortizola i tiroidnih hormona bile su unutar referentnih vrednosti. Analizom cerebrospinalne tečnosti nađena je lako povišena koncenracija proteina, 0,47 g/L, uz urednu glikorahiju i uredan citološki nalaz. Izoelektričkim fokusiranjem likvora dobijen je uredan nalaz. Radiografijom pluća, ultrazvučnim pregledom abdomena, kompjuterizovanom tomografijom, kao i magnetnom rezonancom endokranijuma i vratne kičme dobijeni su uredni nalazi. Elektroencefalografskim pregledom detektovana je diskretna epileptiformna elektrokorikalna aktivnost, potencirana iznad levih moždanih regiona.

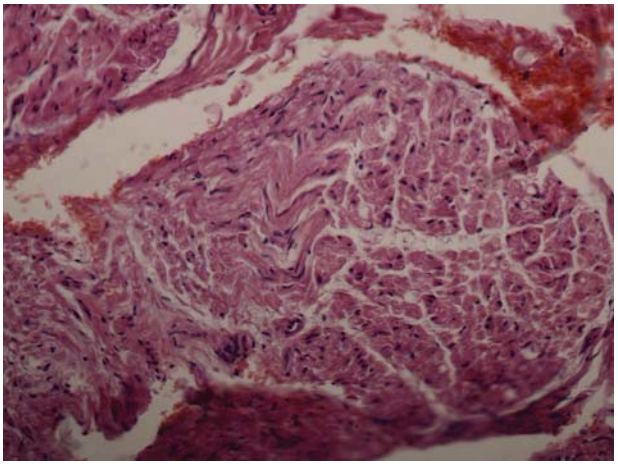
Elektromiografijom dobijeni su svi oblici denervacionih potencijala u mišićima potkolenica i stopala, sa gubitkom motornih jedinica u mišićima stopala i sa neuropatskim potencijalima u mišićima potkolenica uz redukovani interferentni obrazac. U mišićima ruku registrovani su neuropatski potencijali bez znakova denervacije. Elektroneurografijom dobijeno je neznačajno sniženje motornih brzina provođenja kroz *n. peroneus* i *n. tibialis* uz normalnu motornu brzinu provođenja kroz *n. medianus*. Brzine provođenja kroz senzitivne nerve bile su uredne uz sniženje amplituda akcionih potencijala senzitivnih nerava. Elektrofiziološki nalaz ukazao je na akutno ispoljavanje aksonske polineuropatije (slike 1 a–e).



Sl. 1 – Elektrofiziološki nalaz bolesnika sa disulfiramskom polineuropatijom

a) M-valovi *n. medianus* (prvi pregled);
b) M-valovi *n. medianus* (posle šest meseci)
c) Senzorni neurogrami (prvi pregled)
d) Senzorni neurogrami (posle šest meseci)
e) Reinervacioni akcioni mišićni potencijal (AMP)

Izvršena je biopsija *n. suralisa* a potom i patohistološka analiza (kematokrilineozin bojenje) kojom su registrtoavni znaci aksonske degeneracije uz zadebljanje perineuriuma, bez patoloških promena na krvnim sudovima (slika 2).



Sl. 2 – Degeneracija aksona sa znacima zadebljanja perineuriuma (HE, ×100)

Kliničkim ispitivanjem zaključeno je da bolesnik ima akutno nastalu distalnu, simetričnu aksonalnu senzorimotornu polineuropatiju sa dominantnim simptomima neuropatskog bola. Obustavljanjem primene disulfirama, uz mirovanje i primenu vitamina grupe B, benfotiamina i karbamazepina u dozi od 300 mg dnevno, kod bolesnika je posle tri meseca došlo do poboljšanja mišićne snage, otklonjeni su bolovi uz rezidualne i manje dizestezije stopala. Kontrolni elektromiogram (EMG) i elektroneurogram (ENG) ukazali su na značajno poboljšanje nalaza.

Diskusija

Disulfiram se koristi za lečenje alkoholizma od 1947. godine [4]. Lečenje se započinje dnevnom dozom od 800 mg disulfirama sa kasnijim smanjivanjem doze na dozu održavanja od 100 do 200 mg dnevno. Višemesečno uzimanje disulfirama u dnevnoj dozi većoj od 250 mg može uzrokovati neuropatiju, a samo kod malog broja bolesnika toksični efekat disulfirama može uzrokovati neuropatiju optikusa [4] i encefalopatiju [5]. Pretpostavljalo se da je toksični efekat disulfirama posredovan ugljen-disulfidom, produktom metabolizma disulfirama čiji se neurotoksični efekat sastoji u akumulaciji neurofilamenata unutar aksona [6]. Novijim eksperimentalnim istraživanjem je opovrgnuto ranije mišljenje o ulozi ugljen-disulfida u mehanizmu nastanka disulfiramske neuropaije i pokazan direktni toksični efekat disulfirama na Švanove ćelije [7].

Rađene su studije koje su upoređivale efikasnost topiramata u odnosu na disulfiram u smanjenju želje za uzimanjem alkohola [8], kao i poređenje disulfirama sa naltreksononi i acamprosatom [9]. U oba istraživanja disulfiram je pokazao veću efikasnost od poredbenih lekova.

Osim disulfirama postoji niz lekova koji dovode do polineuropatija, a koje se potencijalno mogu sprečiti, i takođe, mogu biti reverzibilne [10]. Sumnja da su neuropatije izazvane medikamentima ili neidentifikovanim toksinima iz okoline postavlja se na osnovu izloženosti jednom agensu i vremenskoj povezanosti sa pojavom neuropatije. Kriterijumi za postavljanje uzročne povezanosti u odnosu na slučajnu udruženost su: jaka dozna zavisnost, stalne manifestacije neuropatije tokom izloženosti toksičnom agensu, bliska povezanost izloženosti i pojave simptoma, poboljšanje poslije isključivanja leka, karakteristična neuropatija na animalnom modelu i isključivanje drugih uzročnika. Ove principe je teško primeniti kod medikamentne i toksičnih neuropatija zato što neuropatija može biti pokrenuta idiosinkratskim dejstvom, zato što se kod hroničnih, malih izloženosti agensu teško povezuje sa odloženim početkom bolesti, što oporavak nakon isključenja može biti minimalan ili odložen, ako je došlo do značajnog oštećenja aksona, zato što životinje na kojima se vrši eksperiment mogu imati drugačiji odgovor od ljudi i zato što može doći do pogoršanja nakon prekidanja uzimanja leka [11]. Kod prikazanog bolesnika diferencijalno dijagnostički prema alkoholnoj neuropatiji bila je odlučujuća klinička slika, pri čemu je isključivanje drugih uzroka akutno nastale neuropatije i dobar oporavak nakon prekida terapije išao u prilog disulfiramskoj neuropatiji.

U ovom radu je prikazana klinička slika neuropatije nastale posle 4-mesečnog lečenja alkoholizma disulfiramom u dnevnoj dozi od 250 mg. Klinički neuropatija je imala akutan početak distalne simetrične senzorimotorne neuropatije sa dominantnim senzitivnim simptomima. Bolesnik je imao simptome neuropatskog bola u stopalima sa dizestezijama u vidu pečenja, sa jako izraženom alodinijom uz jaku zamorljivost nogu pri hodu i ugašene Ahilove reflekse. Ovakva klinička manifestacija odgovara manifestacijama aksonalnih neuropatija sa simptomima koji uvek počinju na najdužim vlaknima i označavaju se kao distalne aksonopatije. Klinička slika našeg bolesnika odgovarala je do sada objavljenim prikazima disulfiramske neuropatije [12, 13]. Kod nije bilo znakova afekcije optičkog živca koja se inače retko opisuje [12], a spastička hipertonija mišića nogu sa klonusom patela mogla je odgovarati afekciji centralnog nervnog sistema koja se, takođe, retko opisuje kao deo kliničke slike disulfiramske intoksikacije [5]. Neuobičajeno ispoljavanje disulfiramske neuropatije je prikazano u literaturi kod jednog bolesnika u vidu paralize glasnica [13]. Kod našeg bolesnika je ubrzo posle obustavljanja terapije disulfiramom došlo do velikog poboljšanja što je zabeleženo i od strane drugih autora [13–15], što ukazuje na reverzibilnost disulfiramskog neurotoksičnog efekta.

Navodi se i nepotpun oporavak kod bolesnika sa težom kliničkom slikom i klinički evidentnim motornim slabostima [11]. U prikazu dva bolesnika drugih autora kod jedne bolesnice sa prethodnom dozom disulfirama od 250 mg dnevno, tokom dva meseca došlo je do delimičnog oporavka, dok je kod drugog bolesnika oporavak bio potpun, iako je uzimao 1600 mg disulfirama na dan tokom jednog meseca, što može ukazivati na individualnu osetljivost, a manje na dozno zavisni neželjeni efekat [16]. Takođe, prikazani bolesnici sa disulfiramskom neuropatijom nisu imali pojačane patelarne reflekse što bi moglo ukazivati i na blagu afekciju centralnog motornog neurona kod našeg bolesnika.

Disulfiramska neuropatija se i pored sličnosti sa alkoholnom neuropaijom, bitno razlikuje po naglom, akutnom početku, subaktunom toku i spontanom oporavku nakon prekida disulfiramske terapije. Elektrofiziološki testovi kod prikazanog bolesnika pokazali su jasne znake aksonalne sensorimotorne neuropatije, što je potvrđeno i u elektrofiziološkim studijama drugih autora [17]. Biopsijom *n. suralisa* kod prikazanog bolesnika otkrivena je aksonalna degeneracija kao primarna patološka promena. Aksonalna degeneracija je uobičajeni nalaz i u radovima drugih autora, i posebno se naglašava nalaz neurofilamentozne aksonopatije sa distendiranim aksonima usled akumulacije neurofilamenata [18]. Morfometrijske studije pokazale su da pored aksonske degeneracije postoji i segmentna demijelinizacija sa remijelinizacijom što se objašnjava toksičnim dejstvom disulfirama, ne samo na akson, već i na Švanove ćelije perifernih nerava [19]. Prema eksperimentalnim podacima, disulfiram inhibira dopamin-beta-hidroksilazu i snižava metabolizam biogenih amina u mozgu čime se može objasniti toksični efekat u indukciji neuropatije i encefalopatije [20]. Ovaj efekat disulfiram ostvaruje sa mnogo većim dozama u odnosu na doze kojima inhibira aldehid-dehidrogenazu i izaziva nepodnošljivost alkohola. Stoga se u cilju izbegavanja toksičnog efekta disulfirama predlaže primena manjih doza u odnosu na doze koje su do sada korišćene u lečenju alkoholizma [21].

Zaključak

Uprkos tome što je još uvek značajan broj polineuropatija nepoznatog uzroka, značaj toksičnih neuropatija ogleda se u tome što se prepoznavanjem njihove kliničke slike, identifikovanjem etiološkog faktora i njegovom eliminacijom može sprečiti evolucija bolesti. Time se omogućuje njihovo efikasnije lečenje za razliku od idiopatskih neuropatija koje se mogu lečiti samo simptomatski. Prikaz našeg bolesnika upravo je potvrdio te mogućnosti u periodu dok još nisu nastupila teška i trajna oštećenja aksona.

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Poziv za reklamiranje u 2012. godini

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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.

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Primeri oblika 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 štampaju se sa proredom 1,5 na posebnom listu hartije. Obeležavaju se arapskim brojevima, redosledom pojavljivanja, u desnom uglu (**Tabela 1**), a svakoj se daje kratak naslov. Objašnjenja se daju u fus-noti, 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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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.

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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.

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Type each table double-spaced on a separate sheet. Number tables consecutively in the order of their first citation in the text in the upper right corner **(Table 1)** and supply a brief title for each. Place explanatory matter in footnotes, 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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